Received: 15 March 2021 | Revised: 28 April 2021 | Accepted: 28 April 2021

DOI: 10.1111/imr.12972

Immunological Reviews WILEY

INVITED REVIEW

INVITED REVIEW THEMED ISSUE

Fibroblasts as confederates of the immune system

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Funding information
Fritz–Thyssen–Stiftung, Grant/Award Number: 2016-01277; Human Frontier Science Program Career Development Award, Grant/Award Number: CDA00017/2016; Deutsche Forschungsgemeinschaft, Grant/Award Number: RI 2787/1-1 AOBJ: 628819; European Research Council Consolidator Grant, Grant/Award Number: ERC-CoG 819933; Else-Kröner-Fresenius-Stiftung, Grant/Award Number: 2016_A21

Abstract

Fibroblastic stromal cells are as diverse, in origin and function, as the niches they fashion in the mammalian body. This cellular variety impacts the spectrum of responses elicited by the immune system. Fibroblast influence on the immune system keeps evolving our perspective on fibroblast roles and functions beyond just a passive structural part of organs. This review discusses the foundations of fibroblastic stromal-immune crosstalk, under the scope of stromal heterogeneity as a basis for tissue-specific tutoring of the immune system. Focusing on the skin as a relevant immunological organ, we detail the complex interactions between distinct fibroblast populations and immune cells that occur during homeostasis, injury repair, scarring, and disease. We further review the relevance of fibroblastic stromal cell heterogeneity and how this heterogeneity is central to regulate the immune system from its inception during embryonic development into adulthood.

KEYWORDS
development, extracellular matrix, fibroblast, immunological niche, scarring, skin, stromal cell, wound healing

1 | INTRODUCTION

"Stromal" cell refers to the cellular component that form and maintain the structural parts of an organ, whereas parenchymal cells perform the specific organ function. Stromal cells, such as fibroblasts, have traditionally been considered as quiescent cells that primarily function to make extracellular matrices. Relevant in the clinic, these cells contribute to excessive connective tissue formation during injury repair, cancer, and fibrosis. However, these dedicated cells, and the niches they create, also orchestrate immunological functions by influencing the differentiation, movement, and activation of immune cells. Recent genetic lineage-tracing and single-cell RNA sequencing studies highlight the diversity of stromal cell populations in tissues and revealed how eclectic stromal cells orchestrate the diversity of immunological functions.

These days, fibroblasts are no longer considered as mere structural components of organs but as dynamic participants in immune processes. We discuss four major mechanisms by which fibroblasts and immune cells interact: (a) paracrine signaling via cytokine and chemokine secretion, (b) direct priming via juxtacrine interactions, and (c) behavioral modulation through extracellular matrix remodeling. Finally, and more recently described, (d) transfer or mobilization of extracellular matrix microenvironments. In the following sections, we review the impact of these four modes of interaction between distinct fibroblast populations and immune cells during homeostasis, injury repair, scarring, and disease in the mammalian skin. Finally, we discuss the origins, of these and other stromal lineages, and their

This article is part of a series of reviews covering Immunological functions of fibroblasts in human health and disease appearing in Volume 302 of Immunological Reviews.

close association with the immune system in an array of organs during development and adulthood.

2 | SKIN STROMA AS AN IMMUNOLOGICAL NICHE IN HOMEOSTASIS

The skin is the first line of contact with the external environment and its homeostasis relies on complex interactions between skin resident fibroblasts and immune cells. The epidermis, considered as the parenchyma of the skin, forms a stratified epithelium of stacked keratinocytes in a gradient of differentiation states. In the *stratum basale*, basal keratinocytes and resident immune Langerhans and T cells dwell above a basement membrane that separates the epidermis from the underlying dermis.[1]

The dermis below further subdivides into interconnected stromal compartments. Directly under the epidermis, there is a thinner and more cellularly dense layer named papillary dermis that contains *papillary fibroblasts*. Underneath, the thicker and matrix-denser reticular dermis hosts *reticular fibroblasts* and skin appendages such as sebaceous glands and hair follicles. Two merging connective tissue layers below, known as superficial and deep fascia, attach the skin to the musculoskeletal system. These layers accommodate adipocytes, blood vessels, nerves, and *fascia fibroblasts*. In addition to fibroblasts, *pericytes* coating capillaries are another stromal component in the skin. Coinhabiting and closely interacting with these stromal populations are immune cells such as dermal dendritic cells, resident macrophages, mast cells, and lymphocytes.[1] The current section describes the skin fibroblasts populations and their influence on immune cells during homeostatic processes, such as hair growth, antigen surveillance, and cell recruitment.

