An-Najah University Journal for Research – A

Natural Sciences

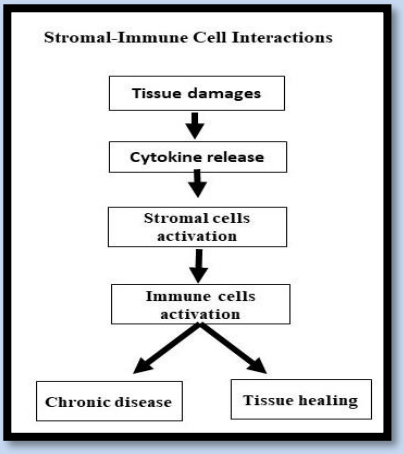
The Emerging Role of Stromal-Immune Cell Interactions in Tissue-Specific Immunity and Disease Progression: A Histological Perspective

Ahmed Mustafa Ahmed[1], Hadeel Kamil Khaleel[1,*] & Taisir Khaleel Ibrahim[2] & Azhar Hussein Kadhim[3]

(Type: Review Article). Received: 9th Jun. 2025, Accepted: 14th Aug. 2025, Published: ×××× DOI: ××××

Accepted Manuscript, In Press

Abstract: Recent advances in immunology and histopathology have highlighted the critical role of stromal-immune cell interactions in shaping tissue-specific immune responses and influencing disease progression. Stromal cells, including fibroblasts, endothelial cells, and pericytes, once considered passive structural components, are now recognized as active players in immune regulation. Through direct cell-cell contact and the secretion of cytokines, chemokines, and extracellular matrix components, stromal cells orchestrate the recruitment, activation, and retention of immune cells within tissues. This dynamic interplay is essential for maintaining immune homeostasis but can also contribute to pathological outcomes in chronic inflammation, autoimmunity, fibrosis, and tumorigenesis. Histological studies using advanced staining techniques and tissue imaging have revealed distinct spatial patterns of stromal-immune interactions across different organs, highlighting their tissue-specific nature. For instance, cancer-associated fibroblasts (CAFs) in tumors create immunosuppressive microenvironments, while in autoimmune diseases like rheumatoid arthritis, stromal cells perpetuate inflammation by sustaining pathogenic immune cell niches. Understanding these cellular crosstalk mechanisms from a histological perspective allows for precise identification of key cellular players and their microenvironmental contexts. Moreover, targeting stromal components and their signaling pathways holds promise for novel therapeutic approaches that modulate local immunity without broadly suppressing systemic immune functions. This review emphasizes the importance of integrating histological insights with immunological research to uncover the complex network of stromal-immune interactions in health and disease. Such integration could lead to more accurate disease models and personalized treatment strategies tailored to the tissue-specific immune landscapes.



Keywords: Stromal cells, Immune cell interactions, Tissue-specific immunity, Histological analysis, Disease progression, Tumor microenvironment.

Introduction to Stromal-Immune Cell Interactions

Over the years, it has become increasingly clear that a complex, dynamic, and reciprocal network of cellular interactions, in which various cell types including stromal, immune, endothelial, and epithelial cells play prominent roles, is orchestrating tissue-specific immunity [1]. As the most abundant cell type in tissues, fibroblasts can sense the immediate environment and either initiate the immune response by producing inflammatory cytokines and chemokines or maintain tissue homeostasis by secreting immunosuppressive signals. Their dual roles are implicated in the pathogenesis of many human diseases including cancer and autoimmunity. Despite heightened interest, understanding of tissue-specific functional heterogeneities of fibroblasts remains limited [2]. As non-hematopoietic cells, unlike hematopoietic cells, tissue-resident fibroblasts arise at early embryonic stages from several distinct progenitor cell sources that are atypical among tissues. The subsequent morphogenetic and signaling cues in the different tissues define pertinent fibroblast populations that are crucial for organogenesis, tissue homeostasis, and stress responses [3]. The immune components interact with tissue-resident fibroblast populations during tissue development (initial phase), inflammation (immunogenic phase), and resolution (immunosuppressive phase) and shape the identities and functional profiles of fibroblasts in a number of ways [4,5].

The precise interactions between immune and stroma cells may involve several specific receptors, ligands, and effector molecules such as cytokines or chemokines. If this can be deciphered at single-cell resolution, with as many tissues or conditions as possible, it may ultimately lay the foundation for the exploration of drug targets. Investigating the emerging roles of stroma-immune cell interactions in tissue-specific immunity and

1 Department of Basic Science, College of Dentistry, Al-Iraqia University, Baghdad, Iraq.
* Corresponding author: hadeel.k.khaleel@aliraqia.edu.iq. ORCID: 0009-0000-1150-8676
2 Department of Biology, College of Science, Tikrit University, Tikrit, Iraq.
3 Department of Medical Physics, College of Science ,Hilla University, Hilla, Iraq.

disease progression across major organ systems would be a valuable endeavor [6]. To achieve this, interdisciplinary collaborations among different disciplines—such as immunology, chemistry, bioimaging, biomedical engineering, and artificial intelligence—may be particularly important [7,8]. A more sophisticated and innovative approach is essential to understand the complexities of immune-stroma cell interactions in tissue homeostasis and its dysregulation in disease settings. The need for diverse cellular model systems that can faithfully recapitulate tissue microenvironments in vivo or ex vivo is obvious at this point [9].

Histological Techniques in Immunology

The emerging field of 'histological immunology,' the application of advanced tissue histology techniques and tools to the study of immunity and immunology, has seen a renaissance over the past decade with young faculty providing new perspectives, technical advances, and compelling models. In this review, a conceptual overview of tissue histology as relevant to immune studies is provided, with an emphasis on practical approaches and pitfalls for those interested in applying histological techniques [10]. In addition, a sampling of recent advances in each general approach—tissue histology, imaging, and systems histology—is presented to illustrate the scope of the current 'golden age' of histological immunology. As emerging histological immunology techniques are applied in new systems, a wealth of details relevant to immune system function will be revealed [11,12]. It has become easier than ever to visualize tissues and the cells within them using methods ranging from classic staining protocols to new molecular imaging techniques. For many years, the demonstration of the presence of cells reactive for specific immune markers has been used as convincing evidence for the involvement of particular tissues or cellular populations in immunity [13,14]. Systemic immunity studies have been aided by advances in flow cytometry and FACS, which allow rapid quantification and obtaining of functional reagents against rare subpopulations, especially in blood. However, flow and cell suspension assays have limitations. For tissues and interactions spanning greater spatial scales than flow cytometry allows, scrutiny of the resident immune cells and/or pathogens in situ is more informative [15]. By analyzing the same tissue or cellular materials with complementary methods, the many phenomena and factors directing system vascularization, cellular recruitment, and immune function through time and space can be comprehensively assessed and modeled, yielding greater understanding and predictive power [16,17]. More tissues can be detected by different CD markers, are summarized in table 1.

Table (1): Quantification of immune cells in tissue samples.

Tissue type	CD markers	Purpose	References
Lymph node	CD_3, CD_20	Lymphoma detection	[18]
Spleen	CD_4, CD_8	Retention and equilibrium in lymphoid tissue	[19]
Gut Associated Lymphoid Tissue	CD_3, CD_4, CD_8, Bu_1, TCRγδ	Immune cell composition	[20]
Lymphoid tissue in the small intestine	RORγ	Homeostasis of the mucosal immune system's function	[21]
Lymphoid tissue	CD4IFNγ	Chronic HIV infection	[22]

The Immune Microenvironment

The tumor microenvironment (TME) is largely composed of non-tumor cells, including a myriad of immune cells with pro- and anti-tumorigenic behaviors. In fact, most cell types in the TME are not tumor cells, and these stromal components also undergo a variety of cellular changes and may possess diverse physical or chemical functions [23]. These tumor-associated cell types arguably convey pathology-inducing characteristics and thus ascribe multifaceted regulatory functions on tumor cells [1]. Stromal cells are categorized into three major cell types: cancer-associated fibroblasts (CAFs), immune cells, and endothelial cells. The TME is thus composed of tissue-resident or -infiltrating stromal cells, recruited immune cells, and tissue architecture-supporting endothelial cells (ECs) [24,25]. Each stromal component either directly or indirectly influences tumor development and progression in a variety of ways from the initiation of tumorigenesis. Interest in tumor-associated fibroblasts began as an offshoot of a long-standing interest in the secretion of extracellular matrix (ECM) proteins to fulfill tumor-stimulating or inhibiting activities [26]. The secretion of growth factors or cytokines to influence tumor growth or progression, respectively, is a well-explored topic area. Stromal signaling to immortalize normal epithelial cells is also a well-studied field of investigation to uncover the early events in tumorigenesis [27].

Immune components of the TME have received increased and more prominent attention. This attention came about due to the successful demonstration of therapeutic efficacy with checkpoint inhibitor-based immunotherapy at the early stage of clinical application. Prior to this successful demonstration, most basic research on immune-oriented tumor biology had been devoted to the question of how tumor cells escape from immune surveillance or education. In contrast, the immune standpoint of TME research has become very popular and will likely expand broadly over the course of time [28,29]. In addition to immune cell types, non-immune cell types within the stroma have been overlooked, and thus substantially less is known about their contribution to the TME [30]. Nonetheless, the investigation of these relatively novel cell types and their functional roles is still at its infancy stage. Many stromal components likely work concertedly to shape a permissive TME for immune escape and tumor progression [31,32]. Thus, major unanswered questions remain regarding the collaborative interplay within the triad of tumor cells, immune cells, and non-immune stroma, and how this interplay is altered in terms of structure, heterogeneity, function, and spatiotemporal context during the progression of cancer [33].

Stromal Cells: Types and Functions

Stromal cells are a heterogeneous tissue-resident cell population which comprises the major components of the stroma in tissues and organs. While anatomy varies, stromal cells often include specialized cells such as endothelial cells, smooth muscle cells, fibroblasts, pericytes, immune cells, and mesenchymal stem cells, as well as the extracellular matrix (ECM) [34] (fig. 1). They are specialized for tissue health, homeostasis, and repair. The dominant stromal cell type of many tissues, interstitial fibroblasts, and their derived myofibroblasts are crucial mediators of tissue health and disease [35]. For example, fibroblasts are critical for maintaining normal architecture and function of skin, heart, and lung. They provide signals which promote epithelial differentiation and organization,

and secrete the ECM, the structural scaffold for tissues and the microenvironment from which many modulators and effector molecules are secreted [36,37]. Studies demonstrate that tissue resident fibroblasts or their precursors secrete a variety of molecules which modulate T cell development, trafficking, activation, and APC function, thus acting in induction and maintenance/expansion of adaptive immune responses [38]. “Stromal vascular fibroblasts recruited and activated by IFNγ are essential for the production of CXCL10 and CX3CL1, which are critical mediators in recruitment, retention, and activation of T cells in maintaining the CD4+ T cell memory pool”. However, fibroblasts are often viewed as a homogeneous population and the predominant cellular component of fibrotic lesions [39]. Type 1 collagen-producing tissue-resident fibroblasts are essential orchestrators of tissue fibrosis. A significantly expanding population of tissue-resident fibroblasts activated and converted into myofibroblasts via myofibroblast differentiation, the epithelial-mesenchymal transition, and apoptosis. Moreover, myofibroblasts promote TGFβ- or PDGF-dependent collagen deposition, resulting in loss of organ function and ultimately organ failure [40].

Integrins are a major family of adhesion receptors involved in the maintenance and remodeling of the extracellular matrix and epithelial-mesenchymal transition. Interactions between integrins and extracellular matrix proteins broadly affect mucosal immunity [41,42]. For example, knockout of the β1 integrin chain in epithelial tissues disrupts the localization of dendritic cells at the epithelial-mucosal interface and inhibits induction of adaptive immunity. Furthermore, a novel role for the αvβ8 integrin has recently been uncovered in regulating production of active transforming growth factor β from latent precursors in Th17-mediated colitis [43]. Understanding the stromal compartment of tissues and organs will shed light on in vivo immune mechanisms that have previously been difficult to interrogate in traditional experimental models or human systems [44,45].

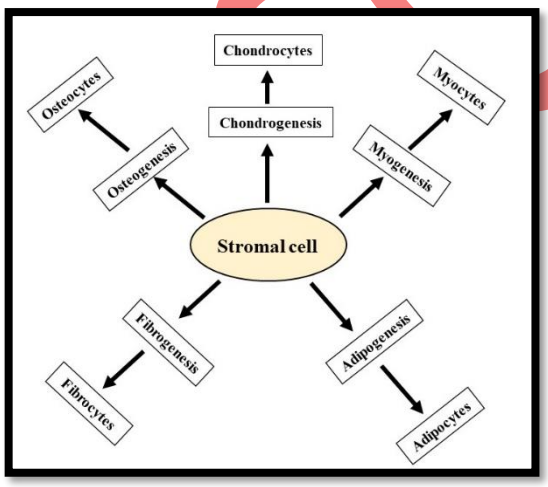


Figure (1): Stromal cells differentiation.

Fibroblasts

Fibroblasts, the main cells of connective tissue, are often considered as merely structural scaffolds that maintain physical integrity and provide cues to neighboring cells [46]. Fibroblasts, however, not only form the physical backbone of tissues but also display a wide spectrum of location-specific functions. Constantly sensing the tissue microenvironment, fibroblasts act as mediators of tissue homeostasis and pathology by receiving and transmitting cues from the immune system, the vasculature, and neighboring cells [47]. The plasticity of fibroblasts poses the question whether the implications of such interactions on tissue homeostasis and immunity differ across tissues. Primary resident fibroblasts have been long appreciated as the most abundant non-hematopoietic stromal cells in all tissues and the main source of extracellular matrix (ECM). They exert diverse functions, ranging from physical support for other cell types to paracrine signaling to meet specific needs of the tissue microenvironment [48]. While fibroblasts are similar in functions and phenotypes regardless of their tissues of origin, tissues do contain specialized and location-specific fibroblasts [49]. Along with immune cells and endothelial cells, fibroblasts actively participate in setting up the tissue microenvironment and are required for the organization of primary and secondary lymphoid organs as well as for post-natal development. Based on the mode of interaction with immune cells, fibroblasts can be classified as lymphoid, splenic, and tertiary [50]. The dynamic and adaptive properties of fibroblasts are crucial for the maintenance of tissue integrity, immunity, homeostasis, and repair processes [51]. Dysregulated activities of fibroblasts have been found to contribute to pathological conditions originating from diverse tissues. Understanding the organization and interactions of resident fibroblasts is essential to decipher how differences in tissue composition and organization of the fibroblast network influence tissue- and organ-specific immunity and tolerance [52].

Single-cell transcriptomic studies have unveiled the heterogeneity of fibroblasts both spatially and temporally. Fibroblast populations have been classified based on shared transcriptional programs and designed as FBNs, largely divided into universal, ubiquitous population’s cross-talk, and specialized fibroblasts. The life-long persistence and plasticity of resident fibroblasts suggest the presence of phenotypically and transcriptionally expansive populations at steady-state that support maintenance of tissue integrity [53]. Resident fibroblasts have also specialized in tissue- and organ-specific functions. Multi-dimensional classification of fibroblast populations and comparison across tissues have revealed conserved signatures, such as ECM-gathering and growth-factor-producing states, which change with age. Fibroblasts are capable of adopting “myofibroblast” phenotypes. Ultimately, the consistent and parallel program shared across distinct tissues, could represent a progenitor-like, omnipotent state [54]. Despite the non-redundant functions, an impressive functional plasticity exists within the fibroblast lineage. During inflammatory stresses, non-immune cells, including fibroblasts, can up-regulate genes normally expressed by immune cells and acquire an activated state [55,56].

Endothelial Cells

Inflammation involves the interaction between infiltrating cells and tissue-resident stromal cells [57]. Technical development over the last two decades has led to the discovery of new stromal cell populations and innovative ways to study them. The stroma has acquired the role of director of the immune response, regulating leukocyte recruitment and organization within the tissue [58]. In physiological conditions, the stroma consists of a number of cell types, including fibroblasts, adipocytes, vascular networks, lymphatic vessels, epithelial cells, and extracellular or matrix components, which provide an

important structural component for tissues [59]. However, there is considerable controversy regarding their role in regulating immunity and tissue inflammation. During inflammatory or immune responses, non-hematopoietic stromal cells play diverse roles in regulating the recruitment, egress, and organization of leukocytes within tissues [60]. They also possess memory characteristics, that is, they are hyper-trophically and functionally altered during secondary or chronic inflammation. In the past few years, there has been a revival of interest in the role of non-hematopoietic stromal cells in leather graft and the retention of memory T cell responses, but most of this research is still in infancy [61,62].

Blood vessels had long been viewed as passive bystanders, rapidly constructing a network to supply tissues with oxygen and nutrients and draining metabolites and waste products. However, analysis of gene expression profiling data sets revealed that endothelial cells (ECs) share a common ancestor with leukocytes, supporting a role for ECs in immune responses [63,64]. Early work demonstrated the ability of ECs from the liver, spleen, and other organs to absorb and degrade antigens, acting as scavenger cells and complementing the activity of macrophages and DCs [65]. They took up circulating immune complexes (ICs), clearing the viral pathogen and generating protective antibodies. Scavenger ECs were proposed to be “an integral component of the innate immune system [66,67].” Liver draining lymph nodes were targeted via lymphatic EC-induced retention of co-expressed peripheral CD4 T cells. Reciprocally, these cells induced specific systemic IgM responses via lymphatic EC-mediated retention of B cells and favored the differentiation into IgA+ B cells via a microbiota-dependent mechanism [68]. ECs interact with the innate and adaptive immune systems both directly and indirectly and are influenced by a plethora of secreted molecules, such as cytokines, chemokines, neuropeptides, and hormones, secreted by neighboring cell types or entering the tissue from the bloodstream [69].

