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

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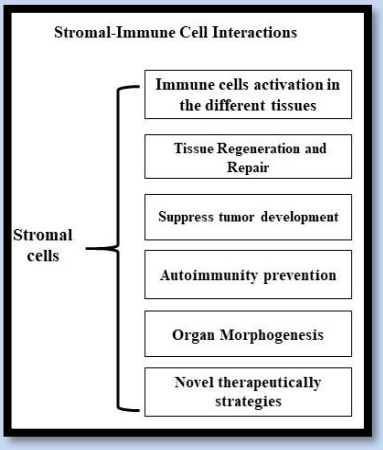
Abstract: Recent advances in immunology and histopathology have highlighted the critical role of stromal-immune cell interactions in shaping tissue-specific immune responses and influencing disease progression. Stromal cells, including fibroblasts, endothelial cells, and pericytes, once considered passive 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 many ways [4].

The precise interactions between immune and stroma cells may involve several specific receptors, ligands, and effector molecules such as cytokines or chemokines [5]. 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 disease progression across major organ systems would be a valuable endeavor [6]. To achieve this, interdisciplinary

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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]. The study aimed to explain the role of stromal cells in immunity, disease progression and histological perspective.

Materials and Methods

A review Pub-Med search was conducted to gather research on stromal cells that was published. In order to refine the review method, we used specific keywords like “Stromal cells,” “including medication,” and immune problems,” along with field tags and Boolean operators. The papers with duplicate information has been removed. The search was sorted by article kinds, including clinical trials, and restricted to publications released during the given time frame. Applying filters for particular diseases, tissue types, techniques, microenvironment, immune cells and article accessibility was another refinement step.

Results and Discussion

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 to 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. 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 [43,44].

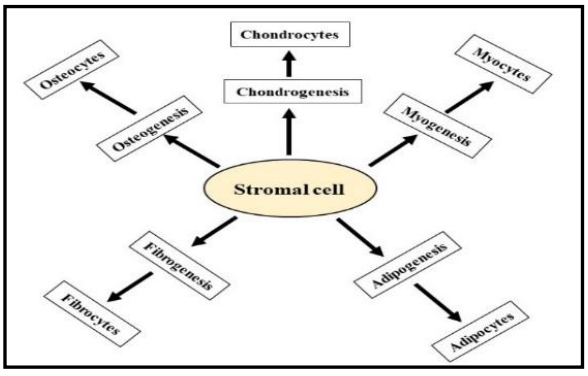

Figure (1): Stromal cells differentiation.

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 [45]. 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 [46]. 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 [47]. While fibroblasts are similar in functions and phenotypes regardless of their tissues of origin, tissues do contain specialized and location-specific fibroblasts [48]. 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 [49]. The dynamic and adaptive properties of fibroblasts are crucial for the maintenance of tissue integrity, immunity, homeostasis, and repair processes [50]. 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 [51].

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 [52]. 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 [53]. 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 [54,55].

Endothelial Cells

Inflammation involves the interaction between infiltrating cells and tissue-resident stromal cells [56]. 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 [57]. 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 [58]. 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 [59]. 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 [60,61].

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 [62,63]. 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 [64]. 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 [65,66].” 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 [67]. 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 [68].

Adipocytes

Adipose tissue is a connective tissue specialized in lipid storage in the form of triglycerides [69]. 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 [70,71]. 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 [72]. 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 [73]. 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 [74]. 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 [75].

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 [76].

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 [77]. 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 [78].

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 [79]. 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 [80]. 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 [81], 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 [82].

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 [83]. 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 [84,85].

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 [86]. Meantime, interrogating heterogeneous cellular states of macrophages or T cells revealed subtypes closely related to clinical significance, requiring further experimental validation in histological immersion [87,88].

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 [89]. 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 [90]. Tissue immune niches offer appropriate local conditions for the recruitment, maturation, maintenance, and training of immune cells [91]. 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 [92,93].

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 [94]. 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 [95]. Both B and T lymphocytes can segregate and form distinct microenvironments to orchestrate the timing and quality of immune responses [96]. 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 [97,98].

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 [99]. 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 [100]. 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, except 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 contains osteoclasts. Macrophages present in other tissues of the adult animal, however, can originate from both the yolk sac and the circulating monocytes from bone marrow [101]. 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 [102].

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 [103]. 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 [104,105]. 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 [106,107]. 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 [108]. 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 [109].

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 [110]. 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 [111]. 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 [112]. 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 [113].

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 [114]. 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 [115,116].

Table (2): Immune cells and their roles.

Cells types	Diseases	Function	references
T cells	Cancer	Regulate local tissue-specific immunity activities	[83]
B cells	Tissue injury	Anti-tumor immunity	[97,98]
Macrophages	Many diseases: atherosclerosis, diabetes, asthma, pulmonary fibrosis, neurodegenerative disorders, cancer	tissue homeostasis and immune responses	[102]
Dendritic cells	Inflamed tissue	promote effector T-cell proliferation	[110]

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 [117]. 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 [118]. 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 [119]. Stromal cells include both structural cells and a large number of different defined and undefined cellular subtypes with profound and diverse immune-related functions [31]. 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 [120]. 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 [121].

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 [122]. 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 [123]. 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 [124].

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 [125]. 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 [126].

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 [127].

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 [128,129].

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 [130]. 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 [131]. 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 [132].

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 [133]. 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 [134]. 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 [135].

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 [136]. 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 [137,138].

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 [139]. 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 [140,141].

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.

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