2.1 | Papillary fibroblasts interact with perifollicular macrophages during the hair cycle

Murine papillary fibroblasts promote hair follicle organogenesis and growth by giving rise to hair-supportive populations such as dermal papilla, dermal sheath, and arrector pili cells.[2] By action of these dedicated mesenchymal cells, hair follicles cycle through rest, growth, and regression phases named telogen, anagen, and catagen, respectively.[3] During this process, several immune cells organize along the hair follicle.[4,5] Perifollicular macrophages subsets have diverse effects on the hair cycle[6,7] and alternate their presence depending on the hair cycle phase.[6,8,9] Interestingly, both macrophage depletion and inhibition,[9,10] and macrophage presence stimulate growth,[11,12] indicating specialized subsets that promote hair growth (anagen) or regression (catagen). Similar to perifollicular macrophages, papillary fibroblast subpopulations also alternate during hair cycle phases suggesting a close cellular relation between papillary fibroblasts and perifollicular macrophages.[13] Lymphocyte function-associated antigen 1 (LFA1) receptor on perifollicular macrophages regulates macrophage functions by interacting with its ligand, intercellular adhesion molecule 1 (Icam1), on dermal fibroblasts. Deletion of Icam1 results in spontaneous hair regression,[14] suggesting an indirect alteration in perifollicular macrophage activity. LFA1-Icam1 interaction promotes survival and cell-cell adhesion,[15,16] suggesting that papillary fibroblasts participate in the regulation of perifollicular macrophage homing and survival during hair cycle (Figure 1).

2.2 | Fibroblasts-produced stroma impact antigen surveillance

Beneficial commensals defend skin from pathological microorganisms.[17] To enable such defense, the immune system must adapt to specific and stable commensal communities.[18] $CD4^+$ regulatory T cells (Tregs) home into the skin perinatally to mediate immunotolerance.[19] Such immunotolerance is indirectly regulated by the extracellular matrix produced by papillary fibroblasts.

Cutaneous Tregs highly express integrin alpha 2 (Itga2) and its blockage alters migration of T cells in vitro.[20,21] Itga2 forms a receptor for type I collagens,[22,23] the most prominent extracellular matrix component of the skin produced by both reticular and papillary fibroblast.[24,25] Besides migration, type I collagens also enhance proliferation of skin Tregs[26] via Itga2.[27]

The glycosaminoglycan, hyaluronan, is another prominent extracellular matrix component that is particularly enriched in the papillary dermis,[28] with which immune cells interact via its receptor CD44. Similar to type I collagens, CD44 function or hyaluronan presence in cultures enhance T-cell migration.[21]

Papillary fibroblasts also produce the extracellular matrix protein tenascin C (Tnc),[29] which induces a stupor state on T cells without affecting their antigen recognition function.[30] In this way, papillary fibroblasts produce an environment that influences Treg migration, proliferation, and activity to ensure immunotolerance.

Commensal and pathological microorganisms are also controlled via antigen surveillance by cutaneous antigen-presenting cells,[31] including dermal dendritic cells and epidermal-embedded Langerhans cells. Upon antigen processing, these cells must traverse the skin stroma into the draining lymph nodes to prime naïve T cells and elicit specific responses.[32]

Fibroblasts promote this mobilization in Langerhans cells and other leukocytes in culture.[33,34] This migration is regulated via activation of the C-X-C chemokine receptor type 4 (Cxcr4) by the C-X-C motif chemokine 12 (Cxcl12),[35] which is expressed by both reticular and papillary fibroblasts.[36,37]

The skin stromal niches also physically influence the migration of antigen-presenting cells. Langerhans cells, being embedded in the epidermis, must traverse into the dermis via pores in the basement membrane[38] aided by the interaction of integrin alpha 6 (Itga6) with laminins (LAMs) in the basement membrane.[39-41] Blocking this interaction reduces Langerhans cells migration into draining lymph nodes.[42] LAMs and other basement membrane