Adipocytes

Adipose tissue is a connective tissue specialized in lipid storage in the form of triglycerides [70]. Adipose tissue can be categorized as either visceral or subcutaneous. White adipose tissue (WAT) is the main type of adipose tissue in the adipose organ. Brown adipose tissue (BAT) is a much smaller metabolically active adipose organ that is responsible for the thermogenic function of adipose tissue. Excessive development of adipose tissue can lead to obesity, which is associated with a substantial decline in health and a variety of metabolic syndromes [71,72]. Adipose tissue has an abundance of resident immune cell types, and the composition of these immune cells markedly shifts upon the development of obesity. The resident immune cells consist of both the innate and adaptive immune systems. Innate immune resident cells include macrophages, dendritic cells, mast cells and natural killer cells [73]. Immune cells of the adaptive immune system include both T and B lymphocytes that are also found in adipose tissue. One of the significant features of obesity-induced inflammation is the accumulation of macrophages in adipose tissue. These immune cells can be further divided into various subsets, including CD11c-expressing pro-inflammatory M1 macrophages and their alternatively activated M2 counterparts with anti-inflammatory properties [74]. A growing number of studies suggest that the interplay of adipocytes with tissue-resident immune cells could regulate adipose tissue inflammation and metabolic homeostasis in obesity. Surface molecules produced by adipocytes may have systemic and local effects on immune cells, which will be discussed in the first part of this review [75]. Alternatively, immune-resident cells in tissues can regulate the function of adipocytes and the entire adipose microenvironment. Although still at a nascent stage of this research field, recent studies utilizing innovative organoid techniques have identified several novel mechanisms of the crosstalk between immunocytes and adipocytes, and their roles in obesity-related metabolic syndromes will be discussed in the second part of this review [76].

Immune Cell Types and Their Roles

Stromal fibroblasts and myofibroblasts have been involved in inflammation, immunity, and tissue repair. Macrophages have been suggested to acquire the myofibroblast phenotype and to grow into tissue-resident macrophages after pro-inflammatory activation in tissues. Fortuitous interactions between resident fibroblasts and infiltrating macrophages may lead to long-lasting functions, of which some may be appropriate to control referencing organismal homeostasis, while others may promote inflammatory havoc and usually chronic disease [77].

In cancer, the myofibroblast phenotype has been suggested to derive from several cell types, including fibroblasts and macrophages. Yet in premises, the contribution of this recruiting process to the fate of tumor cells has not been capitalized on. It has been one of the prominent unexplored areas in cancer research. The difficulty of describing stable interactions conditioning either the fate of myofibroblasts or adjacent tumor cells in physiological conditions has hampered knowledge of proper strategies to counteract gynecological tumors with high epithelial-to-mesenchymal transition (EMT) features [78]. This is particularly true in basal-like breast cancers, and serous high-grade ovarian cancers, where understanding tumor and stroma interactions are urgent areas of investigation to avoid the demise of patients and high recurrence rates [79].

This structural support has earned them the name of “stroma” (literally that which is spread thickly), whilst the isolated and parenchymal cells are denoted as “stroma-free.” Immune cells comprise a heterogeneous population of innate and adaptive cells, either bone marrow-derived or tissue-resident [80]. The immune system acts as the guardian of multicellular organisms, monitoring and responding to environmental changes impacting homeostasis and viability. This entails protecting against the infiltration of foreign entities and unwanted elements inside the body, as well as appropriately resetting the response following its completion [81]. However, a growing body of evidence indicates that immune cells are actively involved in the development and progression of disease rather than only serving a protective role [82], and is summarized in table 2.

T Cells

The studies of the three-dimensional structure of TME have recently emphasized that most of the immune active cells in the TME are heterogeneous and integrated with different ECM structures in 3D texture. The results of histological research focused on the spatial location and 3D texture pattern of each histological structure revealed the hidden roles of stroma

structure for tissue-specific immune activities, tumor invasion, and T cell retention [83].

Scaffold structure of normal tissues was found to be pro-tumor immune structure that positively regulated local immune-reactive T cells in cancer patients. Some immune active cells were confirmed to interact with each stromal structure to regulate local tissue-specific immunity activities, and further emergence of tumor-immune structural conditions [84]. Recent single-cell RNA sequencing of fresh tissue dissociation of different TME disclosed a new immunegap in high-grade type-based cancer patients, which was further detected by a panel of histological assays and a new immune-typing. The correlations of new histological immune-typing and breast cancer disease progression and therapy response were convincingly investigated [85, 86].

The numbers of single-cell transcriptome data-based studies on multi-omics rich TME analyses for pancreatic cancer are rapidly increasing in the recent 3 years, and are intensively focused on the localization and cellular interactions of various immune cells with macrophages and T cells [87]. Meantime, interrogating heterogeneous cellular states of macrophages or T cells revealed subtypes closely related to clinical significance, requiring further experimental validation in histological immersion [88,89].

B Cells

B cells comprise a variety of specialized cell populations regulating humoral immunity, contributing to the maintenance of tissue homeostasis, and maintaining tissue health [90]. For some time, B cells were considered tissue-resident immune cells, but we now know they have to be strictly controlled due to their less-known regulatory functions that may contribute to tolerogenic states or promote tissue autoimmunity [91,92]. Tissue immune niches offer appropriate local conditions for the recruitment, maturation, maintenance, and training of immune cells [93]. These immune niches play an instructive role in the development of immune responses and regulating local immune homeostasis, maintaining immune tolerance to harmless antigens as well as contributing to antigen-specific proinflammatory immune responses [94,95].

B cells co-localize with T cells, dendritic cells, and other immune cells in organized structures in tissues, immune niches called tertiary lymphoid structures (TLS). TLSs are generally referred to as lymphoid aggregates developed in non-lymphoid tissues during pathological conditions, consisting of antigen-specific B follicles and CD4 and CD8 T cell zones, and play an important role in mediating adaptive immunity by recruiting and activating naive T and B lymphocytes [96,97]. However, the capacity of B cells to mediate immune responses and their involvement in the evolution of adaptive immunity depend not only on their absolute numbers but largely on their spatial localization within tissues [98]. Both B and T lymphocytes can segregate and form distinct microenvironments to orchestrate the timing and quality of immune responses [99]. The collection of these spatially organized events influences how incoming antigens are processed, presented, and responded to by T and B lymphocytes to accomplish effective anti-tumor immunity or tissue injury [100,101].

Macrophages

Macrophages are the most plastic and morphologically diverse phagocytes in mammalian systems. Their morphology is closely related to their function, and tissue-resident and infiltrating macrophages were once viewed in simple terms as metallophilic versus matricellular [102]. Following the groundbreaking study of the early development of the CD45^+ mononuclear phagocyte lineage, it became evident that mononuclear phagocytes could be divided not only into these two-bearing distinct fetal origins but also into classes based on their cellular embryonic origin and histogenic development [103]. Recent studies employed flow cytometry, single-cell RNA-seq, and other advanced analytical tools have substantially advanced their subclassification, it is still impossible to generate a comprehensive database of resident and infiltrating tissue macrophages because nearly every tissue examined, with the exception of the brain and bone, has been reported to contain distinct populations of macrophages. Brain macrophages called microglia are derived from the yolk sac, while bone marrow resides osteoclasts. Macrophages present in other tissues of the adult animal, however, can be originated from both the yolk sac and the circulating monocytes from bone marrow [104]. Moreover, macrophages can move between the circulation and tissues in the processes of tissue homeostasis and immune responses. Notably, ley bodily tissues may harbor one to three macrophage populations, each serving unique tissue and immune functions. Due to their plasticity and heterogeneity, many macrophage-related diseases, including atherosclerosis, diabetes, asthma, pulmonary fibrosis, neurodegenerative disorders, and cancer and metastasis, have been defined [105].

To equate the embryonic origins of resident tissue macrophages does not consider the possible existence of distinct ontogeny or subclasses. It is not uncommon to find resident tissue macrophages at either embryo or adult, or both origins, bearing functional relevance [106]. For example, surface expression of the anchored Class-A scavenger receptor (Mrc1) is usually used to define alternatively activated and steady-state phagocytic macrophages; however, circulating monocyte-derived macrophages also expressed it in mineralized tissues, pulmonary mucosa, and even the intestine following pathologic stimuli [107,108]. In humans, neonatal pulmonary alveolar macrophages are progeny of localized fetal monocytes harboring embryonic origins. Whether these newly formed lung macrophages ever contribute to alveolar macrophages or fetal monocytes cease their dynamic migration into the lung remains unresolved. In many cases, the functional relevance of distinct embryonic macrophage origins was not analyzed along with their ontogeny [109,110]. For example, nascent Ca^2+ influx-regulated neutrophil bactericidal maturation occurs before the development of the bone marrow resident neutrophil population; therefore, resident tissue macrophages and tissues are heavily influenced by their ontogeny even in the adult stage [111]. It is possible that some phenotypic and functional differences between tissue macrophage origins may fade or be modified with time after birth or in steady-state circumstances. To provide effector differentiation type that is relevant to coordinate tissue microenvironment, neutralization of non-specifically activated macrophages is required [112].

Dendritic Cells

DCs were first described in the early 1980s as a potent antigen-presenting cell population distinct from macrophages and B lymphocytes. Humans have both myeloid and plasmacytoid DCs, which upon encountering antigens undergo maturation and migration processes that optimize their ability to prime naive T-cells. After extensive loss of the initial DCs that arrive at the inflamed tissue site, some DCs can persist for considerable periods, especially by migrating via the lymphatics to draining lymph nodes in which they promote effector T-cell proliferation [113]. These tissue-resident DCs are critical for tissue-specificity of T-cell activation. Whereas, initiation is directed by inflammatory signals, the tissue-resident DCs remain in peripheral tissues and migrate to draining LNs, where they can further support effector T-cell proliferation. CD103+ DCs are found in the majority of epithelial tissues, with the exception of skin [114]. On the contrary, mucosal tissues are specially enriched in various DC subtypes. In heart, brain, indices, and lungs, resident CD103+ DCs have been shown to withstand most acute inflammation, potentially acting to limit tissue damage [115]. Moreover, tissue-resident DCs can shape the peripheral T-cell repertoire, thus in the long run, tissue-specific immunity. Enteric, CD103+ DCs maintain the functional competence of IL-10-producing Treg cells and particularly promote Treg-cell differentiation fate in the gut, whereas few of them can induce T-cell differentiation into Th17 in the presence of microbial signals [116].

Systemic inflammation led to activation of tissue-resident DCs across diverse tissues, with substantial induction of type III interferon signaling. Different tissue-resident DCs respond differently. However, upon establishment of DC-steering inflammation, they become active participants in disease progression [117]. Despite growing evidence indicating a pivotal function of most tissue-resident DCs in shaping T-cell immunity in a tissue-specific manner, the specific roles of tissue-resident DCs in chronic inflammation remain less explored. Likewise, how phototherapy influences the differentiation, and activation states of tissue-resident DCs remains unclear. Most of current techniques applied to study the in vivo function of DCs in chronic inflammation are injurious and unintendedly affect DCs in several aspects [118,119].

Table (2): Immune cells and their roles.

Cells types	Diseases	Function	references
T cells	Cancer	Regulate local tissue-specific immunity activities	[84]
B cells	Tissue injury	Anti-tumor immunity	[100, 101]
Macrophages	Many diseases: atherosclerosis, diabetes, asthma, pulmonary fibrosis, neurodegenerative disorders, cancer	tissue homeostasis and immune responses	[105]
Dendritic cells	Inflamed tissue	promote effector T-cell proliferation	[113]

Interactions between Stromal and Immune Cells

Interactions between immune and stromal cells play a pivotal role in the maintenance of tissue homeostasis, tissue development and repair, as well as in the progression or resolution of chronic inflammatory processes and diseases. Stromal cells are defined as non-hematopoietic, non-epithelial, and non-endothelial cells present in most tissues and organs of multicellular organisms [120]. Immune cell types and their effector functions display a remarkable continuum of changes depending on the tissue context, cellular interactions, and local cues that are comprehensively integrated initially examined as mere bystanders of immune responses and developmental processes, tissue-resident stromal cells are now recognized as complex and dynamic micro-organisms in their own right. Global analysis of the cell types present in mammalian and human tissues has uncovered an impressive cellular diversity [121]. With ground-breaking histological and imaging approaches, some of which were pioneered by early scientists studying tissue development and effector functions of the immune system in vivo, it has become clear that, in addition to immune cell compartments, tissues are also composed of a remarkably diverse range of non-immune cells collectively referred to as stroma [122]. Stromal cells include both structural cells and a large number of different defined and undefined cellular subtypes with profound and diverse immune-related functions [123]. Whereas bone marrow, liver, and skin stroma have long been studied, efforts to characterize tissue-resident stromal cells in other organs and at fine resolution are still in their infancy. Recent studies have revealed important and diverse immune-related functions of stroma, including the capture and transport of antigens, regulation of tissue- and site-specific immunity, pharmacologic modulation of immune responses and responses to immunotherapy, as well as dysregulation in settings of chronic inflammation, maladaptive immune responses, autoimmunity, and cancer [124]. However, our understanding of how the various stroma-immune cell interactions are established in naïve tissues, how they are recast during development after perturbation or in disease, and how they in turn modulate the spatio-temporal organization of immune cells and their functional responses is still very limited. Nonetheless, it is now clear that a close interplay between stroma and a diverse array of immune cells is crucial for the dynamic maintenance of different tissue microenvironments [125].

Cytokine Signaling

Cytokines are small signaling proteins produced by a variety of cells including leukocytes and non-immune cells that modulate immune responses and tissue homeostasis [126]. Autocrine and paracrine interactions mediated by the cytokine networks are believed to play a major role in directing the function, proliferation, and survival of stromal and immune cells. It is now widely recognized that chemokine gradients control the first steps in the recirculation of immune cells through tissues and lymphatics [127]. The functional roles of cytokines in cell positioning or stabilization of lymphocyte interactions were investigated in the context of either immune cell function in tissue immunity or the role of cellular behavior in the gross structure of the immune system [128]. However, the range of functions and organizations that regulated cellular communication with the use of a common set of signaling pathways are explored more

generally. Just as periphery tissues continuously produce chemokines that control T cell recirculation and presentation of antigens, it was proposed that peripheral tissues respond to tissue damage by secreting a host of cytokines that bring many of the effector T cells from the tumors into the circulation [129].

Flattened tissue-resident fibroblasts embedded in the extracellular matrix rapidly lose their flat morphology and develop a semi-circular shape. On a time, scale of hours, the dynamics of stable connections between the migrating fibroblasts are found to cause a striking expansion in the area of the tissue subjected to tissue damage. NET-derived chemokines attract the precursors of blood vessels greatly increasing the concentration of the vehicles of another set of signaling pathways that suddenly hit and totally re-organize the original flat tissue [130,131]. Only a small number of matured endothelial cells will serve as conduits for the newly sprouting blood vessels to form further from fibroblast monolayers. During cancer progression, it is believed that different sorts of profibrotic factors lead to the chronic activation of fibrobasts which conceptually resemble the fast-invasive fibroblasts in response to an acute damage [132]. Massive communication among the fibroblasts and other irrelevant cells that were just a part of a unitary tissue less than a day before will render the tissue patchy or desmoplastic. Figuratively the organ is eaten away and fibrous or stony lumps will ultimately remain. Long-lasting low-grade inflammation mediated by a variety of the polymorphonuclear cells are believed to be the main instigator of fibrotic changes even in cancers [133].

Cell-Cell Interactions

The tumor microenvironment (TME) is known to be composed of heterogeneous populations of each component, exhibiting distinct phenotypes and functional states [134]. Cancer cell heterogeneity affects anti-cancer treatments, and individual differences in tumor-associated normal stromal cells and infiltrating immune cells can influence tumor progression and radiotherapy response [135]. Cells within the TME communicate with each other through various ways, including direct membrane-membrane contact, release of soluble factors such as cytokines, growth factors, exosomes, and microvesicles containing proteins and RNAs. Recent advances in single-cell RNA sequencing technologies have enabled dissection of stromal cell phenotypes and states within the TME, and have propelled the field into the omics era [136]. However, much less attention has been directed to the study of cell-cell or cell-matrix interactions within the TME. How TME cells interact with each other, how their phenotype changes with proximity, and how physical interactions alter cell behaviors are among the questions to be investigated for a more comprehensive understanding of the TME [137,138].

Only a limited number of approaches have been developed and applied to tackle these questions forming a fruitful area of future research. The best-known methods for the study of cell-cell interactions are functional assays [139]. Immune-tumor interaction has been studied using co-cultures of different cell types with readouts such as cytokine secretion and TCR sequencing, however, the readout must be statistically analyzed and interpreted with great caution. While some small molecules are potent cell-cell communication inhibitors, they remain largely unexplored due to feasibility constraints [140,141]. Indeed, for the above approaches, potential technical solutions should be pursued. As an experimental belonging to the “benchtop” family, bioengineering-based methods, such as microfluidics, cellular barcoding, and iChip, for high-throughput screening, have the potential to affordably access multiple parameters of TME interactions [142].

Tissue-Specific Immune Responses

Tissue-specific immunity exists in healthy tissues, which are associated with an abundance of effector memory and T follicular helper (Tfh) cells and an absence of T-regulatory subtypes [143]. Tissue prestige immunity is often downregulated with age or upon infection. When scheming the context of vaccination or therapy, relevant tissues are key and homing motifs or salting out signals may be useful design considerations [144]. Tumors include large antigen landscapes that may elicit broad responses if accessible via lymphoid conduits. Recently, tissue context was incorporated into systems vaccinology approaches that inform vaccine-based prime-boost strategies. Such ongoing effects are anchored to dynamic cellular networks involving non-immune cells that are frequent and dense in the periphery. A context-specific dynamic balance of type I interferons and TGF-β emanating from the niche was also harnessed to cue antigen-specific immunity in a translational autoimmune setting [145].

The stress-activated signaling machinery, which models how threshold levels of involvement in cellular transmigration elicit tissue-quenched immunity, is being investigated together with an in-situ imaging strategy. When model tissues are inflamed, intrinsic tissue properties partially cripple immunity at early times and later activate context-appropriate tropisms [146]. These effects are partially reversible. Continuing interaction with readiness and viewing platform user groups ensures up-to-date relevance and open-ended potential. Importantly accurate heralds of internal state need validation from longitudinal pilot human studies. In addition to standard vaccine measurements, the next generation of models will manifest effects on the immune milieu, gauge long-term immunological feedbacks, and predict time-dependent locations of immune alterations [147].

Consent and ethics are key facets of dealings with human tissues properly constrained collaboration with hospitals and strategies to gain consent are needed, as are internal review boards and guidance. Non-standard data on the patient's side benefits predictive capabilities and deep machine learning approaches. The results of cancer therapies or modulating immune therapy or risk will be tested to confirm the translational potential of the new models [148].

Lymphoid Tissue

An important step forward in our understanding of tissue-organised immunity has come from the recognition of lymphoid tissue structures as complex, dynamic microenvironments designed to promote effective immune responses. Understanding how to translate/restore stroma-organised immunity will provide opportunities for therapeutic gain in a variety of diseases including cancer and chronic inflammatory disorders [149]. Analysis of cardiac or other solid tissues in health and disease reveal the remarkable heterogenicity of tissue stroma, both structurally and functionally. For example, fibrotic scars after myocardial infarction contain myofibroblast cells that differ morphologically and functionally from cells in the healthy cardiac interstitium [150,151]. Analysis of different skeletally/viscerally-associated tissues reveals both shared,

evolutionarily conserved features with lymphoid tissues as well as differences that may account for their varied immunological roles [152]. Each lymphoid or lymphoid-associated organ encompasses distinct groups of resident cells and a unique microenvironment that together perform organ-specific functions and guide immune responses [153]. The relative importance of these synergistic microenvironmental mechanisms will dictate the type/intensity of immune response and also how the stroma influences the early and subsequent stages of pathogen control/set-point immunity versus infection persistence. An emergent understanding of diseases affecting the lymphoid system are also being highlighted and how modified structures may be targeted for outcomes in the immunotherapeutic treatment of a variety of immune-related diseases [154]. The definitions and concepts of lymphoid tissue that were introduced with an emphasis on the histological perspective, are also recognised as having relevance for non-lymphoid tissues in health, infection and chronic inflammation [155].

Tissue-embedded immune compartments can be broadly defined as being organised (lymphoid, lymphoid-like) or disorganised (lymphoid-uncertain). Lymphoid tissue is defined as cell aggregates that can be recognised in histological sections as dense, multi-cell-cohabitating foci frequently encapsulated and displaying cellular zoning [156]. The types of functions that can be attributed peripheral lymphoid tissues are then outlined. Lymphoid-like tissues, in contrast to organised lymphoid groups, also perform immune functions. Lymphoid structures can be either intrinsic to the tissue or, as is also recognized in the case of lymph nodes draining tissues [157]. Data is presented focusing initially on lymph nodes (and the lymphatic system) where the immune interactive role of stroma and the bi-directional interplay with advancing leukocytes are strongly evident. The lymphatic system is also highlighted as an organ that is intimately ontogenically and functionally associated with lymphoid tissues. Emerging aspects of both embryonic and post-natal acquisition processes, along with a staging of lymphoid tissue maturation, development and structural refinement in development, are discussed [158].

Non-Lymphoid Tissue

Non-lymphoid T cell homeostasis is primarily orchestrated by non-hematopoietic stroma cells (types 1-3) forming unique environments where mature T cells constantly recirculate. These cells were partly notorious for their small number, considering the popularity of other cell types mainly involved in antigen presentation [159]. However, other components of T cell-homing tissue need to be taken into consideration: High Endothelial Venules (HEVs) are the anatomical gateways for T cells residing in lymphoid tissues or flowing in the blood stream to enter into the stroma of non-lymphoid tissues; Additionally, to enter into the tissue proper, T cells need to leave the HEVs to shear stresses rapidly decaying in the cortical tissue; T cells need to interrogate the stroma geometry for the presentation of specific cognate costimulatory signals, and Flexible communication enables some of them to interact with stroma cells themselves [160,161]. These cytoskeleton-induced dynamical interaction processes are believed to work as a spatio-temporal bandpass filter that regulates the retention and function of T cells across the scales in space and time, ultimately defining the precision of tissue microenvironments. Such spatio-temporal filtering processes were found to be partially dysregulated in the cases of chronic inflammation and cancer initiation, prompting the emergence of novel rules of T cell retention. Spatio-temporally elastic microenvironments defining local tissue T cell immunity is discussed [162].

The regulation of the mechanisms enabling immune cells egress from the tissue into the lymphatic system is poorly understood. Some immune cells utilize different lymphatic exit routes [163]. For example, in addition to the lymphatic pore, dendritic cells and monocytes access the lymphatics via the mesenteric lymphatic vessel. With the aid of techniques to study interstitial flow and ex vivo imaging of this poorly accessible immune system, additional understanding of the directional migration and entry into lymphatics of B cells, macrophages, and plasma cells was gained. Additionally, directionality in egress to the lymph node may depend on differential signaling by S1P receptors and translocalizing the competitive role of the CD4 dim subset of Tfh cells via PD-1 [164].

Role of Stromal-Immune Interactions in Disease

Interactions between immune cells and stroma cells in the tumor microenvironment (TME) are highly complex and structurally and chemically heterogeneous. These interactions include direct mechanisms mediated by cell-surface receptors, indirect ones mediated by secreted factors, and the bidirectional nature of the relationship. Tumor necrosis factor (TNF) potently stimulates the production of chemokines (CXCL5) in mesenchymal stem cells via TNF receptors (TNFRs). Neutrophils infiltrate inflamed tissues and secrete TNF, thereby recruiting mesenchymal stem cells from the bone marrow [165]. The consequent mesenchymal stem cell-secreted CXCL5 then sustains neutrophil traction within tissues and forms a positive feedback loop. Moreover, studies in breast cancer and peritoneal mesothelioma models have uncovered the non-autonomous roles of immune cells in promoting cancer-associated fibroblasts. These studies suggest tackling stroma activation as a tractable strategy in combination with immunotherapy [166].

Recent evidence suggests the stroma as an important orchestrator of immunity associated with “scar-like” tissue. Hematopoietic cells, such as macrophages and mast cells, infiltrate the stroma before the onset of adaptive immunity [167]. The tissue-resident fibroblasts at the disease site become activated and proliferate when exposed to the mediators secreted by infiltrating innate immune cells. Retaining immune cues, stroma-derived factors promote the recruitment and activation of cytotoxic T lymphocytes (TCs) at later times. Stroma-derived immune-activating cytokines and chemokines further mediate the recruitment and retention of TCs, thereby fueling atopic dermatitis-like inflammation in tissues [168].

Studies have revealed that the TME and its components are highly heterogeneous and complex. In this context, a more systematic and structural understanding of TME constituents is necessary to boost the effectiveness of targeted therapy against the TME components. Additionally, preclinical validation is regarded essential for candidate therapeutics, which is currently mostly validated on genetically engineered mouse models. However, such approaches are limited in their ability to replicate the heterogenic features of human tumors [169]. Hence, a 3D-servible platform for culturing human TME assembloids is developed to systematically investigate the TME and its

agonistic action during tumor growth and target-tissue remodeling. This method allows for the unbiased generation of assembloids composed of both tumor cells and TME components, permitting sequencing-based characterization of their spatial organization and multi-cellular signaling mapping. Furthermore, a 3D serviceable TME assembloid approach is presented for screening chemical and biological candidates to enhance anti-cancer efficacy [170]

Cancer Progression

Tumors affect the surrounding tissues and can alter the identities and functions of tissue resident cells and the orchestrating signaling pathways. As a result of bi-directional cell−cell cross-talk, malignant cells can create a tissue-specific tumor microenvironment (TME) that exhibits distinct histopathological features in different organs, contributing to malignant, chemoresistant, and metastatic behavior [171]. Immunotherapy targeting immune infiltration or activation is being widely investigated in recent years, including the application of immune checkpoint inhibitors against cytotoxic T lymphocyte antigen-4 (CTLA-4) or programmed cell death 1/programmed cell death-ligand 1 (PD-1/PD-L1) for systemic solid tumors [172]. The immune cell component of TME is intricately dependent on the tissue type. In many cases, tissue-resident and extrinsic innate immune cells, including macrophages, natural killer (NK) cells, and mast cells, establish a tissue-specific immune response that suppresses tumor progression. However, tumor progression and drug resistance may also be driven by the activation of tissue-specific immune cells [173].

Emerging concerns arise regarding the targeting of immune responses in TME. Much of the effort is enlisted to bolster the natural immune responses for the treatment of tumors. However, some mechanisms of tumor immune evasion have been neglected, especially in the discovery of new drugs class or by precision medicine approaches [174]. Tumor cell-intrinsic drivers and/or specific epigenetic changes often dictate these immune evasion mechanisms, resulting in histologically identical tumors exhibited various responses to immune checkpoint inhibitors (ICIs) and/or immune activating agents. To address these issues, a deeper understanding of tissue-specific immunity and its interactions with malignant cells would be essential, encompassing an understanding of cell types, signaling pathways, and landscape changes along with patient response types [175, 176].

Potential mechanism studies providing histological perspectives with novel models examining the interactions of tissue-resident immune cells with malignant cells are highlighted. There is much to be learned from how the identity of stromal-immune cells is maintained during tumor progression, and how tissue recruitment or involvement is shaped [177]. This absolute focus on malignant cells will lead to undervaluing the role of non-cell-intrinsic mechanisms in tumor biology. Consequently, tumor progression and drug resistance cannot be fully understood by crediting them solely to actual driver variants. Instead, it would be far more logical to take tissue context into consideration [178].

Autoimmune Diseases

For many years, it was widely accepted that in the course of autoimmune diseases, monocyte recruitment is the decisive parameter for the prognosis of the outcome of the disease. However, very recently a new histotopographic analysis strategy was introduced to study the spatiotemporal coordination of cells in a wide variety of tissue inflammatory responses [179]. Surprisingly, the analyses revealed that tissue-resident macrophages play a much larger role than expected previously. Notably, this histotopographic perspective is provided by the application of cellular tracing technology wherein specific types of immune cells are traced in different niches using genetically encoded, florescent proteins [180]. The analysis is applicable on a wide spectrum of inflammatory diseases including autoimmune diseases and provides an entirely new perspective of cellular plasticity over both phases of immunomodulatory responses, the first step wherein the immune response is initiated and adjusted, and a later phase wherein persistent inflammation is resolved or peripherally tolerated [181]. The new perspective opens both exciting opportunities and challenges for future clinical and fundamental research in immunology. Between these challenges is how to develop novel imaging modalities to study these interactions in human tissue samples from patients with autoimmune diseases. The rapidly advancing imaging technologies offer numerous new opportunities to deep-dive into the complex immune regulation in chronic inflammation in situ [182]. The challenge lies to bring this knowledge into immunotherapy. An obvious next step will be using biologics against specific immune cell types. However, innovative strategies will need to be developed to target the network interactions of multiple immune cell types in a tissue-local or even niche-specific context. The latter can be achieved using a combination of key features such as passive cellular traps or scaffolds together with bioactive drugs targeting the immune cell types of interest [183]. An even more exciting challenge will be to catch the cells off-guard in unstimulated tissues, using radiolabeling strategies or genetically encoded effector functions to precisely target the interactions of interest at their moment of activation. Human genetic studies have identified several key immune pathways involved in autoimmunity. Understanding how these pathways impact cell-tissue interactions in the early phases of disease induction is needed to identify new therapeutic target classifications [184].

Infectious Diseases

Sexually transmitted viral infections such as Human Immunodeficiency Virus (HIV) and herpes simplex virus (HSV) infection persist for many years in specific tissues. Preclinical and early clinical observations suggested that high local viral loads were associated with a local aggressive immunity. In addition to direct tissue pathology due to excessive inflammation, aggressive tissue immunity would lead to rapid invasion of the adjacent tissues, which would increasingly cause systemic antiviral immunity [185]. This would then further promote the emergence of quasi-species, death of T cells involved in tissue protection, rupture of sanctuaries, and even increase in viral load [186]. Despite the absence of a cure, the use of antiretroviral drugs has markedly decreased mortality and morbidity. Importantly, the dramatic decrease in peripheral HIV loads did not correlate with similar decreases in HIV loads in the tissues [187, 188]. Current consensus is that long-lived viral reservoirs persist in certain lymphoid tissues and the central nervous system and that the drugs cannot enter these tissues. To prevent these viral reservoirs and the development of AIDS, aggressive local HIV immunity in the genital tract and gut is

required very early after infection before widespread dissemination through the tissues [189].

Animal model development: The pathogenesis and host responses of HIV and SIV are exquisitely studied in the non-human primate model, and several virus host systems have been developed. Based on the first non-human primate virus, the Macaque Simian Immunodeficiency Virus (SIV) model, several immunogenicity and prophylactic vaccine approaches are being pursued to prevent HIV infection [190,191]. However, advances in curative therapies have lagged behind, mostly due to therapy development complexity, late-stage diagnosis, and disinterest of pharmaceutical industries. This epidemic urgently warrants a parallel effort to develop effective HIV tissue antiviral drugs and therapies [192].

Histological Changes in Disease States

To facilitate the discussion of histological changes due to immune responses, recent advances in histological methods that allow high-throughput analysis and mapping of all cells in a sample have to be appreciated [193]. Approaches that allow the simultaneous visualization of up to hundreds of the proteins present in tissue, or 1000s of their transcripts, have recently been developed. These methods employ custom-built microscopes combined with sensitive imaging agents, tolerant image alignment algorithms and machine learning or statistical models [194, 195]. New methods are becoming accessible that allow for intense spatial analysis of data output using the low-cost instruments present in most labs. These new techniques are set to allow important advancements in the field of tissue-resident immune responses. Importantly, these rapidly expanding possibilities change the scale and nature of the analysis of the functioning of the immune response [196]. Instead of looking for larger scale patterns or focusing experimentally on a small number of components, the possibility of using multiple forms of systematic analysis can deliver observations at multiple scales [197]. At the same time, these new analyses will require careful development of theory and data organization formats. Consequently, it is likely that a revolution in the field will take place enabling, for better or worse, detailed visualizations of previously invisible phenomena. Recent key insights into the importance of the spatial arrangement of immune cells and the intention for visible phenomena to be analyzed systematically rather than picked apart piece by piece, are expected to trigger a renaissance in the field of tissue-resident immunity [198]. Key genetic discoveries will provide tools to continuously visualize the same cell over long periods. The comprehensive mapping of all components of tissues, including those approached here from an immune side, will provide powerful insight into the processes and forces behind the development of immune processes and aberrations in health and disease [199].

Altered Cell Populations

Alterations in immune cells and their capacity to signal to other cell types (stromal cells, aberrant mesenchymal cells, and tumor cells) are hallmarks of the cancerimmunoediting process. Accumulating evidence implicates aberrant signaling of oncogenic pathways in tumor cells, as well as of immune cells in the uptake of onco-fetal antigens, remodeling of the stroma/canalicular network, and neovascularization as hallmarks of malignant progression [200]. Modifications in antigen presentation machinery in immune cells and aberrant immunity against a new set of antigens derived from significantly mutated proteins are likely events that lead to immunoediting. Stromal and immune cells are critical components of the tumor microenvironment (TME). These cells can either collaborate with or oppose malignancies. This review focuses on recent studies of three such unusual stromal/immune cells: 1. dormant (quiescent) fibro-adipocytes, 2. Onco-fetal antigen-presenting MHC-IIhighCD74+ tumor macrophages, and 3. Eosinophil-lined aberrant lymphatics [201]. There is accumulating pathology and genetic evidence that alterations in mature myeloid cell functionality can augment malignancy. However, little is known about how additional genetic and social cues acting on non-canonical cell types affect the ability of tissues to house diseases that otherwise would not occur [202].