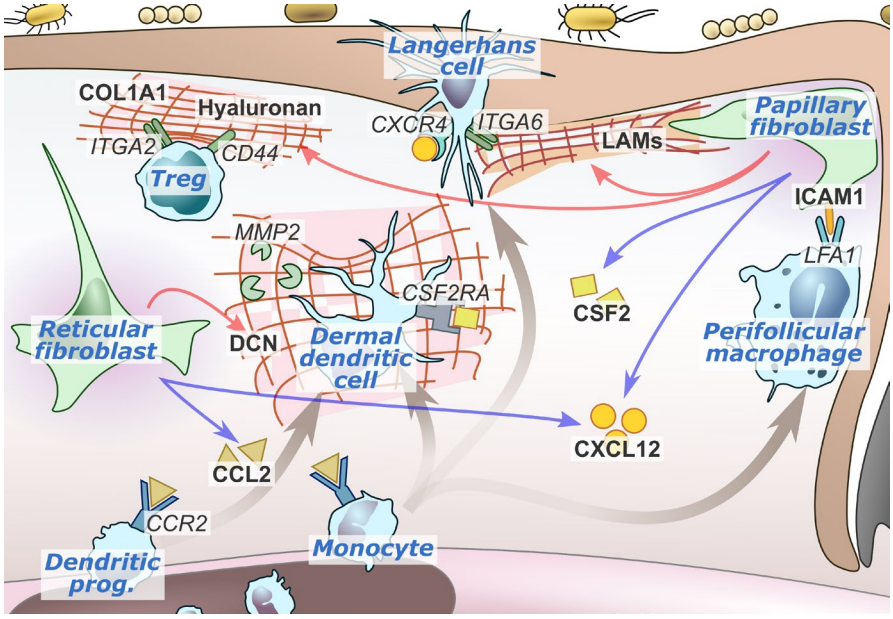

FIGURE 1 Stromal-immune interactions in the healthy skin. Papillary fibroblasts regulate hair growth by modulating the function of perifollicular macrophages via Icam1 juxtacrine interactions. Papillary fibroblasts also generate the hyaluronan-rich papillary dermis stroma that adheres to Tregs that are responsible for immunotolerance. The LAMs-rich pores in the epidermal basement membrane, also produced by papillary fibroblasts, indirectly mediate the migration of Langerhans cells in charge of external antigen surveillance. Migration of Langerhans cells is directly stimulated by Cxcl12, which is secreted by papillary and reticular fibroblasts. Reticular fibroblasts recruit monocytes and dendritic progenitors by secreting Ccl2. The recruited cells then, mediated by papillary and reticular fibroblasts, differentiate into dermal dendritic cells, macrophages, and Langerhans cells. Stromal-produced ligands and extracellular matrix proteins are in bold and connected by blue and red arrows, respectively. Immune cell-expressed receptors are in italics. Differentiation trajectories are depicted with graded brown arrows

components are produced by papillary fibroblasts,[43,44] indicating that papillary fibroblasts may control and regulate the migration of antigen-presenting cells from the skin to draining lymph nodes (Figure 1).

2.3 | Fibroblasts mediate recruitment and differentiation of immune progenitors

The replenishment of skin resident immune cells is also mediated by the action of skin fibroblasts. Bone marrow-derived monocytes that infiltrate the skin stroma differentiate into macrophages,[45,46] monocyte-derived dendritic cells,[47] or monocyte-derived Langerhans cells.[45,48]

Fibroblast recruit circulating progenitors via secretion of the chemokine (C-C motif) ligand 2 (Ccl2),[49,50] a powerful chemoattractant for bone marrow-derived monocytes and dendritic cell precursors.[51] Monocyte infiltration initiates in deeper layers of the skin,[52] suggesting that reticular and fascia fibroblasts are the primary agents that engage and recruit monocytes.

Once monocytes differentiate into resident macrophages in the reticular dermis, the proteoglycan decorin[25] promotes their adhesion, quiescence, and survival.[53]

Conversely, bone marrow-derived dendritic cell precursors differentiate into mature dendritic cells in the presence of the colony-stimulating factor 2 (Csf2),[54] which is preferentially expressed by papillary fibroblasts.[55] This suggests that the fibroblast-produced compartmentalized niches, namely papillary and reticular dermis, differentially influence monocyte and dendritic cells fate in the skin.

3 | WOUND FIBROBLAST ARISE DURING WOUND HEALING AND SCARRING

Skin repair in response to injury comprises a complex collection of cellular interactions from resident and recruited cells that often end up in patches of fibrous tissue that replace the damaged skin. Unbalance in these interactions can result in chronic non-healing wounds, or oppositely, in pathological overwhelming scars.

The wound healing and scarring processes are classically divided into three temporally distinct phases with defined cellular activities.[1] In the hemostasis and inflammatory phase, that follows injury, the platelet-mediated clotting cascade seals the open wound and prevents bleeding. Then on, inflammatory cells rush in via signals from resident cells at the damaged site to clear debris and remove pathogens. Following the inflammatory phase, a proliferation phase ensues where new connective tissue develops. A provisional stroma is formed where new blood vessels restore the tissue oxygen supply while re-epithelialization of the damaged epidermis occurs. During the last remodeling phase, the provisional stroma matures into a fibrous tissue or scar with a limited tensile

strength that lacks skin appendages such as hair follicles and sweat glands (Figure 2).

Throughout these different phases, stromal communities constantly regulate immune activity through a specialized population of fibroblasts termed as *wound fibroblasts*. This transient fibroblast population appears at injured areas where they communicate with immune cells to orchestrate the wound response and scar formation. The cellular origins of wound fibroblasts have been a matter of considerable debate. Lineage-tracing methods have shown that wound fibroblasts are mostly derived from reticular and fascia but not papillary fibroblasts.[2,56,57] More recently, studies from our group, using anatomical fate mapping, revealed that fascia fibroblasts are the major contributor to wound fibroblasts.[58-60] Other studies have suggested additional, non-stromal, and sources. For example, fibrocyte is a term given to bone marrow-derived monocytic cells with transcriptional fibroblast-like traits, whose presence is associated with fibrosis and chronic inflammation.[61,62] The idea of a cell subset with dual immune and stromal features is reinforced by recent single-cell RNA sequencing studies showing that some wound fibroblasts express myeloid markers.[63,64] Additional studies indicate that subcutaneous adipocytes could serve as yet another source of wound fibroblasts.[65-67] These apparent cross-lineage interconversions have been deduced primarily from morphological and marker expression changes, definitive proof of interconversion between myeloid- and adipocyte-derived cells to wound fibroblasts await more rigorous studies.

3.1 | Wound fibroblasts modulate immune responses

Regardless of their genealogical origins, wound fibroblasts activate immune cells during the inflammatory phase by producing pro-inflammatory cytokines, such as tumor necrosis factor, interferon gamma, and interleukins 6 and 12. These fibroblasts also release a wide range of C–C and C–X–C chemokines, to further recruit immune cells to injury sites, including Cxcl1 and Cxcl8 for neutrophils, Ccl1, Ccl2, Ccl3, and Cxcl10 for monocytes and macrophages, and Ccl5, Cxcl12, and Cx3cl1 for T-cell recruitment. Wound fibroblasts also secret hematopoietic growth factors such as colony-stimulating factor 1 (Csf1), Csf2, and Csf3, which further fortifies the immune response.[68]

Wound fibroblasts also modulate immune cell behavior, retention, and survival in wounds sites via juxtacrine interactions and by upregulating surface adhesion molecules in response to the pro-inflammatory environment in wounds. For example, the elevated expression of Icam1 and vascular cell adhesion molecule 1 (Vcam1) on fibroblasts promotes fibroblasts-monocyte and fibroblast-macrophage interactions.[69,70]

The higher Icam1 expression on wound fibroblasts further increases the chance of wound fibroblasts contacting immature dendritic cells expressing the Icam1 binding partner, integrin beta 2 (Itgb2). Wound fibroblasts also express costimulatory molecules such as CD40,[71] which interact with its ligand CD154 (CD40L) expressed on immature dendritic cells. The enhanced Icam1-Itgb2 and CD40-CD154 co-stimulation induce dendritic cell maturation and higher T-cell activation potency. With this mechanism, wound fibroblasts act as potent inducer of dendritic cell differentiation and function during their trafficking from skin to lymph nodes.[72]

Wound fibroblasts also influence the movement and activation of inflammatory cells in wounds by modifying their surrounding niche by producing matrix-degrading enzymes such as matrix metalloproteinases 2 and 9, and lysyl oxidase, thus, loosening the extracellular matrix and facilitating the invasion of inflammatory cells to injury sites. Furthermore, wound fibroblasts sense the changing interstitial flow and fluid pressure caused by the inflammatory edema and respond by modulating the physical properties of the immune microenvironment, including rigidity, porosity, elasticity, and viscosity,[73] making it more immunologically active (Figure 3).

In addition to wound fibroblasts, other stromal populations also mediate immune cell behavior during the inflammatory phase. Skin

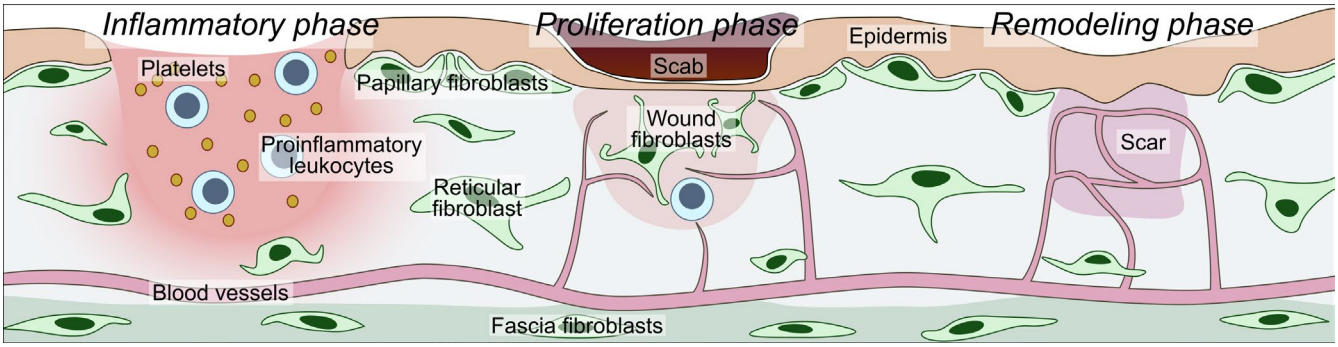

FIGURE 2 The wound healing and scarring process. The wound healing divides into three general phases, during which specific cellular activities occur: (1) immediately after an injury and during the hemostasis and inflammatory phase, activated platelets trigger the clotting cascade to prevent blood loss. Shortly after, inflammatory leukocytes rush into the injury site to remove tissue debris and pathogens. (2) During the following proliferation phase, wound fibroblasts restore the dermal extracellular matrix while angiogenesis and re-epithelialization restore tissue homeostasis. Wound fibroblasts derive from several sources, including fascia and reticular fibroblasts. (3) During the last remodeling phase, myofibroblasts continue to deposit extracellular material that ends up generating scar tissue devoid of skin appendages, low on cellular content, and with a deprecated elasticity