Tissue Remodeling

Tissue remodeling is a complex process involving interactions between stromal cells and immune cells in tissues. The immune system is usually regarded as separate from tissues, but stroma possesses antigen-presenting cells (APC) capable of initiating immune responses. Interactions between stroma and immune cells are universally regulated, though tissue specificity is crucial due to non-immune cell regulation of tissue-specific immune activities. Stromal cells come in various forms, like fibroblasts, epithelium, lymphatic vessels, and high endothelial venules (HEV), and can be distinguished by molecular, spatial, and structural features. Unique to tissues are specialized fibroblasts, chemokine expressors, and antigen-retaining structures [203].

Immune-specific tissue remodeling occurs in many diseases. Inflammation involves swelling, and growth of blood and lymphatic vessels, which is crucial for leukocyte entry into tissues. Naïve lymphocytes enter tissues through HEVs, where they are activated by tissue-resident APC and undergo clonal expansion and differentiation to effector cells. Antigen-expressing plasma cells leave via afferent lymphatic vessels [204]. Effector T cells return to blood vessels via efferent lymphatics. In chronic uncontrolled inflammation, aggravated by autoimmunity, cancer, or chronic infection, extensive remodeling of lymphatics and blood vessels occurs. The tissue architecture is distorted, and immune cells aberrantly migrate to the resident tissue. The knowledge of tissue remodeling mechanisms after immune responses is limited [205,206].

Solid organs with high cellularity undergo distinct remodeling after the resolution of antigenic stimulation. The secondary lymphoid organ tissue structure remains mostly intact, but immune responses can lead to significant changes in the stroma structure, cellularity, and function. HEV and SCS, both niche structures for T and B cell interaction, are heavily remodeled [207]. T-helping cells have diverse roles, including enhancing the function of amyloid-β (Aβ)-specific monoclonal antibodies through providing T-help in an aged 5xFAD mouse model of Alzheimer's disease. Interaction of CD4+ T cells with APCs induces the expression of ICAM-1 on FDCs with Ipm, which is essential for triggering the catch-bond type interaction between memory BCRs and Ags [208].

Therapeutic Implications

Exactly how to reverse or alter the protective behaviors of the stroma that contribute to therapy resistance remains unclear.

Maintaining active cross-talk between the epithelium and surrounding cells in an evolving process is likely vital for promoting developmental progression and limiting malignant conversion in healthy tissues. The identification of these mechanisms in cancer would provide a more precise understanding of how to target precisely this behavior without detrimentally affecting healthy tissues. Understanding how to design and implement therapeutic interventions targeting these mutually dependent relationships will be critical for the development of effective treatment approaches for more treatment-responsive diseases [209].

Although most cells within solid tumors are thought to be normal, non-cancerous cells, these host cells have vastly different functional capacities. Few of the biological interactions, spatiotemporal functional roles, or therapeutic contributions of the many different populations of stromal cells have yet to be comprehensively studied [210]. It may be that different types of stromal cells exhibit disparate contributions to tumorigenesis at various stages and within distinct niches in the pancreatic TME. Consequently, the channeled efforts to develop stroma-targeted therapies or drugs capable of turning off stromal growth factors require extensive understanding and consideration of the complexity of the TME [211].

Leveraging new tools and insights toward fully characterizing the diverse array of cellular and acellular components of the stroma, as well as the integrated mapping of cellular crosstalk and functional states across spatiotemporal scales, places scientists in a fortuitous position to tackle these important questions [212]. Considering that diverse components of the stroma participate in tumorigenesis at nearly every step in progression and response to therapy, refining and characterizing the underlying sources of this heterogeneity are challenges that beg for thorough consideration and investigation. In addition to its transformative impact on basic understanding, a clearer depiction of stroma heterogeneity may reveal previously unrealized therapeutic strategies and avenues for intervention [213].

Targeting Stromal Cells

The development of stroma-targeting strategies is expected to induce unforeseen effects on immunity, which may create either overt risks or unexplored therapeutic opportunities. The stroma is an important yet often overlooked part of tissue, which together with the parenchyma constructs and maintains its function. The stroma is also a common site of alterations that drive diseases such as cancer and fibrosis. Multiple chronic inflammatory lesions in stroma tend to become indifferent from one another and eventually progress into organlicant tumors. Tumorigenesis models where parenchymal cells expressing oncogenes are engineered are well-studied; however, it remains largely unknown how diverse types of stroma with asymmetric alterations in cellularity and matrix components shape tissue and promote disease progression [214].

To comprehensively understand the function of differentiated stromal components, it is essential to classify ilstrosoma by their developmental origin and layer, and to analyze their role in tissue homeostasis and disease progression. These approaches are expected to reveal hitherto unknown aspects of the dynamic interactions between the parenchyma and stroma, as well as that between non-immune and immune tumor-associated cells. Progress in functional studies has highlighted the significance of non-immune cells in modulating tumor behaviors. Emerging roles of atypical fibroblasts in promoting cancer immunity may also offer opportunities to benefit from tumor targeting. However, for stromal cells to become a valid therapeutic target, a deeper understanding of their tissue-specificity and their complex and sometimes dual roles is still required. Comprehensive characterization and understanding of diverse stromal cells are expected to open up new frontiers in disease-targeted therapy [215].

The immune system plays a critical role in determining the progression and outcomes of various cancers. Various systemically delivered chemotherapeutic agents and immune checkpoint blockade antibodies to enhance immune responses against malignant cells have been actively used therapeutic strategies to counter the neoplastic growth. The tumor microenvironment (TME), composed of malignant cells, immune inflammatory cells, and non-immune stromal constituents, dictates both the efficacy and the resistance mechanisms of these therapies [216]. Deciphering the intricate interactions among their subtypes within the TME is, therefore, of paramount importance to efficiently develop and administer the appropriate therapeutic regimens. Intensive studies have begun to dissect the tumor- and tissue-specific heterogeneity of malignant cells and immune cells. However, despite the recent recognition of the context-dependent dynamics of diverse fibrous, vascular, and adipose tissue-resident non-immune stromal cell types, their dual relationship with immune cells remains elusive [217].

Immune Modulation Strategies

In order to successfully apply immune modulation strategies, including immune checkpoint blockades or new immune-based therapies, specific knowledge on the extracellular matrix (ECM) and mechanisms of recruitment and regulation of immune cells including adaptive, innate and innate-like cells on the immune privileges, in different tissues or organs is essential. These knowledge gaps are especially prominent in tissues developed based on immune disregulation due to tissue-specific stromal-immune crosstalk including but not limited to cancer, chronic infection, metabolic or sterile inflammation, and fibrosis [218, 219].

Both innate and adaptive immune cells have plasticity. Although innate immune cells including innate-like lymphocytes are included in the initial events of immunity, they can have regulatory functions in return. Tissues with chronic immune- or inflammation would be hijacked by them with a regulatory function from a proinflammatory function at initial phase, consequently impacting disease progression [220]. With the sometimes-finding-infiltration of regulatory immune cells in proinflammatory diseases, they paradoxically have a steering function regulating disease progression and therefore require additional monitoring strategies according to the progressions [221]. Similar immune plasticity, paradigm shifting immune treatment from depletion or antagonization to reprograming immune cells would be necessary to resolve the questions of immune unavailable and poorly efficacious, or adverse effects including but not limited to invasion or enhanced metastasis of novel immune treatments. Therefore, strategies on systemic or tissue-targeting administration with temporal monitoring of the spatio-temporal dynamics of recruited immune cells are highly interesting for the resolution of aforementioned questions [222].

Future Directions in Research

Currently available gene expression datasets enable large-scale studies of different aspects of organ immunity or cancer types to unveil broader trends in stromal-immune cell interactions. Such datasets can also be mined to study new histological specimens. Recent computational approaches harnessing the power of gene expression data to uncover luminal molecular subtypes offer one such application [223]. For tissues with previously studied immunity, multiplexed imaging techniques could be employed to study the relationship of stromal-immune cell interactions with the cellular and molecular context of the tissue. For example, intravital TCR sequencing in developing embryonic organs or using a barrier-healing model [224]. Defining developmental and barrier disruption contexts that rely on organized patterns of immune cell recruitment is an underexplored area that will complement the studies of other multicellular organisms that evolve monodirectional immune sweeps, such as flies [225].

How stroma-derived secreted proteins shape and regulate organ immunogenicity across multiple contexts is an important but challenging aspect to study. Insights into the roles of secreted components from the stroma could arise from overexpressing, knocking down, or modifying known signaling proteins in specific tissues or organoid models and combining this with multiplexed imaging and uncontrolled immunetic challenges [226]. In addition, employing chemical libraries or mutation datasets designed to probe the biochemical features of protein secretability could yield large insights into how complex stroma-derived signals from diseased tissues and organs shape immunity. It will also be important to devise models to study the composition and potential cooption of such signals within a mutant cell/disease foreground at later stages in multi-cellular organisms [227, 228].

Generating models to query specific aspects of stromal immunity both in isolation and with immune cells will also be a key aspect of future directions. Perhaps one further investigative direction on the possible function of “immune cells-stroma” synapse mimicking structures in organizing patterns of communication will link well understood aspects of these actor classes in other immune contexts to their roles in tissue homeostasis/disease [229]. Most of these areas are complex and challenging, yet the rewards will be gigantic in understanding how tissue specific immunity is built and coopted during disease progression [230,231].

Emerging Technologies

Technological advances in imaging, manipulation, and analysis have opened new experimental avenues for studying the interactions of immune and stromal cells within the tissue microenvironment, with potential for enhanced understanding of the dynamic dialogue governing tissue-specific immunity [232]. Polyparametric flow cytometry enables the high-dimensional profiling of innate and adaptive immune cell populations within tissues, revealing their phenotypes and functional states. Multiplexed tissue imaging provides high-quality investigation of immune populations using histopathological assays, as well as newly developed imaging modalities. Combining these imaging capabilities with algorithms to detect, segment, and classify tissue-resident immune populations and quantifying their interactions and spatial organization has revealed knowledge about immune cells localizing to tissues [233]. Emerging adaptive manipulators allow the live-cell mechanistic analysis of interactions among multiple populations using opto, acousto, and electro-mechanical tools. Together these technologies permit quantitative imaging and manipulation of immune cells in tissues while maintaining tissue integrity and architecture over long time-scales, opening new avenues for studying the interactions of multiple immune populations which will combine depth of characterization with spatio-temporal quantitative information [234].

One advantage of the described methodologies is their flexibility, enabling the addition of imaging, analysis, manipulation, or readout modalities to target questions across diverse tissue types or cell populations [235]. Heterogeneous populations distributed throughout complex 3D tissue can be easily studied to assess how altered immune ontology or interactions affect tissue function and pathology. The choice of modality can be adapted to best answer questions of interest, from high-throughput interrogations of population state and organization, to mechanistic analysis of biophysical interactions, to quantifying effector function [236]. All modes can be easily automated to enable massive data collection efforts, increasing the scale at which knowledge can be gained [237]. Ongoing experimental and analysis developments will significantly enhance the capabilities and utility of these methodologies, paving the way towards a quantitative systems-level understanding of immune-stromal interactions in both health and disease. Ultimately, the hope is to define how the immune ontology of cells residing or trafficking within tissues shapes local tissue immunity, impacting disease severity and progression [238].

Clinical Applications

The main challenge in translational research is the reliable determination of clinically relevant targets. Generally, immunotherapy targets are investigated using animal models of disease. However, models of inflammatory diseases often take several weeks to months to develop. For this reason, syngeneic tumor models are widely used for the evaluation of immunotherapy targets and strategies. Usually, cancer in a mouse model is modeled by injecting mouse tumor cell lines into the ear, footpads, or previously manipulated tissues [239]. Tumors grow within several days. By contrast, the acquisition of solid adult tissue explants and the preservation of cellular composition and spatiotemporal localization are difficult due to the tissue processing and culturing protocols. Reconstructing pathologic tissue-immune architecture from a small biopsy is clinically and experimentally significant as well. To mimic the tumor microenvironment ex vivo, healthy tissues before tumor development, tissues from individuals excluded from clinical studies, or tumors excised before medical treatments can be obtained. Introduced a method for the production of a histological tissue-immune architecture from FFPE or frozen tissue [240, 241].

Concerning tissue types, cancers comprise breast, prostate, colorectal, liver, lung, and stomach cancers. Non-cancerous tissues comprise skin, heart, vessels, visceral fat, and brain-collagen. Since tissue shapes can be adjusted to develop new organism structures, various directions of growth can be obtained [242]. Growth factors can also be easily added to media to affect organogenesis. Moreover, organismal changes,

including shrinking and disintegration or shedding, can be simulated by manipulating a perfusion fluid with hyaluronidase or force < 20 mmHg, respectively. Direct mass multiplication of tissues is also possible [243]. Current research is focused on the impact of stroma-immune interactions in the treatment and progression of cancers such as colorectal, breast, and prostate cancers or diseases such as rheumatoid arthritis and diabetes with histological perspectives [244].

Case Studies

Tumor-associated fibroblasts (TAFs) are often thought of as a histological curiosity—an unusual population of cells that segregate near blood vessels in the stroma as a characteristic of many human tumors. Tumor stroma is one of the original cancer hallmarks proposed more than a decade ago and has expanded to include then recognized causal connections between cancer-associated fibroblasts and excessive collagen deposition and rigidity and, more recently, chemotherapeutic responses and immune evasion [245]. While compelling and pivotal discoveries have been made connecting TAF with specific cancer hallmarks, there remains clear need for additional insights focused on the broader involvement of stroma in non-malignant, pre-malignant, and advanced tumors. Application of contemporary analytical techniques combined with a broader perspective on the role of stroma in solid tumors will provide important details needed for many aspects of a more complete understanding of the tumor microenvironment (TME) [246].

Non-immune stromal cell types have important implications for tumor progression and therapeutic efficacy. The physical architecture of the stroma, especially the amount and composition of the extracellular matrix (ECM), is a hallmark of many solid tumors [247]. The stroma in normal tissues is physically organized and restricts cancer cell invasion. Tumors gain hypoxia, cell crowding, and aberrant growth, which mediate injury signals that remodel the ECM and promote chemo-resistance. Overall, the late-reforming stroma guides the plasticity of tumor cells from an invasive toward another growth state, ultimately giving rise to multiple, quiescent, and resistant tumors. There are many implications for future studies focusing on ECM and non-immune cell interactions over a range of tumors. The opportunity to use or to discover inhibitors that interrupt the remodeling process will be exciting to pursue both for basic biological and for therapeutic purposes [248].

Breast Cancer

Breast cancer is the most frequently diagnosed malignant tumor of women in North America, affecting more than 192,000 annually [249]. Standard treatment modalities for breast cancer include surgical intervention and radiation therapy for localized disease and systemic chemotherapy, receptor targeting, and immunotherapy for advanced disease. Improvements in treatment options have resulted in a substantial reduction in breast cancer-associated mortality; nevertheless, these advances have plateaued and 40% of women diagnosed with breast cancer still succumb to disease [250]. Thus, there is an urgent need for new therapeutic approaches targeting the factors that influence disease pathogenesis and progression [251]. The majority of breast cancers are believed to arise from genetic and epigenetic changes in genes involved in the regulation of proliferation and differentiation. New blood or lymphatic vessels are formed in tissue through the closely regulated, sequential interactions of a variety of proangiogenic factors with their receptors [252]. Evidence supports the hypothesis that the initial disease-promoting alterations in stroma cell responses occur prior to the development of mammary neoplasia and may promote progression to malignancy. The differentiation of CSCs to tumor cells triggers a cascade of stromal cell responses leading to a supportive tumor microenvironment [253]. The tumor stroma is composed of a number of cell types including (myo)fibroblasts, vascular cells, infiltrating leukocytes, and specialized mesenchymal support cells. Tumor-infiltrating leukocytes (TILs) are the most frequent immune cells infiltrating solid cancer and have been implicated as causal players in the development of breast, prostate, pancreatic, and colorectal cancer [254]. Careful study of breast cancer histology has led to the discovery of an unexpected diversity in the cellular composition, molecular architecture, spatial distribution, and cell-cell interactions within tumor microenvironments and their relationships to patient prognosis. Among these, a prominent role for TILs in breast cancer biology has emerged, and accumulation of specific subsets has been correlated with markedly improved prognosis [255, 256]. However, it is becoming clear that unambiguously defining the roles of immune cells in the regulation of tumor progression is a daunting task. This focuses on the roles of innate and adaptive leukocytes as regulators of breast carcinogenesis and describes experimental data indicating potentially large therapeutic advantages of targeting these immune cell types in patients with breast cancer [257].

Chronic Inflammation

Chronic inflammation underlies many diseases in human medicine, such as rheumatoid arthritis, atherosclerosis, severe asthma, inflammatory bowel disease, or chronic skin inflammatory diseases. Cancer is a complication of chronic inflammation, which induces changes in the stroma leading ultimately to tumor progression. Chronic inflammation occurs when tissue-resident cells fail to resolve the immune response due to continuous exposure to a pathogen or aggravating factor. Chronic inflammatory disease progression is characterized by an accumulation of new immune effector cells recruited indirectly by altered stromal cells [258]. These chronic recruitment and activation mechanisms can feed back the process and recruit new classes of immune effectors. Alterations in the stroma also lead past a certain time point to the acquisition of cancer hallmarks, providing further aggravation loops. In this section cellular mechanisms underlying those events are discussed. Inflammation involves the complex interaction between infiltrating cells and tissue-resident cells. These non-hematopoietic stromal cells (SCs) are now known to orchestrate the immune response by controlling leukocyte recruitment and organization within the tissue [259,260].

In healthy sites, the stroma provides an important structural component for tissues and emits factors like CCL21 and CCL19 to promote the formation of secondary lymphoid organs such as lymph nodes. Those molecules also generate gradients for the attraction of naïve HEVs and leukocytes on new nodes. Under pathogen threat, tissue-resident fibroblasts and SCs rapidly produce a panel of chemokines and adhesion molecules. Those SC-derived factors recruit blood-derived leukocytes while providing organization for the newly inflamed tissue [261]. After pathogen clearance, the inflammation resolves, and the stroma

returns to a homeostatic state. However, in chronic inflammation, the stroma acquires novel features critical for the development of the pathological process [262]. First, inflammation persists as chronic tissue-resident SCs continue to secrete factors that indirectly but accurately recruit blood-derived leukocytes. Second, the SCs develop an activated phenotype and secrete factors that directly activate monocyte-derived cells. These new interactions feedback the process and recruit new classes of blood-derived effector cells [263].

Ethical Considerations in Immunological Research

The immune system is complex with diverse capabilities, and as such, different aspects are being studied to identify paths for a better understanding of immune system processes and more effective therapies against immune system-associated diseases. Historically, immunology was the forte of very few investigators as it required technical capabilities and equipment that were not present in most laboratories. However, with technological leaps and improvements, it is now possible to investigate immune system-related processes and pathways in schools and laboratories that do not specialize in the field [264]. Bretscher relates how difficult it was for him to get the attention of investigators to look at how the immune system can recognize ID markers of other species/objects and that this mechanism is central to activation, regulation and tolerance of the acquired immune response in protective and pathological situations. For those investigators, different questions were relevant and the current state of confusion in the field was not anticipated [265]. The focus of his research with Schloen has been to provide definitions of such ID tags and molecular descriptions of the molecular basis of recognition, something that usually takes much of the attention of a new graduate student. Bretscher points out that once the begging questions to pursue are identified, it is not often an issue to find suitable laboratories and advisors in what is happening in the discipline [266]. On the contrary, there are guards for the discipline and safety of students in many areas of focus not often encountered in life sciences. The isolation that can still happen in schools in far parts of the world can be problematic; how to be integrated in the global research environment in life sciences and still be capable of rational consideration of observations must be better considered and action taken [267, 268].

Estes et al. highlight that as the field of viral persistence matures, new areas of research into HIV/SIV infections are becoming more prominent. In an effort to disentangle some of the complexities of the virology, immunology, and molecular biology of these systems, researchers are asked to consider what tools are needed to effectively visualize the immune system [269]. On the subject of humanized mice in modeling human HIV infection, developing imaging reagents that can capitalize on recent improvements in two-photon video microscopy is essential [270].

Conclusion

Tissue-resident stromal cells modulate the behavior of immune cells and in turn are also functionally modulated in immune responses. The historical view of immunology of the immune response focused on hematopoietic immune cells. Over the years it became evident that by producing cytokines and chemokines tissue-resident stromal cells essentially shape the immune response outcomes. On the contrary, they have been regarded as relatively inert cells mechanistically modified by immune cell interactions. However, tissue-resident stromal cells can also be actively modulated through immune modulatory signals produced by infiltrating immune cells during acute and chronic inflammation. This bidirectional interaction has been highlighted in many tissues and organs containing diverse types of stromal cells including fibroblasts, antigen presenting cells, pericytes, and endothelial cells. Nevertheless, in particular tissues, the action of specific immune-modulatory signals on one side and on specific types of stromal cells on the other side has remained largely unexplored. The recent advent of single-cell genomics technologies and sophisticated tools for single-cell manipulation have substantially extended our understanding of cellular interactions in health and diseases including the analysis of stroma-immune cell interactions at unprecedented resolution. Perhaps the best studied tissue in this regard is the lymphoid system, where critical and often complex cellular interactions have been dissected in detail. However, many of the lymphoid tissues share similarities in terms of cell types, differentiation states, and functional roles and hence findings in these tissues cannot always be simply translated to other non-lymphoid sites. During immune responses, besides recruiting and activating circulating immune cells, tissue-resident stromal cells profoundly re-organize at diverse levels and coordinate the immune responses taking place. Depending on the properties of the invading pathogens, the immune responses in terms of magnitude and qualitative, can be quite different, and consequently, the modifications of stromal cells might differ substantially and become more tissue-specific. Stromal cell-immune cell interactions are likely to also change substantially during tumorigenesis and tumor progression, and additional histological analysis of virtually all solid tumors with respect to the presence and cellular interactions of the relevant immune and stromal cell types is likely to provide new insights into novel therapeutical strategies.

Disclosure Statement

- **Ethics approval and consent to participate:** The authors declare to their adherence to publication ethics and their approval of the publication of their work.
- **Consent for publication:** The publication of the article is approved by the authors.
- **Availability of data:** The information is available for request.
- **Author's Contribution:** The authors attest to the following contributions they made to the review: Ahmed Mustafa and Hadeel Kamil contributed to the ideation of the study and writing of the manuscript. The general concept of the research, text editing, and proofreading were all done by Taisir Khaleel and Azhar Hussein. Every author looked over and gave their approval to the final work.
- **Declaration of Competing Interest:** The authors say they don't have any known personal or financial relationships or financial interests that could have seemed to affect the work in this study.
- **Funding:** There is no funding.
- **Acknowledgments:** The authors would like to express their gratitude to Department of Basic Science, College of Dentistry, Al-Iraqia University for facilitate the work. Additionally, they express their gratitude to the An-Najah

University Journal for Research - A Natural Sciences, (www.najah.edu) for their insightful feedback that improved the review's quality.

References

1]. Mun JY, Leem SH, Lee JH, Kim HS. Dual relationship between stromal cells and immune cells in the tumor microenvironment. Frontiers in immunology. 2022 Apr 6;13:864739.

2]. Barone F, Nayar S, Buckley CD. The role of non-hematopoietic stromal cells in the persistence of inflammation. Frontiers in immunology. 2013 Jan 14;3:416.

3]. Poholek AC. Tissue-specific contributions to control of T cell immunity. Immunohorizons. 2021 Jun 1;5(6):410-23.

4]. Weisberg SP, Ural BB, Farber DL. Tissue-specific immunity for a changing world. Cell. 2021 Mar 18;184(6):1517-29.

5]. Mass E, Nimmerjahn F, Kierdorf K, Schlitzer A. Tissue-specific macrophages: how they develop and choreograph tissue biology. Nature Reviews Immunology. 2023 Sep;23(9):563-79.

6]. Mun JY, Leem SH, Lee JH, Kim HS. Dual relationship between stromal cells and immune cells in the tumor microenvironment. Frontiers in immunology. 2022 Apr 6;13:864739.

7]. Wu B, Shi X, Jiang M, Liu H. Cross-talk between cancer stem cells and immune cells: potential therapeutic targets in the tumor immune microenvironment. Molecular Cancer. 2023 Feb 21;22(1):38.

8]. Xu M, Zhang T, Xia R, Wei Y, Wei X. Targeting the tumor stroma for cancer therapy. Molecular Cancer. 2022 Nov 2;21(1):208.

9]. Ni Y, Zhou X, Yang J, Shi H, Li H, Zhao X, Ma X. The role of tumor-stroma interactions in drug resistance within tumor microenvironment. Frontiers in cell and developmental biology. 2021 May 20;9:637675.

10]. Fletcher AL, Malhotra D, Acton SE, Lukacs-Kornek V, Bellemare-Pelletier A, Curry M, Armant M, Turley SJ. Reproducible isolation of lymph node stromal cells reveals site-dependent differences in fibroblastic reticular cells. Frontiers in immunology. 2011 Sep 12;2:35.

11]. Estes JD, LeGrand R, Petrovas C. Visualizing the immune system: providing key insights into HIV/SIV infections. Frontiers in immunology. 2018 Mar 2;9:423.

12]. Lasek W. Cancer immunoediting hypothesis: History, clinical implications and controversies. Central European Journal of Immunology. 2022 Apr 1;47(2):168-74.

13]. Mann DL. The emerging field of cardioimmunology: past, present and foreseeable future. Circulation research. 2024 Jun 7;134(12):1663-80.

14]. Haage V, De Jager PL. Neuroimmune contributions to Alzheimer's disease: a focus on human data. Molecular Psychiatry. 2022 Aug;27(8):3164-81.

15]. Rowley AF, Coates CJ, Whitten MM, editors. Invertebrate pathology. Oxford University Press; 2022 Feb 8.

16]. Auerbach A, Schmieg JJ, Klassen M, Nelson A, Aguilera NS. HIV, measles, and syphilis: histopathologic characteristics of lymphatic system involvement of three reemerging infectious diseases. Histopathology. 2024 Dec 27.

17]. Böhmig GA, Halloran PF, Feucht HE. On a long and winding road: alloantibodies in organ transplantation. Transplantation. 2023 May 1;107(5):1027-41.

18]. Hosseini I, Gadkar K, Stefanich E, Li CC, Sun LL, Chu YW, Ramanujan S. Mitigating the risk of cytokine release syndrome in a Phase I trial of CD20/CD3 bispecific antibody mosunetuzumab in NHL: impact of translational system modeling. NPJ systems biology and applications. 2020 Aug 28;6(1):28.

19]. Thome JJ, Grinshpun B, Kumar BV, Kubota M, Ohmura Y, Lerner H, Sempowski GD, Shen Y, Farber DL. Long-term maintenance of human naïve T cells through in situ homeostasis in lymphoid tissue sites. Science immunology. 2016 Dec 2;1(6):eaah6506.

20]. Madej JP, Bednarczyk M. Effect of in ovo-delivered prebiotics and synbiotics on the morphology and specific immune cell composition in the gut-associated lymphoid tissue. Poultry science. 2016 Jan 1;95(1):19-29.

21]. Goverse G, Labao-Almeida C, Ferreira M, Molenaar R, Wahlen S, Konijn T, Koning J, Veiga-Fernandes H, Mebius RE. Vitamin A controls the presence of RORγ+ innate lymphoid cells and lymphoid tissue in the small intestine. The Journal of Immunology. 2016 Jun 15;196(12):5148-55.

22]. Velu V, Mylvaganam GH, Gangadhara S, Hong JJ, Iyer SS, Gumber S, Ibegbu CC, Villinger F, Amara RR. Induction of Th1-biased T follicular helper (Tfh) cells in lymphoid tissues during chronic simian immunodeficiency virus infection defines functionally distinct germinal center Tfh cells. The Journal of Immunology. 2016 Sep 1;197(5):1832-42.

23]. Yenyuwadee S, Aliazis K, Wang Q, Christofides A, Shah R, Patsoukis N, Boussiotis VA. Immune cellular components and signaling pathways in the tumor microenvironment. InSeminars in cancer biology 2022 Nov 1 (Vol. 86, pp. 187-201). Academic Press.

24]. Hamad AA, Mustafa HM, Mohsein OA. Detection of the levels of immune cytokines (IL4, IL5, TNF-α) in school-age and preschoolers with an Ascaris lumbricoides infection. Journal of Parasitic Diseases. 2024 Dec;48(4):782-7.

25]. Wu Y, Niu D, Deng S, Lei X, Xie Z, Yang X. Tumor-derived or non-tumor-derived exosomal noncodingRNAs and signaling pathways in tumor microenvironment. International Immunopharmacology. 2022 May 1;106:108626.

26]. Li Z, Zhang X, Liu C, Ma J. Non-immune cell components in the gastrointestinal tumor microenvironment influencing tumor immunotherapy. Frontiers in Cell and Developmental Biology. 2021 Oct 13;9:729941.

27]. Kim SJ, Khadka D, Seo JH. Interplay between solid tumors and tumor microenvironment. Frontiers in Immunology. 2022 May 30;13:882718.

28]. Lateef D, Nasser N, Mohsein O. The relationships between Aplein, Vaspin and thyroid hormone levels in obese diabetic and non-diabetic women. Journal of Experimental and Clinical Medicine. 2024;41(2):239-45.

29]. Mao X, Xu J, Wang W, Liang C, Hua J, Liu J, Zhang B, Meng Q, Yu X, Shi S. Crosstalk between cancer-associated fibroblasts and immune cells in the tumor microenvironment:

new findings and future perspectives. Molecular cancer. 2021 Dec;20:1-30.

30]. Faisal AN, Abbas AM, Mohsein OA. Histological and Cytokine-Based Biomarkers in the Early Diagnosis of Cancer: Biomarker Berbasis Histologi dan Sitokin dalam Diagnosis Dini Kanker. Indonesian Journal on Health Science and Medicine. 2025 Feb 13;2(2):10-21070.

31]. Zhou C, Liu Q, Xiang Y, Gou X, Li W. Role of the tumor immune microenvironment in tumor immunotherapy. Oncology Letters. 2022 Feb;23(2):53.

32]. Gao S, Hsu TW, Li MO. Immunity beyond cancer cells: perspective from tumor tissue. Trends in cancer. 2021 Nov 1;7(11):1010-9.

33]. Fu T, Dai LJ, Wu SY, Xiao Y, Ma D, Jiang YZ, Shao ZM. Spatial architecture of the immune microenvironment orchestrates tumor immunity and therapeutic response. Journal of hematology & oncology. 2021 Jun 25;14(1):98.

34]. Hao X, Sun G, Zhang Y, Kong X, Rong D, Song J, Tang W, Wang X. Targeting immune cells in the tumor microenvironment of HCC: new opportunities and challenges. Frontiers in cell and developmental biology. 2021 Nov 12;9:775462.

35]. Giacomini C, Granéli C, Hicks R, Dazzi F. The critical role of apoptosis in mesenchymal stromal cell therapeutics and implications in homeostasis and normal tissue repair. Cellular & Molecular Immunology. 2023 Jun;20(6):570-82.

36]. Mannino G, Russo C, Maugeri G, Musumeci G, Vicario N, Tibullo D, Giuffrida R, Parenti R, Lo Furno D. Adult stem cell niches for tissue homeostasis. Journal of Cellular Physiology. 2022 Jan;237(1):239-57.

37]. Manetti M. Molecular morphology and function of stromal cells. International Journal of Molecular Sciences. 2021 Dec 14;22(24):13422.

38]. Pasztoi M, Ohnmacht C. Tissue niches formed by intestinal mesenchymal stromal cells in mucosal homeostasis and immunity. International Journal of Molecular Sciences. 2022 May 6;23(9):5181.

39]. Honan AM, Chen Z. Stromal cells underlining the paths from autoimmunity, inflammation to cancer with roles beyond structural and nutritional support. Frontiers in cell and developmental biology. 2021 May 25;9:658984.

40]. Soliman H, Theret M, Scott W, Hill L, Underhill TM, Hinz B, Rossi FM. Multipotent stromal cells: One name, multiple identities. Cell stem cell. 2021 Oct 7;28(10):1690-707.

41]. Ali Q, Ma S, La S, Guo Z, Liu B, Gao Z, Farooq U, Wang Z, Zhu X, Cui Y, Li D. Microbial short-chain fatty acids: a bridge between dietary fibers and poultry gut health—a review. Animal bioscience. 2022 Apr 30;35(10):1461.

42]. Wang L, Xu J, Xue P, Liu J, Luo L, Zhuge D, Yao Q, Li X, Zhao Y, Xu H. Thermo-sensitive hydrogel with mussel-inspired adhesion enhanced the non-fibrotic repair effect of EGF on colonic mucosa barrier of TNBS-induced ulcerative colitis rats through macrophage polarizing. Chemical Engineering Journal. 2021 Jul 15;416:129221.

43]. Nabeta H. Q-Griffithsin interactions and utility for the prevention and treatment of Mucosal infections. 2021. 12: 3766. https://doi.org/10.18297/etd/3766

44]. Chimbayo ET. Investigating the effect of HIV infection on TCR repertoire diversity and Mycobacterium tuberculosis-specific T cell function in Malawian adults (Doctoral dissertation, University of Glasgow).

45]. Maccioni L, Fu Y, Horsmans Y, Leclercq I, Stärkel P, Kunos G, Gao B. Alcohol-associated bowel disease: new insights into pathogenesis. Egastroenterology. 2023 Aug 18;1(1).

46]. Wong ZY, Nee E, Coles M, Buckley CD. Why does understanding the biology of fibroblasts in immunity really matter?. Plos Biology. 2023 Feb 6;21(2):e3001954.

47]. Mustafa HM, Hamad AA, Mohsein OA. Investigating specific calprotectin and immunological markers associated with intestinal infections caused by Entamoeba histolytica. Iranian Journal of Veterinary Medicine. 2024 Oct 1;18(4):535-44.