stroma is lined with a dense network of blood and lymphatic vessels, which form migratory circuits for immune cells during inflammation and wound repair. Pericytes are stromal cells with smooth-muscle characteristics that encase the microvasculature and small blood vessels. Due to this intimate interaction with the endothelium, pericytes are critical mediators of the migration of circulating immune cells. Similar to wound fibroblasts, pericytes recruit several immune cells such as T cells, natural killer cells, neutrophils, and monocytes/macrophages via secretion of several cyto/chemokines, such as Cxcl10, Cxcl1, Ccl2, and via overexpression of adhesion molecules such as Icam1 and Vcam1.[74]

3.2 | Wound fibroblasts mobilize immunologically active tissue

In addition to directly interacting with immune cells via paracrine/juxtacrine factors and indirectly modifying the surrounding immune microenvironment, we have recently described a novel way by which wound fibroblasts impact on the immune cell activity during repair. In this new process, fibroblasts physically translocate immunologically active tissue containing embedded immune cells into injury sites. In response to deep injuries, fascia fibroblasts migrate collectively upwards into wounds[59,60] steering the surrounding extracellular matrix and the diverse range of embedded immune cells within, including fascia tissue-resident monocytes and macrophages.[58] By applying such a tissue steering mechanism, stromal cells ensure the presence of relevant immune cells where they are most needed.

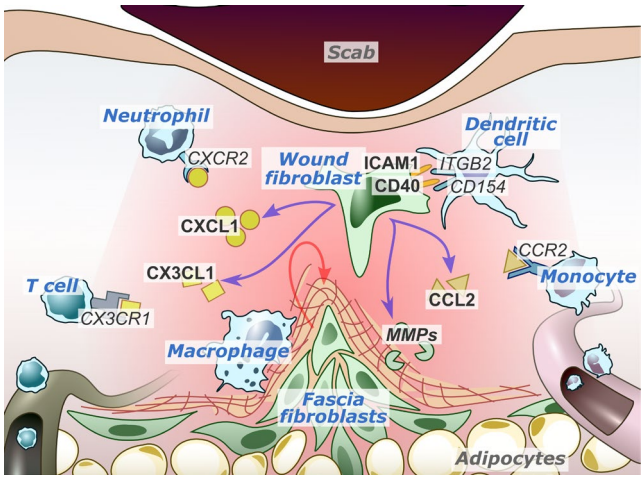

FIGURE 3 Wound fibroblasts orchestrate the immune response during wound healing. Wound fibroblasts regulate immune cell functions directly by (1) releasing soluble factors, such as Cxcl1, Cx3cl1, and Ccl2, that attract inflammatory cells. (2) Juxtacrine interactions, via Icam1 and CD40 expression, activate dendritic cells. (3) Mobilizing immunologically active extracellular matrix from the fascia. and (4) remodeling the wound stroma via MMPs secretion to allow immune cell infiltration. Stromal-produced ligands and extracellular matrix proteins are in bold and connected by blue and red arrows, respectively. Immune cell-expressed receptors are in italics

The immunologically active fascia extracellular matrix is rich in hyaluronan, fibronectin 1 (Fn1), and elastin, all of which regulate immune cell trafficking and function. For instance, the hyaluronan receptor, CD44, is expressed by monocytes and macrophages and hyaluronan recognition plays a role in macrophage polarization during wound healing.[75,76]

The fascia connective tissue further instructs immune response by modulation of its biomechanical properties during injury. For example, manipulation of the fascia system by compressing and stretching the subcutaneous fascia is commonly used by physiotherapists to resolve inflammation and manage pain. In a fascia inflammation-induced mouse model, manipulation of the fascia system practices reduced neutrophil counts and increased levels of interleukin 4 and transforming growth factor-beta (TGF-beta), pointing to an anti-inflammatory effect by modulating fascia connective tissue biomechanics.[77] Future work in this area will reveal the clinical relevance of how changing fascia tissue biomechanics can affect its immunological activity and the pivotal interactions between stromal and immune populations, to support wound repair and regeneration (Figure 3).

3.3 | Immune dysregulation by pathological fibroblasts

When the reciprocal crosstalk between wound fibroblasts and inflammatory cells is not resolved properly during the proliferation phase of wound healing, it leads to a vicious cycle that switches acute inflammation into a chronic persistent inflammation, which results in pathological scarring and fibrosis.