48]. Smilde BJ, Botman E, de Vries TJ, de Vries R, Micha D, Schoenmaker T, Janssen JJ, Eekhoff EM. A Systematic Review of the Evidence of Hematopoietic Stem Cell Differentiation to Fibroblasts. Biomedicines. 2022 Nov 28;10(12):3063.

49]. Higaki K, Aiba S, Shimoyama T, Omatsu Y, Nagasawa T. Universal fibroblasts across tissues can differentiate into niche cells for hematopoietic stem cells. Cell Reports. 2025 May 27;44(5).

50]. Sbierski-Kind J, Mroz N, Molofsky AB. Perivascular stromal cells: directors of tissue immune niches. Immunological Reviews. 2021 Jul;302(1):10-31.

51]. Okeke C, Silas U, Okeke C, Chikwendu C. Current trends on hemopoietic stem cells. Current Stem Cell Research & Therapy. 2021 Feb 1;16(2):199-208.

52]. Omatsu Y, Nagasawa T. Identification of microenvironmental niches for hematopoietic stem cells and lymphoid progenitors—bone marrow fibroblastic reticular cells with salient features. International Immunology. 2021 Dec 1;33(12):821-6.

53]. Lendahl U, Muhl L, Betsholtz C. Identification, discrimination and heterogeneity of fibroblasts. Nature communications. 2022 Jun 14;13(1):3409.

54]. Deng CC, Hu YF, Zhu DH, Cheng Q, Gu JJ, Feng QL, Zhang LX, Xu YP, Wang D, Rong Z, Yang B. Single-cell RNA-seq reveals fibroblast heterogeneity and increased mesenchymal fibroblasts in human fibrotic skin diseases. Nature communications. 2021 Jun 17;12(1):3709.

55]. Buechler MB, Pradhan RN, Krishnamurty AT, Cox C, Calviello AK, Wang AW, Yang YA, Tam L, Caothien R, Roose-Girma M, Modrusan Z. Cross-tissue organization of the fibroblast lineage. Nature. 2021 May 27;593(7860):575-9.

56]. Mohammad S, Mohsen A, Jalil I. Assessing the prevalence of bacterial vaginosis among infertile women in Thi-Qar Province, Iraq. Infection Epidemiology and Microbiology. 2024 Dec 10;10(4):0-.

57]. Amersfoort J, Eelen G, Carmeliet P. Immunomodulation by endothelial cells—partnering up with the immune system?. Nature Reviews Immunology. 2022 Sep;22(9):576-88.

58]. Zhao Y, Shen M, Wu L, Yang H, Yao Y, Yang Q, Du J, Liu L, Li Y, Bai Y. Stromal cells in the tumor microenvironment: accomplices of tumor progression?. Cell death & disease. 2023 Sep 4;14(9):587.

59]. Elmusrati A, Wang J, Wang CY. Tumor microenvironment and immune evasion in head and neck squamous cell carcinoma. International journal of oral science. 2021 Dec;13(1):24.

60]. Qureshi HA, Zhu X, Yang GH, Steadele M, Pierce RH, Futran ND, Lee SM, Méndez E, Houghton AM. Impact of HPV status on immune responses in head and neck squamous cell carcinoma. Oral Oncology. 2022 Apr 1;127:105774.

61]. Hilo ZQ, Mahmood A, Mohsein OA. Genomic Insights into Staphylococcus aureus: Mechanisms of Antibiotic Resistance and Virulence Gene Expression. European Journal of Ecology, Biology and Agriculture. 2024 Nov 1;1(5):29-48.

62]. Apollonio B, Ioannou N, Papazoglou D, Ramsay AG. Understanding the immune-stroma microenvironment in B cell malignancies for effective immunotherapy. Frontiers in oncology. 2021 Mar 25;11:626818.

63]. Roy P, Orecchioni M, Ley K. How the immune system shapes atherosclerosis: roles of innate and adaptive immunity. Nature Reviews Immunology. 2022 Apr;22(4):251-65.

64]. Fang J, Lu Y, Zheng J, Jiang X, Shen H, Shang X, Lu Y, Fu P. Exploring the crosstalk between endothelial cells, immune cells, and immune checkpoints in the tumor microenvironment: new insights and therapeutic implications. Cell death & disease. 2023 Sep 4;14(9):586.

65]. Tobal R, Potjewijd J, Empel VP, Ysermans R, Schurgers LJ, Reutelingsperger CP, Damoiseaux JG, Paassen PV. Vascular remodeling in pulmonary arterial hypertension: the potential involvement of innate and adaptive immunity. Frontiers in medicine. 2021 Dec 22;8:806899.

66]. Geindreau M, Ghiringhelli F, Bruchard M. Vascular endothelial growth factor, a key modulator of the anti-tumor immune response. International Journal of Molecular Sciences. 2021 May 4;22(9):4871.

67]. Deets KA, Vance RE. Inflammasomes and adaptive immune responses. Nature immunology. 2021 Apr;22(4):412-22.

68]. Weng J, Couture C, Girard S. Innate and adaptive immune systems in physiological and pathological pregnancy. Biology. 2023 Mar 3;12(3):402.

69]. Wang J, He M, Yang M, Ai X. Gut microbiota as a key regulator of intestinal mucosal immunity. Life Sciences. 2024 Apr 6:122612.

70]. Makki K, Froguel P, Wolowczuk I. Adipose tissue in obesity-related inflammation and insulin resistance: cells, cytokines, and chemokines. International Scholarly Research Notices. 2013;2013(1):139239.

71]. Mustafa HM, Hamad AA, Mohsein OA. Entamoeba histolytica and Giardia lamblia predominance in Iraq's southern governorates. International Journal of Environmental Health Engineering. 2024 Apr 1;13(1):10.

72]. Trim WV, Lynch L. Immune and non-immune functions of adipose tissue leukocytes. Nature Reviews Immunology. 2022 Jun;22(6):371-86.

73]. Gray JI, Farber DL. Tissue-resident immune cells in humans. Annual review of immunology. 2022 Apr 26;40(1):195-220.

74]. Corvera S. Cellular heterogeneity in adipose tissues. Annual review of physiology. 2021 Feb 10;83(1):257-78.

75]. Michailidou Z, Gomez-Salazar M, Alexaki VI. Innate immune cells in the adipose tissue in health and metabolic disease. Journal of innate immunity. 2022 Jan 3;14(1):4-30.

76]. Ismail MA, Faisal AN, Hadi QN, Mohsein OA. Exploring the Genetic Variability of Escherichia coli Pathotypes in Urinary Tract Infections: Implications for Diagnostics and Treatment. Cent Asian J Med Nat Sci. 2024;6(1):179-91.

77]. Davidson S, Coles M, Thomas T, Kollias G, Ludewig B, Turley S, Brenner M, Buckley CD. Fibroblasts as immune regulators in infection, inflammation and cancer. Nature Reviews Immunology. 2021 Nov;21(11):704-17.

78]. Venugopal H, Hanna A, Humeres C, Frangogiannis NG. Properties and functions of fibroblasts and myofibroblasts in myocardial infarction. Cells. 2022 Apr 20;11(9):1386.

79]. Schuster R, Rockel JS, Kapoor M, Hinz B. The inflammatory speech of fibroblasts. Immunological reviews. 2021 Jul;302(1):126-46.

80]. Younesi FS, Miller AE, Barker TH, Rossi FM, Hinz B. Fibroblast and myofibroblast activation in normal tissue repair and fibrosis. Nature Reviews Molecular Cell Biology. 2024 Aug;25(8):617-38.

81]. Chalkidi N, Paraskeva C, Koliaraki V. Fibroblasts in intestinal homeostasis, damage, and repair. Frontiers in Immunology. 2022 Aug 10;13:924866.

82]. Cavagnero KJ, Gallo RL. Essential immune functions of fibroblasts in innate host defense. Frontiers in Immunology. 2022 Dec 15;13:1058862.

83]. Almohaisen FL, Hadi AM, Kadhim SJ, Mohsein OA. Cytokines' Impact on Postpartum Hair Loss After First C-Section in Women 28-38: Dampak Sitokin terhadap Kerontokan Rambut Pasca Persalinan Setelah Operasi Caesar Pertama pada Wanita 28-38. Indonesian Journal on Health Science and Medicine. 2025 Mar 24;2(1):10-21070.

84]. Shimpi AA, Fischbach C. Engineered ECM models: Opportunities to advance understanding of tumor heterogeneity. Current opinion in cell biology. 2021 Oct 1;72:1-9.

85]. Tan K, Naylor MJ. Tumour microenvironment-immune cell interactions influencing breast cancer heterogeneity and disease progression. Frontiers in Oncology. 2022 May 13;12:876451.

86]. De Visser KE, Joyce JA. The evolving tumor microenvironment: From cancer initiation to metastatic outgrowth. Cancer cell. 2023 Mar 13;41(3):374-403.

87]. Kolesnikoff N, Chen CH, Samuel MS. Interrelationships between the extracellular matrix and the immune microenvironment that govern epithelial tumour progression. Clinical Science. 2022 Mar;136(5):361-77.

88]. Sutherland TE, Dyer DP, Allen JE. The extracellular matrix and the immune system: A mutually dependent relationship. Science. 2023 Feb 17;379(6633):eabp8964.

89]. Vitale I, Shema E, Loi S, Galluzzi L. Intratumoral heterogeneity in cancer progression and response to immunotherapy. Nature medicine. 2021 Feb;27(2):212-24.

90]. Abbas ZK, Hilo ZQ, Hussein WS, Mohsein OA. Immunological biomarkers and their role in the diagnosis and prognosis of leishmaniasis: A case–control study. Tropical Parasitology. 2025 Jan 1;15(1):33-41.

91]. Lerman I, Mitchell DC, Richardson CT. Human cutaneous B cells: what do we really know?. Annals of Translational Medicine. 2021 Mar;9(5):440.

92]. Suchanek O, Clatworthy MR. Homeostatic role of B-1 cells in tissue immunity. Frontiers in Immunology. 2023 Sep 8;14:1106294.

93]. Posner DA, Lee CY, Portet A, Clatworthy MR. Humoral immunity at the brain borders in homeostasis. Current Opinion in Immunology. 2022 Jun 1;76:102188.

94]. Yu Y, Lu C, Yu W, Lei Y, Sun S, Liu P, Bai F, Chen Y, Chen J. B cells dynamic in aging and the implications of nutritional regulation. Nutrients. 2024 Feb 8;16(4):487.

95]. Ribeiro F, Perucha E, Graca L. T follicular cells: The regulators of germinal center homeostasis. Immunology Letters. 2022 Apr 1;244:1-1.

96]. Cancro MP, Tomayko MM. Memory B cells and plasma cells: The differentiative continuum of humoral immunity. Immunological reviews. 2021 Sep;303(1):72-82.

97]. MacFawn IP, Bruno TC. Tertiary Lymphoid Structure Formation and Function in the Tumor Microenvironment. InHandbook of Cancer and Immunology 2024 Jan 11 (pp. 1-31). Cham: Springer International Publishing.

98]. Cui C, Craft J, Joshi NS. T follicular helper cells in cancer, tertiary lymphoid structures, and beyond. InSeminars in immunology 2023 Sep 1 (Vol. 69, p. 101797). Academic Press.

99]. Faisal AN, Mohsein OA. Comprehensive Study on Gynecomastia: Clinical Features, Pathophysiology, Morphologic, and Microscopic Features. Central Asian Journal of Medical and Natural Science. 2025;6(2):775-89.

100]. Ruffin AT, Cillo AR, Tabib T, Liu A, Onkar S, Kunning SR, Lampenfeld C, Atiya HI, Abecassis I, Kürten CH, Qi Z. B cell

signatures and tertiary lymphoid structures contribute to outcome in head and neck squamous cell carcinoma. Nature communications. 2021 Jun 7;12(1):3349.

101]. Werner F, Wagner C, Simon M, Glatz K, Mertz KD, Läubli H, Griss J, Wagner SN. A standardized analysis of tertiary lymphoid structures in human melanoma: disease progression-and tumor site-associated changes with germinal center alteration. Frontiers in Immunology. 2021 Jun 24;12:675146.

102]. Marinkovic T, Marinkovic D. Biological mechanisms of ectopic lymphoid structure formation and their pathophysiological significance. International Reviews of Immunology. 2021 Jul 4;40(4):255-67.

103]. Mowat AM, Scott CL, Bain CC. Barrier-tissue macrophages: functional adaptation to environmental challenges. Nature medicine. 2017 Nov 1;23(11):1258-70.

104]. Franziska W. Cellular characterization of yolk sac-derived macrophages (Doctoral dissertation, Dissertation, München, Ludwig-Maximilians-Universität, 2021).

105]. Hussein TA, Al-Shammari MJ, Alqaisy MR, Mohsein OA. Emerging biomarkers in cancer detection and prognosis: A comprehensive review. Int. J. Immunol. 2025;7(1):01-12.

106]. Elhag S, Stremmel C, Zehrer A, Plocke J, Hennel R, Keuper M, Knabe C, Winterhalter J, Gölling V, Tomas L, Weinberger T. Differences in cell-intrinsic inflammatory programs of yolk sac and bone marrow macrophages. Cells. 2021 Dec 17;10(12):3564.

107]. Ito C, Hikosaka-Kuniishi M, Yamazaki H, Yamane T. Multiple cell populations generate macrophage progenitors in the early yolk sac. Cellular and Molecular Life Sciences. 2022 Mar;79(3):159.

108]. Hellman L. Phenotypic and functional heterogeneity of monocytes and macrophages. International Journal of Molecular Sciences. 2023 Sep 25;24(19):14525.

109]. Lokka E. FOETAL MONOCYTES AND THEIR JOURNEY FROM LIVER TO PERIPHERY. 2023. 66-74.

110]. True H, Blanton M, Sureshchandra S, Messaoudi I. Monocytes and macrophages in pregnancy: The good, the bad, and the ugly. Immunological reviews. 2022 Jul;308(1):77-92.

111]. Lee CZ, Ginhoux F. Biology of resident tissue macrophages. Development. 2022 Apr 15;149(8):dev200270.

112]. Goh I, Botting RA, Rose A, Webb S, Engelbert J, Gitton Y, Stephenson E, Quiroga Londoño M, Mather M, Mende N, Imaz-Rosshandler I. Yolk sac cell atlas reveals multiorgan functions during human early development. Science. 2023 Aug 18;381(6659):eadd7564.

113]. Abdulhussien AA, Farhan ZM, Mohsein OA. The Clinico-Pathological Role of Horizontal Gene Transfer in the Ability of Pseudomonas Aeruginosa to Cause Disease in Lung Tissue. European Journal of Medical and Health Research. 2025 Jan 1;3(1):27-34.

114]. Liu G, Wang Z, Li S. Heterogeneity and plasticity of tissue-resident memory T cells in skin diseases and homeostasis: a review. Frontiers in Immunology. 2024 May 8;15:1378359.

115]. Jacobse J, Li J, Rings EH, Samsom JN, Goettel JA. Intestinal regulatory T cells as specialized tissue-restricted immune cells in intestinal immune homeostasis and disease. Frontiers in Immunology. 2021 Aug 4;12:716499.

116]. Cui G, Abe S, Kato R, Ikuta K. Insights into the heterogeneity of iNKT cells: tissue-resident and circulating subsets shaped by local microenvironmental cues. Frontiers in Immunology. 2024 Feb 19;15:1349184.

117]. Huang Y, Zhou L, Zhang H, Zhang L, Xi X, Sun Y. BMDCs induce the generation of the CD103+ CD8+ tissue-resident memory T cell subtype, which amplifies local tumor control in the genital tract. Cellular Immunology. 2022 Apr 1;374:104502.

118]. Chen K, Gu X, Yang S, Tao R, Fan M, Bao W, Wang X. Research progress on intestinal tissue-resident memory T cells in inflammatory bowel disease. Scandinavian Journal of Immunology. 2023 Dec;98(6):e13332.

119]. Nobs SP, Kopf M. Tissue-resident macrophages: guardians of organ homeostasis. Trends in immunology. 2021 Jun 1;42(6):495-507.

120]. M. L. Meizlish, R. A. Franklin, X. Zhou, et al., "Tissue homeostasis and inflammation," *Annual Review of Immunology*, vol. 39, pp. 127-154, 2021.

121]. Alexandre YO, Schienstock D, Lee HJ, Gandolfo LC, Williams CG, Devi S, Pal B, Groom JR, Cao W, Christo SN, Gordon CL. A diverse fibroblastic stromal cell landscape in the spleen directs tissue homeostasis and immunity. Science immunology. 2022 Jan 7;7(67):eabj0641.

122]. Abdulhussien AA, Farhan ZM, Mohsein OA. The Clinico-Pathological Role of Horizontal Gene Transfer in the Ability of Pseudomonas Aeruginosa to Cause Disease in Lung Tissue. European Journal of Medical and Health Research. 2025 Jan 1;3(1):27-34.

123]. Arora L, Pal D. Remodeling of stromal cells and immune landscape in microenvironment during tumor progression. Frontiers in Oncology. 2021 Mar 8;11:596798.

124]. Noack M, Miossec P. Importance of lymphocyte–stromal cell interactions in autoimmune and inflammatory rheumatic diseases. Nature Reviews Rheumatology. 2021 Sep;17(9):550-64.