Several factors in stromal cells regulate the acute-to-chronic transition of inflammation. Adhesion molecules, such as Icam1, on wound fibroblasts, mediate interactions with leukocytes during the normal wound-healing process. However, the persistent overexpression of Icam1 leads to a skin fibrotic disorder named scleroderma, both in mutant mice[78] and human patients.[79] The high expression of Icam1 leads to an abnormal enhanced and persistent interaction between *scleroderma fibroblasts* and leukocytes such as T cells[78] and mast cells.[80] This enhanced cell interaction results in further activation of both scleroderma fibroblasts and associated leukocytes, thus amplifying the fibrotic response. Consistent with this, Icam1 deficiency significantly suppressed development of scleroderma. Compared to normal fibroblasts, scleroderma fibroblasts also adhere strongly to extracellular matrix components, such as LAMs, Fn1, and collagens I, IV, and VI. This strong adherence enhances matrix stiffens and augments the recruitment and activation of leukocytes.

Another trigger of chronic inflammation is the local mechanical forces that fibroblasts exert on connective tissues, which leads to tissue contraction. For example, large area burn scars, hypertrophic scars, and keloids are very often associated with both persistent inflammation and skin contracture.[81] Intriguingly, one of the surgical techniques used after removal of keloids is the use of subcutaneous/

fascial tensile reduction sutures. The suturing of fascia, in addition to dermal and superficial sutures, reduces tension on the edges of the wound. This procedure significantly decreases the inflammation in the skin and prevents the resurgence of pathological scars.[81]

Another example where enhanced crosstalk between fibroblasts and immune cells drives pathologic scars occurs in Dupuytren's disease, which is a localized fibrotic condition of the connective tissue underneath the palm and fingers that leads to contractures in the fingers. In this disease, overexpression of Icam1 is also involved in the progression of contractures and fibrosis. Using single-cell RNA sequencing, Layton and colleagues identified a functionally distinct *ICAM1^{+} fibroblast* subset isolated from Dupuytren's nodules across multiple patients. ICAM1^{+} fibroblasts also express inflammatory chemokines such as interleukin 6 (IL6), indicating enhanced leukocyte chemotaxis potential.[82] The authors proposed *ICAM1^{+}IL-6^{High} fibroblasts* as the key stromal population that sustain inflammation and stromal activation leading to fibrosis progression in Dupuytren's disease.

Dysregulation of cytokine and chemokine release from wound fibroblasts is also implicated in the pathogenesis of chronic inflammatory skin diseases, such as psoriasis and atopic dermatitis. As compared to healthy fibroblasts, fibroblasts from psoriatic plaques are deficient in the prostaglandin E2 signaling pathway, which is important for the resolution of inflammation. The reduced release of prostaglandin E2 from *psoriatic fibroblasts* leads to the polarization of macrophages toward a pro-inflammatory phenotype.[83] Using single-cell RNA sequencing, He and colleagues recently identified a *psoriatic fibroblast* subset that was unique to skin lesions of atopic dermatitis, featured with an over-expressed profile of CCL2 and CCL19 cytokines. In consequence, the crosstalk between fibroblasts and dendritic cells that express the CCL19 receptor, CCR7, is augmented. The dysregulated dendritic cell behavior results in increased T-cell migration and polarization toward type 2 inflammation in atopic dermatitis.[84]

Similarly, in rheumatoid arthritis, single-cell RNA sequencing identified a disease-associated *synovial fibroblast* subset. This synovial fibroblast subset is characterized by cadherin 11 (CDH11) expression and is threefold more abundant in rheumatoid arthritis than in osteoarthritis. These fibroblasts localize to the perivascular zone in inflamed synovium, secrete pro-inflammatory cytokines, and maintain the chronic inflammation that leads to joint destruction in arthritis.[85] CDH11-mediated adhesion between synovial fibroblasts increases their migration and invasion. This synergizes the activation of more fibroblasts to produce matrix metalloproteinases, cytokines, and chemokines that promote chronic inflammation.

Pathological fibroblasts are also central in the progression of tumors. In analogy to wound fibroblasts,[86,87] *cancer-associated fibroblasts* are key immune modulators in skin tumors. Increasing evidence suggests that a reciprocal feedback loop between cancer-associated fibroblasts and leukocytes is essential to protect the tumor from the immune surveillance.[88] In general, cancer-associated fibroblasts directly dampen immune cell recruitment and effector functions by cytokine/chemokine/growth factor secretion and cell-cell interaction, and indirectly suppress immune cell trafficking and polarization via extracellular matrix remodeling and vascular permeability.[89] Cancer-associated fibroblasts, therefore, hijack and modify the mechanisms wound fibroblasts use during the normal wound-healing process to regulate the tumor niche. In sarcomas, such as in *dermatofibrosarcoma protuberans*, cancer-associated fibroblasts directly suppress the recruitment and activation of leukocytes by secreting a characteristic cocktail of inhibitory factors.[90] Whereas in the case of melanoma, basal cell carcinoma, and squamous cell carcinoma, cancer-associated fibroblasts change their basic glycogen metabolism to create a competitive metabolic microenvironment that suppresses the immune cell functions but supports oxidative cancer cells.[91]

Evidently, interactions between stromal populations and immune cells are bi-directional and immune cells greatly affect and shape the function of various fibroblast communities. For example, TGF-beta and the type 2 cytokines are well-known immunological drivers of connective tissue matrix deposition and skin fibrosis.[92] Also, it has recently been shown that skin Tregs are essential in suppressing fibroblast activation and dermal fibrosis.[93] For a more detailed description of the instructions from immune cells to stromal populations, the reader is referred to several excellent reviews on the subject.[94,95]

4 | STROMAL AND IMMUNE INTERACTIONS BEYOND SCARRING

For each individual organ niche, stromal cells produce specific extracellular matrices rich in macromolecules, such as collagen and elastic fibers that confer specific biochemical and biomechanical traits. Such dedicated microenvironments, sustained by stromal cells, intimately influence the function of immunological agents. In this section, we briefly describe the developmental origins of the mammalian stromal lineages and provide examples of stromal niches that regulate the behavior of immune cells.

4.1 | Origins of stromal cell populations

Stromal populations are highly conserved in mammals and are almost identical between human and mouse, which is thus the natural model for stromal cells studies. Genetic lineage-tracing methods[96] are particularly informative to trace stromal cell origins in diverse mouse organs. With these systems, specific cell populations can be tagged with reporter proteins, such as green fluorescent protein, Lac-Z. The tagging can be directed to specific cell populations by using cre-recombinase driver lines under promoters of genes specifically expressed in the target cells. An additional temporal control can be obtained by using chemically triggerable recombinase lines, thus allowing the controlled tagging of cells in time and space. By tracing the location and phenotypical changes of the resulting lineage of past tagged cells, the genealogical cell tree of tissues can be inferred.

Using this technology, the origin of virtually all stromal populations of internal organs traces back to a single source from the coelomic epithelium during development. The coelomic epithelial cells form the mesothelial linings of internal organs such as the epicardium of the heart, the pleura of lungs, the peritoneum, and the linings of kidneys and liver. The coelomic epithelial cells and the mesothelial linings specifically express the mesothelin (MSLN) gene. Lineage tracing of $MSLN^+$ cells, tagged during mid-term development and observed in late fetal stages, proved that the vast majority of stromal populations of internal organs originated from these progenitors. Furthermore, $MSLN^+$ mesothelial cells keep contributing to the stromal cell pool perinatally and modestly in adult stages.[97]

Naturally, the regional specification on the mesothelial precursors results in the kaleidoscope of stromal populations observed in different organs. All stromal components in the heart originate from mesothelial cells of the epicardium expressing the transcription factor 21. In contrast, Wilms tumor 1 homolog-expressing pleural and peritoneal mesothelium give rise to lung and liver stromal populations, respectively.[98-100]

The minimal contribution of mesothelial cells to the stromal pool in adult stages suggests that, after this regional specification occurs, each population has the capacity to self-replenish.[100] Additionally, organs might harbor progenitors that continuously replenish the stromal populations. Such is the case of the spleen, where a multipotent progenitor gives rise to all stromal populations of the young adult spleen.[101]

Due to its ability to differentiate into stromal lineages, the mesothelium also participates in inflammatory processes and influence immune cell behavior.[102] Under injury conditions, mesothelial cells secrete chemokines that recruit neutrophils, monocytes, and macrophages.[103-105] This mediates the transmigration of peritoneal macrophages into internal organs.[106] In the peritoneum, patches of stromal cells secrete neutrophil-attracting chemokines and generate lymphoid aggregates that remove peritoneal contaminants during peritonitis. Expression of the mesothelial marker Pdpn and single-cell RNA sequencing placed the stromal population in a mesothelial lineage.[107]

Damaging mesothelial linings, after injuries such as thoracic surgery, often results in surgical adhesions across organ surfaces. Postsurgical adhesions are dense connective tissue bridges populated by fibroblast-like stromal cells. Complementary lineage-tracing methods prove that the stromal cells in postsurgical adhesion originate from peritoneal Msln- and endothelial protein C receptor-expressing mesothelial cells.[108,109] During this mesothelial-to-mesenchymal transition, mesothelial cells actively recruit neutrophils that produce neutrophil extracellular traps, which further contributes to the pathological scar formation between mesothelial linings of internal organs.[103]