125]. Guven-Maiorov E, Acuner-Ozbabacan SE, Keskin O, Gursoy A, Nussinov R. Structural pathways of cytokines may illuminate their roles in regulation of cancer development and immunotherapy. Cancers. 2014 Mar 25;6(2):663-83.

126]. Yang Y, Wang Y. Autocrine, Paracrine, and Endocrine Signals That Can Alter Alveolar Macrophages Function. Reviews of Physiology, Biochemistry and Pharmacology. 2022 Dec 7:177-98.

127]. Johnston EK, Abbott RD. Adipose tissue paracrine-, autocrine-, and matrix-dependent signaling during the development and progression of obesity. Cells. 2023 Jan 25;12(3):407.

128]. Harvanová G, Duranková S, Bernasovská J. The role of cytokines and chemokines in the inflammatory response. Alergologia Polska-Polish Journal of Allergology. 2023;10(3):210-9.

129]. Batrash F, Shaik A, Rauf R, Kutmah M, Zhang J. Paracrine Regulation and Immune System Pathways in the Inflammatory Tumor Microenvironment of Lung Cancer: Insights into Oncogenesis and Immunotherapeutic Strategies. Cancers. 2024 Mar 10;16(6):1113.

130]. Mosser DM, Hamidzadeh K, Goncalves R. Macrophages and the maintenance of homeostasis. Cellular & molecular immunology. 2021 Mar;18(3):579-87.

131]. Habanjar O, Bingula R, Decombat C, Diab-Assaf M, Caldefie-Chezet F, Delort L. Crosstalk of inflammatory cytokines within the breast tumor microenvironment. International journal of molecular sciences. 2023 Feb 16;24(4):4002.

132]. Rentschler M, Braumüller H, Briquez PS, Wieder T. Cytokine-Induced Senescence in the Tumor Microenvironment and Its Effects on Anti-Tumor Immune Responses. Cancers 2022, 14, 1364 [Internet]. 2022

133]. Gaskill PJ, Khoshbouei H. Dopamine and norepinephrine are embracing their immune side and so should we. Current opinion in neurobiology. 2022 Dec 1;77:102626.

134]. Jia Q, Wang A, Yuan Y, Zhu B, Long H. Heterogeneity of the tumor immune microenvironment and its clinical relevance. Experimental hematology & oncology. 2022 Apr 23;11(1):24.

135]. Zhang A, Miao K, Sun H, Deng CX. Tumor heterogeneity reshapes the tumor microenvironment to influence drug resistance. International journal of biological sciences. 2022 Apr 24;18(7):3019.

136]. Wu F, Fan J, He Y, Xiong A, Yu J, Li Y, Zhang Y, Zhao W, Zhou F, Li W, Zhang J. Single-cell profiling of tumor heterogeneity and the microenvironment in advanced non-small cell lung cancer. Nature communications. 2021 May 5;12(1):2540.

137]. Xue R, Zhang Q, Cao Q, Kong R, Xiang X, Liu H, Feng M, Wang F, Cheng J, Li Z, Zhan Q. Liver tumour immune microenvironment subtypes and neutrophil heterogeneity. Nature. 2022 Dec 1;612(7938):141-7.

138]. Salemme V, Centonze G, Avalle L, Natalini D, Piccolantonio A, Arina P, Morellato A, Ala U, Taverna D, Turco E, Defilippi P. The role of tumor microenvironment in drug resistance: emerging technologies to unravel breast cancer heterogeneity. Frontiers in oncology. 2023 May 17;13:1170264.

139]. Lenz G, Onzi GR, Lenz LS, Buss JH, Dos Santos JA, Begnini KR. The origins of phenotypic heterogeneity in cancer. Cancer Research. 2022 Jan 1;82(1):3-11.

140]. Biswas A, De S. Drivers of dynamic intratumor heterogeneity and phenotypic plasticity. American Journal of Physiology-Cell Physiology. 2021 May 1;320(5):C750-60.

141]. Ge R, Wang Z, Cheng L. Tumor microenvironment heterogeneity an important mediator of prostate cancer progression and therapeutic resistance. NPJ precision oncology. 2022 May 4;6(1):31.

142]. Smart M, Goyal S, Zilman A. Roles of phenotypic heterogeneity and microenvironment feedback in early tumor development. Physical Review E. 2021 Mar;103(3):032407.

143]. Group Young Researchers in Inflammatory Carcinogenesis, Wandmacher AM, Mehdorn AS, Sebens S. The heterogeneity of the tumor microenvironment as essential determinant of development, progression and therapy response of pancreatic cancer. Cancers. 2021 Sep 30;13(19):4932.

144]. van Gisbergen KP, Zens KD, Münz C. T-cell memory in tissues. European journal of immunology. 2021 Jun;51(6):1310-24.

145]. Bala N, McGurk AI, Zilch T, Rup AN, Carter EM, Leddon SA, Fowell DJ. T cell activation niches—Optimizing T cell effector function in inflamed and infected tissues. Immunological reviews. 2022 Mar;306(1):164-80.

146]. Szabo PA. Axes of heterogeneity in human tissue-resident memory T cells. Immunological Reviews. 2023 Jul;316(1):23-37.

147]. Cheng L, Becattini S. Intestinal CD8+ tissue-resident memory T cells: From generation to function. European Journal of Immunology. 2022 Oct;52(10):1547-60.

148]. Hirahara K, Kokubo K, Aoki A, Kiuchi M, Nakayama T. the role of CD4+ resident memory T cells in local immunity in the mucosal tissue–protection versus pathology–. Frontiers in immunology. 2021 Apr 21;12:616309.

149]. Makris S, De Winde CM, Horsnell HL, Cantoral-Rebordinos JA, Finlay RE, Acton SE. Immune function and dysfunction are determined by lymphoid tissue efficacy. Disease models & mechanisms. 2022 Jan 1;15(1):dmm049256.

150]. Rossi A, Belmonte B, Carnevale S, Liotti A, De Rosa V, Jaillon S, Piconese S, Tripodo C. Stromal and immune cell dynamics in tumor associated tertiary lymphoid structures and anti-tumor immune responses. Frontiers in Cell and Developmental Biology. 2022 Jul 8;10:933113.

151]. Shou Y, Johnson SC, Quek YJ, Li X, Tay A. Integrative lymph node-mimicking models created with biomaterials and computational tools to study the immune system. Materials Today Bio. 2022 Mar 1;14:100269.

152]. Zhao H, Wang H, Zhou Q, Ren X. Insights into tertiary lymphoid structures in the solid tumor microenvironment: anti-tumor mechanism, functional regulation, and immunotherapeutic strategies. Cancer biology & medicine. 2021 Nov 1;18(4):981-91.

153]. Bertuzzi C, Sabattini E, Agostinelli C. Immune microenvironment features and dynamics in Hodgkin lymphoma. Cancers. 2021 Jul 20;13(14):3634.

154]. Zhang Y, Xu M, Ren Y, Ba Y, Liu S, Zuo A, Xu H, Weng S, Han X, Liu Z. Tertiary lymphoid structural heterogeneity determines tumour immunity and prospects for clinical application. Molecular Cancer. 2024 Apr 6;23(1):75.

155]. Yousefpour P, Ni K, Irvine DJ. Targeted modulation of immune cells and tissues using engineered biomaterials. Nature reviews bioengineering. 2023 Feb;1(2):107-24.

156]. Zhou Z, Pang Y, Ji J, He J, Liu T, Ouyang L, Zhang W, Zhang XL, Zhang ZG, Zhang K, Sun W. Harnessing 3D in vitro systems to model immune responses to solid tumours: a step towards improving and creating personalized immunotherapies. Nature Reviews Immunology. 2024 Jan;24(1):18-32.

157]. Fridman WH, Meylan M, Petitprez F, Sun CM, Italiano A, Sautès-Fridman C. B cells and tertiary lymphoid structures as determinants of tumour immune contexture and clinical outcome. Nature reviews Clinical oncology. 2022 Jul;19(7):441-57.

158]. Leal JM, Huang JY, Kohli K, Stoltzfus C, Lyons-Cohen MR, Olin BE, Gale Jr M, Gerner MY. Innate cell microenvironments in lymph nodes shape the generation of T cell responses during type I inflammation. Science immunology. 2021 Feb 12;6(56):eabb9435.

159]. Roubanis A. Investigating the metabolism of regulatory T cells in non-lymphoid tissues using a genetic approach and an in vivo adaptation of SCENITH (Doctoral dissertation, Sorbonne Université).

160]. Asam S, Nayar S, Gardner D, Barone F. Stromal cells in tertiary lymphoid structures: Architects of autoimmunity. Immunological reviews. 2021 Jul;302(1):184-95.

161]. Vanderbeck AN. Notch in the Niche: How Stromal Notch Ligands Regulate T Cell Development and Differentiation in Secondary Lymphoid Tissues (Doctoral dissertation, University of Pennsylvania).

162]. Johansson-Percival A, Ganss R. Therapeutic induction of tertiary lymphoid structures in cancer through stromal remodeling. Frontiers in immunology. 2021 May 27;12:674375.

163]. Sonar SA, Watanabe M, Nikolich JŽ. Disorganization of secondary lymphoid organs and dyscoordination of chemokine secretion as key contributors to immune aging. InSeminars in immunology 2023 Nov 1 (Vol. 70, p. 101835). Academic Press.

164]. Yasmin H, Ramesh RP, Joseph AM, Kishore U. Fibroblast heterogeneity and its role in generating protective immunity in the secondary lymphoid organs. Frontiers in immunology. 2025 Apr 3;16:1519789.

165]. Lütge M, Pikor NB, Ludewig B. Differentiation and activation of fibroblastic reticular cells. Immunological Reviews. 2021 Jul;302(1):32-46.

166]. Gavil NV, Cheng K, Masopust D. Resident memory T cells and cancer. Immunity. 2024 Aug 13;57(8):1734-51.

167]. BOŻYK, Aleksandra, et al. Tumor microenvironment—A short review of cellular and interaction diversity. Biology, 2022, 11.6: 929.

168]. FARC, Ovidiu; CRISTEA, Victor. An overview of the tumor microenvironment, from cells to complex networks. Experimental and therapeutic medicine, 2021, 21.1: 96.

169]. Pernot S, Evrard S, Khatib AM. The give-and-take interaction between the tumor microenvironment and immune cells regulating tumor progression and repression. Frontiers in immunology. 2022 Apr 13;13:850856.

170]. Zhang Z, Chen X, Gao S, Fang X, Ren S. 3D bioprinted tumor model: a prompt and convenient platform for overcoming immunotherapy resistance by recapitulating the tumor microenvironment. Cellular Oncology. 2024 Aug;47(4):1113-26.

171]. Huppert LA, Green MD, Kim L, Chow C, Leyfman Y, Daud AI, Lee JC. Tissue-specific Tregs in cancer metastasis: opportunities for precision immunotherapy. Cellular & molecular immunology. 2022 Jan;19(1):33-45.

172]. Gao Y, Li J, Cheng W, Diao T, Liu H, Bo Y, Liu C, Zhou W, Chen M, Zhang Y, Liu Z. Cross-tissue human fibroblast atlas reveals myofibroblast subtypes with distinct roles in immune modulation. Cancer Cell. 2024 Oct 14;42(10):1764-83.

173]. Lu Q, Kou D, Lou S, Ashrafizadeh M, Aref AR, Canadas I, Tian Y, Niu X, Wang Y, Torabian P, Wang L. Nanoparticles in tumor microenvironment remodeling and cancer immunotherapy. Journal of Hematology & Oncology. 2024 Apr 2;17(1):16.

174]. Jackson GA, Adamson DC. Similarities in Mechanisms of Ovarian Cancer Metastasis and Brain Glioblastoma Multiforme Invasion Suggest Common Therapeutic Targets. Cells. 2025 Jan 23;14(3):171.

175]. Duan S, Sawyer TW, Witten BL, Song H, Else T, Merchant JL. Spatial profiling reveals tissue-specific neuro-immune interactions in gastroenteropancreatic neuroendocrine tumors. The Journal of pathology. 2024 Mar;262(3):362-76.

176]. Mishchenko TA, Turubanova VD, Gorshkova EN, Krysko O, Vedunova MV, Krysko DV. Glioma: bridging the tumor microenvironment, patient immune profiles and novel personalized immunotherapy. Frontiers in Immunology. 2024 Jan 11;14:1299064.

177]. Yehya A, Youssef J, Hachem S, Ismael J, Abou-Kheir W. Tissue-specific cancer stem/progenitor cells: Therapeutic implications. World Journal of Stem Cells. 2023 May 26;15(5):323.

178]. Yang Q, Li M, Yang X, Xiao Z, Tong X, Tuerdi A, Li S, Lei L. Flourishing tumor organoids: History, emerging technology, and application. Bioengineering & Translational Medicine. 2023 Sep;8(5):e10559.

179]. Hwang DG, Choi YM, Jang J. 3D bioprinting-based vascularized tissue models mimicking tissue-specific architecture and pathophysiology for in vitro studies. Frontiers in bioengineering and biotechnology. 2021 May 31;9:685507.

180]. Basic M, Peppermüller PP, Bolsega S, Bleich A, Bornemann M, Bode U, Buettner M. Lymph node stromal cells from different draining areas distinctly regulate the development of chronic intestinal inflammation. Frontiers in Immunology. 2021 Feb 16;11:549473.

181]. Jenkins SJ, Allen JE. The expanding world of tissue-resident macrophages. European journal of immunology. 2021 Aug;51(8):1882-96.

182]. Mu X, Li Y, Fan GC. Tissue-resident macrophages in the control of infection and resolution of inflammation. Shock. 2021 Jan 1;55(1):14-23.

183]. Dick SA, Wong A, Hamidzada H, Nejat S, Nechanitzky R, Vohra S, Mueller B, Zaman R, Kantores C, Aronoff L, Momen A. Three tissue resident macrophage subsets coexist across organs with conserved origins and life cycles. Science immunology. 2022 Jan 7;7(67):eabf7777.

184]. Cao M, Wang Z, Lan W, Xiang B, Liao W, Zhou J, Liu X, Wang Y, Zhang S, Lu S, Lang J. The roles of tissue resident macrophages in health and cancer. Experimental Hematology & Oncology. 2024 Jan 16;13(1):3.

185]. Lérias JR, Paraschoudi G, De Sousa E, Martins J, Condeço C, Figueiredo N, Carvalho C, Dodoo E, Castillo-Martin M, Beltrán A, Ligeiro D. Microbes as master immunomodulators: immunopathology, cancer and personalized immunotherapies. Frontiers in Cell and Developmental Biology. 2020 Jan 23;7:362.

186]. Zhu J, Miner MD. Local Power: The Role of Tissue-Resident Immunity in Human Genital Herpes Simplex Virus Reactivation. Viruses. 2024 Jun 25;16(7):1019.

187]. Jonjić S. Tissue-specific antiviral immunity. Cellular & Molecular Immunology. 2024 Sep;21(9):941-2.

188]. Pereira MV, Galvani RG, Gonçalves-Silva T, de Vasconcelo ZF, Bonomo A. Tissue adaptation of CD4 T lymphocytes in homeostasis and cancer. Frontiers in Immunology. 2024 Apr 16;15:1379376.

189]. Wang R, Song S, Qin J, Yoshimura K, Peng F, Chu Y, Li Y, Fan Y, Jin J, Dang M, Dai E. Evolution of immune and stromal cell states and ecotypes during gastric adenocarcinoma progression. Cancer Cell. 2023 Aug 14;41(8):1407-26.

190]. Ibidapo-Obe O, Bruns T. Tissue-resident and innate-like T cells in patients with advanced chronic liver disease. JHEP Reports. 2023 Oct 1;5(10):100812.

191]. Kamalinia H, Mostaghimi T, Taheri M, Shirzad M, Pasha AA, Yahyapour Y, Moudi E, Sadeghi F. Higher viral load of BK polyomavirus in urothelial bladder tumors compared with nontumoral bladder tissues. Future Virology. 2023 Mar 1;18(4):243-52.

192]. Ferraro E, Germanò M, Mollace R, Mollace V, Malara N. HIF-1, the Warburg effect, and macrophage/microglia polarization potential role in COVID-19 pathogenesis. Oxidative Medicine and Cellular Longevity. 2021;2021(1):8841911.

193]. Stossi F, Singh PK, Safari K, Marini M, Labate D, Mancini MA. High throughput microscopy and single cell phenotypic image-based analysis in toxicology and drug discovery. Biochemical Pharmacology. 2023 Oct 1;216:115770.

194]. Bosisio FM, Van Herck Y, Messiaen J, Bolognesi MM, Marcelis L, Van Haele M, Cattoretti G, Antoranz A, De Smet F. Next-generation pathology using multiplexed immunohistochemistry: mapping tissue architecture at single-cell level. Frontiers in oncology. 2022 Jul 29;12:918900.

195]. Zhang Y, Kang L, Wong IH, Dai W, Li X, Chan RC, Hsin MK, Wong TT. High-throughput, label-free and slide-free histological imaging by computational microscopy and unsupervised learning. Advanced Science. 2022 Jan;9(2):2102358.

196]. Einhaus J, Rochwarger A, Mattern S, Gaudillière B, Schürch CM. High-multiplex tissue imaging in routine pathology—are we there yet?. Virchows Archiv. 2023 May;482(5):801-12.

197]. Yang L, Pijuan-Galito S, Rho HS, Vasilevich AS, Eren AD, Ge L, Habibovic P, Alexander MR, de Boer J, Carlier A, van Rijn P. High-throughput methods in the discovery and study of biomaterials and materiobiology. Chemical reviews. 2021 Mar 11;121(8):4561-677.

198]. Ahmed R, Augustine R, Valera E, Ganguli A, Mesaeli N, Ahmad IS, Bashir R, Hasan A. Spatial mapping of cancer tissues by OMICS technologies. Biochimica et Biophysica Acta (BBA)-Reviews on Cancer. 2022 Jan 1;1877(1):188663.

199]. Patkulkar PA, Subbalakshmi AR, Jolly MK, Sinharay S. Mapping spatiotemporal heterogeneity in tumor profiles by integrating high-throughput imaging and omics analysis. ACS omega. 2023 Feb 7;8(7):6126-38.

200]. Khalaf K, Hana D, Chou JT, Singh C, Mackiewicz A, Kaczmarek M. Aspects of the tumor microenvironment involved in immune resistance and drug resistance. Frontiers in immunology. 2021 May 27;12:656364.

201]. Papadas A, Huang Y, Cicala A, Dou Y, Fields M, Gibbons A, Hong D, Lagal DJ, Quintana V, Rizo A, Zomalan B. Emerging roles for tumor stroma in antigen presentation and anti-cancer immunity. Biochemical Society Transactions. 2023 Nov 30;51(6):2017-28.

202]. Mohammad S. The influence of stromal fibroblast on antigen-presenting cell function and alteration of their biology (Doctoral dissertation, University of Nottingham).

203]. Harryvan TJ, de Lange S, Hawinkels LJ, Verdegaal EM. The ABCs of antigen presentation by stromal non-professional antigen-presenting cells. International Journal of Molecular Sciences. 2021 Dec 23;23(1):137.

204]. Kawasaki T, Ikegawa M, Kawai T. Antigen presentation in the lung. Frontiers in immunology. 2022 May 9;13:860915.

205]. Typiak M, Żurawa-Janicka D. Not an immune cell, but they may act like one—cells with immune properties outside the immune system. Immunology and Cell Biology. 2024 Jul;102(6):487-99.

206]. Zhao Y, Li Q, Ouyang Q, Wu L, Chen X. Activated mesangial cells acquire the function of antigen presentation. Cellular Immunology. 2021 Mar 1;361:104279.

207]. González LO, Eiro N, Fraile M, Beridze N, Escaf AR, Escaf S, Fernández-Gómez JM, Vizoso FJ. Prostate cancer tumor stroma: responsibility in tumor biology, diagnosis and treatment. Cancers. 2022 Sep 11;14(18):4412.

208]. Dzobo K, Dandara C. The extracellular matrix: its composition, function, remodeling, and role in tumorigenesis. Biomimetics. 2023 Apr 5;8(2):146.

209]. Cox TR. The matrix in cancer. Nature Reviews Cancer. 2021 Apr;21(4):217-38.

210]. Shimoda M, Ohtsuka T, Okada Y, Kanai Y. Stromal metalloproteinases: Crucial contributors to the tumor microenvironment. Pathology international. 2021 Jan;71(1):1-4.

211]. Colombo E, Cattaneo MG. Multicellular 3D models to study tumour-stroma interactions. International journal of molecular sciences. 2021 Feb 5;22(4):1633.

212]. Ruze R, Song J, Yin X, Chen Y, Xu R, Wang C, Zhao Y. Mechanisms of obesity-and diabetes mellitus-related pancreatic carcinogenesis: a comprehensive and systematic review. Signal transduction and targeted therapy. 2023 Mar 24;8(1):139.

213]. Baghy K, Ladányi A, Reszegi A, Kovalszky I. Insights into the tumor microenvironment—components, functions and therapeutics. International Journal of Molecular Sciences. 2023 Dec 15;24(24):17536.

214]. Sharma V, Letson J, Furuta S. Fibrous stroma: Driver and passenger in cancer development. Science signaling. 2022 Mar 8;15(724):eabg3449.

215]. Murphy KJ, Chambers CR, Herrmann D, Timpson P, Pereira BA. Dynamic stromal alterations influence tumor-stroma crosstalk to promote pancreatic cancer and treatment resistance. Cancers. 2021 Jul 12;13(14):3481.

216]. Pederzoli F, Raffo M, Pakula H, Ravera F, Nuzzo PV, Loda M. Stromal cells in prostate cancer pathobiology: friends or foes?. British journal of cancer. 2023 Apr 6;128(6):930-9.

217]. Karamanos NK, Theocharis AD, Piperigkou Z, Manou D, Passi A, Skandalis SS, Vynios DH, Orian-Rousseau V, Ricard-Blum S, Schmelzer CE, Duca L. A guide to the composition and functions of the extracellular matrix. The FEBS journal. 2021 Dec;288(24):6850-912.

218]. Pfisterer K, Shaw LE, Symmank D, Weninger W. The extracellular matrix in skin inflammation and infection. Frontiers in cell and developmental biology. 2021 Jul 6;9:682414.

219]. Pompili S, Latella G, Gaudio E, Sferra R, Vetuschi A. The charming world of the extracellular matrix: a dynamic and protective network of the intestinal wall. Frontiers in medicine. 2021 Apr 16;8:610189.

220]. Zhang W, Liu Y, Zhang H. Extracellular matrix: an important regulator of cell functions and skeletal muscle development. Cell & bioscience. 2021 Mar 31;11(1):65.

221]. Bandzerewicz A, Gadomska-Gajadhur A. Into the tissues: Extracellular matrix and its artificial substitutes: Cell signalling mechanisms. Cells. 2022 Mar 7;11(5):914.

222]. Potekaev NN, Borzykh OB, Medvedev GV, Pushkin DV, Petrova MM, Petrov AV, Dmitrenko DV, Karpova EI, Demina OM, Shnayder NA. The role of extracellular matrix in skin wound healing. Journal of Clinical Medicine. 2021 Dec 18;10(24):5947.

223]. Webb S, Haniffa M. Large-scale single-cell RNA sequencing atlases of human immune cells across lifespan: Possibilities and challenges. European Journal of Immunology. 2023 Dec;53(12):2250222.

224]. Jing Y, Yang J, Johnson DB, Moslehi JJ, Han L. Harnessing big data to characterize immune-related adverse events. Nature Reviews Clinical Oncology. 2022 Apr;19(4):269-80.

225]. Fan J, Shen Y, Chen C, Chen X, Yang X, Liu H, Chen R, Liu S, Zhang B, Zhang M, Zhou G. A large-scale integrated transcriptomic atlas for soybean organ development. Molecular Plant. 2025 Apr 7;18(4):669-89.

226]. Yamamoto Y, Shirai Y, Edahiro R, Kumanogoh A, Okada Y. Large-scale cross-trait genetic analysis highlights shared genetic backgrounds of autoimmune diseases. Immunological Medicine. 2025 Jan 2;48(1):1-0.

227]. McKellar DW, Walter LD, Song LT, Mantri M, Wang MF, De Vlaminck I, Cosgrove BD. Large-scale integration of single-cell transcriptomic data captures transitional progenitor states in mouse skeletal muscle regeneration. Communications Biology. 2021 Nov 12;4(1):1280.

228]. Uniken Venema WT, Ramírez-Sánchez AD, Bigaeva E, Withoff S, Jonkers I, McIntyre RE, Ghouraba M, Raine T, Weersma RK, Franke L, Festen EA. Gut mucosa dissociation protocols influence cell type proportions and single-cell gene expression levels. Scientific Reports. 2022 Jun 14;12(1):9897.

229]. Digre A, Lindskog C. The Human Protein Atlas—Spatial localization of the human proteome in health and disease. Protein science. 2021 Jan;30(1):218-33.

230]. Hao M, Gong J, Zeng X, Liu C, Guo Y, Cheng X, Wang T, Ma J, Zhang X, Song L. Large-scale foundation model on single-cell transcriptomics. Nature methods. 2024 Aug;21(8):1481-91.

231]. Yang F, Wang W, Wang F, Fang Y, Tang D, Huang J, Lu H, Yao J. scBERT as a large-scale pretrained deep language model for cell type annotation of single-cell RNA-seq data. Nature Machine Intelligence. 2022 Oct;4(10):852-66.

232]. Jimenez MT, Michieletto MF, Henao-Mejia J. A new perspective on mesenchymal–immune interactions in adipose tissue. Trends in immunology. 2021 May 1;42(5):375-88.

233]. Zubkova E, Kalinin A, Beloglazova I, Kurilina E, Menshikov M, Parfyonova Y, Tsokolaeva Z. Artificial Tertiary Lymphoid Structures: Exploring Mesenchymal Stromal Cells as a Platform for Immune Niche Formation. International Journal of Molecular Sciences. 2024 Dec 11;25(24):13286.

234]. Sabit H, Arneth B, Pawlik TM, Abdel-Ghany S, Ghazy A, Abdelazeem RM, Alqosaibi A, Al-Dhuayan IS, Almulhim J, Alrabiah NA, Hashash A. Leveraging Single-Cell Multi-Omics to Decode Tumor Microenvironment Diversity and Therapeutic Resistance. Pharmaceuticals. 2025 Jan 10;18(1):75.

235]. Liu W, Wang X, Yu Y, Lin W, Xu H, Jiang X, Yuan C, Wang Y, Wang X, Song W, He Y. Inflammatory Cell Interactions in the Rotator Cuff Microenvironment: Insights From Single-Cell Sequencing. International Journal of Genomics. 2025;2025(1):6175946.

236]. Seferbekova Z, Lomakin A, Yates LR, Gerstung M. Spatial biology of cancer evolution. Nature Reviews Genetics. 2023 May;24(5):295-313.

237]. Pascual-Reguant A, Kroh S, Hauser AE. Tissue niches and immunopathology through the lens of spatial tissue profiling techniques. European Journal of Immunology. 2024 Feb;54(2):2350484.

238]. Cheng B, Yu Q, Wang W. Intimate communications within the tumor microenvironment: stromal factors function as an orchestra. Journal of Biomedical Science. 2023 Jan 4;30(1):1.

239]. Liu L, Xu L, Wu D, Zhu Y, Li X, Xu C, Chen K, Lin Y, Lao J, Cai P, Li X. Impact of tumour stroma-immune interactions on survival prognosis and response to neoadjuvant chemotherapy in bladder cancer. EBioMedicine. 2024 Jun 1;104.

240]. Feng Y, Ma W, Zang Y, Guo Y, Li Y, Zhang Y, Dong X, Liu Y, Zhan X, Pan Z, Luo M. Spatially organized tumor-stroma boundary determines the efficacy of immunotherapy in colorectal cancer patients. Nature Communications. 2024 Nov 26;15(1):10259.

241]. Zhang Y, Coleman M, Brekken RA. Perspectives on hypoxia signaling in tumor stroma. Cancers. 2021 Jun 20;13(12):3070.

242]. Edwards P, Kang BW, Chau I. Targeting the stroma in the management of pancreatic cancer. Frontiers in Oncology. 2021 Jul 14;11:691185.

243]. Perucca A, Llonín AG, Benach OM, Hallopeau C, Rivas EI, Linares J, Garrido M, Sallent-Aragay A, Golde T, Colombelli J, Dalaka E. Micro Immune Response On-chip (MIRO) models the tumour-stroma interface for immunotherapy testing. Nature Communications. 2025 Feb 3;16(1):1279.

244]. Thomas R, Jerome JM, Krieger KL, Ashraf N, Rowley DR. The reactive stroma response regulates the immune landscape in prostate cancer. Journal of Translational Genetics and Genomics. 2024 Jul 24;8(3):249-77.

245]. Hanahan D. Hallmarks of cancer: new dimensions. Cancer discovery. 2022 Jan 1;12(1):31-46.

246]. Mortezaee K, Majidpoor J. Key promoters of tumor hallmarks. International journal of clinical oncology. 2022 Jan;27(1):45-58.

247]. Swanton C, Bernard E, Abbosh C, André F, Auwerx J, Balmain A, Bar-Sagi D, Bernards R, Bullman S, DeGregori J, Elliott C. Embracing cancer complexity: Hallmarks of systemic disease. Cell. 2024 Mar 28;187(7):1589-616.

248]. Nallasamy P, Nimmakayala RK, Parte S, Are AC, Batra SK, Ponnusamy MP. Tumor microenvironment enriches the stemness features: the architectural event of therapy resistance and metastasis. Molecular cancer. 2022 Dec 22;21(1):225.

249]. DeNardo DG, Coussens LM. Inflammation and breast cancer. Balancing immune response: crosstalk between adaptive and innate immune cells during breast cancer progression. Breast cancer research. 2007 Aug;9:1-0.

250]. Cha YJ, Koo JS. Role of tumor-associated myeloid cells in breast cancer. Cells. 2020 Jul 27;9(8):1785.

251]. Kazemi MH, Sadri M, Najafi A, Rahimi A, Baghernejadan Z, Khorramdelazad H, Falak R. Tumor-infiltrating lymphocytes for treatment of solid tumors: It takes two to tango?. Frontiers in immunology. 2022 Oct 28;13:1018962.

252]. Zhao Y, Deng J, Rao S, Guo S, Shen J, Du F, Wu X, Chen Y, Li M, Chen M, Li X. Tumor infiltrating lymphocyte (TIL) therapy for solid tumor treatment: progressions and challenges. Cancers. 2022 Aug 27;14(17):4160.

253]. Wang S, Sun J, Chen K, Ma P, Lei Q, Xing S, Cao Z, Sun S, Yu Z, Liu Y, Li N. Perspectives of tumor-infiltrating lymphocyte treatment in solid tumors. BMC medicine. 2021 Jun 11;19(1):140.

254]. Whiteside TL. Tumor-infiltrating lymphocytes and their role in solid tumor progression. InInteraction of immune and cancer cells 2022 Feb 14 (pp. 89-106). Cham: Springer International Publishing.

255]. Li B. Why do tumor-infiltrating lymphocytes have variable efficacy in the treatment of solid tumors?. Frontiers in immunology. 2022 Oct 21;13:973881.

256]. Qin M, Chen G, Hou J, Wang L, Wang Q, Wang L, Jiang D, Hu Y, Xie B, Chen J, Wei H. Tumor-infiltrating lymphocyte: features and prognosis of lymphocytes infiltration on colorectal cancer. Bioengineered. 2022 Jun 1;13(6):14872-88.

257]. Paijens ST, Vledder A, de Bruyn M, Nijman HW. Tumor-infiltrating lymphocytes in the immunotherapy era. Cellular & molecular immunology. 2021 Apr;18(4):842-59.

258]. Buch MH, Eyre S, McGonagle D. Persistent inflammatory and non-inflammatory mechanisms in refractory rheumatoid arthritis. Nature Reviews Rheumatology. 2021 Jan;17(1):17-33.

259]. Brown P, Pratt AG, Hyrich KL. Therapeutic advances in rheumatoid arthritis. Bmj. 2024 Jan 17;384.

260]. Finckh A, Gilbert B, Hodkinson B, Bae SC, Thomas R, Deane KD, Alpizar-Rodriguez D, Lauper K. Global epidemiology of rheumatoid arthritis. Nature Reviews Rheumatology. 2022 Oct;18(10):591-602.

261]. Sharma A, Goel A. Pathogenesis of rheumatoid arthritis and its treatment with anti-inflammatory natural products. Molecular Biology Reports. 2023 May;50(5):4687-706.

262]. Davies K, Dures E, Ng WF. Fatigue in inflammatory rheumatic diseases: current knowledge and areas for future research. Nature Reviews Rheumatology. 2021 Nov;17(11):651-64.

263]. Radu AF, Bungau SG. Management of rheumatoid arthritis: an overview. Cells. 2021 Oct 23;10(11):2857.

264]. Bretscher P. What Determines the Class of Immunity an Antigen Induces? A Foundational Question Whose Rational Consideration Has Been Undermined by the Information Overload. Biology. 2023 Sep 19;12(9):1253.

265]. Sompayrac LM. How the immune system works. John Wiley & Sons; 2022 Nov 7.

266]. Daëron M. The immune system as a system of relations. Frontiers in Immunology. 2022 Sep 13;13:984678.

267]. Munteanu C, Schwartz B. The relationship between nutrition and the immune system. Frontiers in nutrition. 2022 Dec 8;9:1082500.

268]. Nedunchezhiyan U, Varughese I, Sun AR, Wu X, Crawford R, Prasadam I. Obesity, inflammation, and immune system in osteoarthritis. Frontiers in immunology. 2022 Jul 4;13:907750.

269]. Wiertsema SP, van Bergenhenegouwen J, Garssen J, Knippels LM. The interplay between the gut microbiome and the immune system in the context of infectious diseases throughout life and the role of nutrition in optimizing treatment strategies. Nutrients. 2021 Mar;13(3):886.

270]. Li Q, Wang Y, Sun Q, Knopf J, Herrmann M, Lin L, Jiang J, Shao C, Li P, He X, Hua F. Immune response in COVID-19: what is next?. Cell Death & Differentiation. 2022 Jun;29(6):1107-22.