Skin stromal cells originate from a separate embryonic lineage from that of internal organ stroma. This external barrier contains stromal populations that originate from distinct embryonic lineages. For example, back-skin fibroblasts originate from somitic progenitors expressing the engrailed 1 (En1) gene, while ventral and limb skin populations originate from paired related homeobox 1 (Prrx1)-expressing progenitors. Although these two lineages comprise the vast majority of stromal populations in the adult skin, complementary lineages persist in low numbers. These En1- and Prrx1-naïve fibroblast lineages (ENFs and PNFs respectively), which never expressed either gene, thrive during mid-to-late development and progressively get replaced by the En1-past and Prrx1-positive fibroblast lineages (EPFs and PPFs, respectively).[110,111] Functional experiments after transplanting either EPFs or ENFs showed that the abundant EPF cells possess an intrinsic capacity to produce scar tissue, while the ENFs promoted the generation of healthy normal stroma,[110,112] pointing out the need to further explore and identify additional and physiological heterogeneous stromal lineages. These observations also indicate that organs undergo dramatic changes in stromal cell composition during development. In the skin, this lineage exchange of regenerative ENFs to scarring EPFs leads to a phenotypic shift in the skin's response to injury, namely from regeneration in development to scarring in adults.

The 3rd major stromal source derives from neural crest-derivatives that contributes to the stromal populations in craniofacial organs, such as the oral mucosa and brain stroma.[113,114] Interestingly, heterotopic transplantation of oral mucosa fibroblast into the skin stroma, and vice versa, had no influence on the intrinsic qualities of these populations, as they generated their native tissue architectures even when placed in a new environment.[110] This indicates that each individual stroma microenvironment is the direct result of their resident stromal population. And is not the environment that dictates the behavior of the resident stromal cells.

The advent of rapidly evolving single-cell-omics, aided by the promptly appearing algorithms dedicated in predicting intercellular interactions, has unveiled an unexpected fibroblast diversity. For instance, single-cell sequencing of human hearts revealed six cardiac fibroblast populations that are differently distributed between the atria and ventricles and likely possess different fibrotic potential.[115] Interestingly, one such population was predicted to interact with immune cells via secretion of the CD74-ligand, macrophage migration inhibitory factor, highlighting the potential of single-cell sequencing to uncover details of stromal-immune interactions in several biological set ups.

The combination of these novel informative methods with lineage-tracing techniques will become the new gold standard when studying the origin and heterogeneity of stromal populations as well as to reveal their specialized interaction mechanisms with immune cells.

4.2 | Stromal niche for early immune development

Stromal cells are central to the immune system from its inception during development. The cells that give rise to all blood cells, the hematopoietic stem and progenitor cells (HSPCs), endure a journey along a variety of embryonic niches before allocating into their final residence in the marrow of long bones. Primordial HSPCs surge from the “hemogenic endothelium” in the Aorta-Gonad-Mesonephros

region. In humans, the HSPCs appear between day 27 and 40 after fertilization; and at 10-14 days post-coitum in mouse embryos.[116-118] HSPCs then migrate into the fetal liver, in which they settle until late fetal stages, when they migrate into the bone marrow and secondary lymphoid organs such as spleen and lymph nodes. At each step, HSPCs experience pivotal interactions with multiple stromal lineages that facilitate their migration, survival, and differentiation.

Stromal cells regulate HSPCs in the Aorta-Gonad-Mesonephros region of the mouse embryo through various interaction mechanisms. In the Aorta-Gonad-Mesonephros region, HSPCs interact with a specific class of stromal cells expressing aminopeptidase N (Anpep) and the lymphocyte antigen 6A (Ly6a). These particular, *Ly6a^{+}Anpep^{+} stromal cells* promote long-term maintenance of HSPCs[119-123] via the production of Cxcl12 cytokine and Kit ligand. The membrane-bound Kit ligand on stromal cells binds and activates the tyrosine kinase receptor Kit on HSPCs triggering a juxtacrine signal that regulates proliferation through the mitogen-activated protein kinase pathway.[124] The stromal-secreted Ccxl12 binds to Cxcr4 on HSPCs and promotes their homing into, and maintenance in, the Aorta-Gonad-Mesonephros region.[125,126] An additional stroma-immune interaction mechanism in the Aorta-Gonad-Mesonephros region involves the biosynthesis of hyaluronan.[127,128] When secreted by stromal cells, hyaluronan interacts with the CD44 receptor on HSPCs enabling their mobilization to their niches.[129] Indeed, CD44 expression marks the early hemogenic cells in the Aorta-Gonad-Mesonephros region and blocking its interaction with hyaluronan decreases HSPC generation.[130] Accordingly, degradation of hyaluronan prevents HSPCs forming from human embryonic stem cells.[131] In summary, stromal cells influence the early development, proliferation, and passage of HSPC through the Aorta-Gonad-Mesonephros region through three separate mechanisms: via direct cell-cell binding via Kit ligand, through secretion of the cytokine Cxcl12, and thirdly by generating a hyaluronan-rich niche in the Aorta-Gonad-Mesonephros (Figure 4A).

4.3 | Mesothelial-derived stromal cells regulate hematopoiesis in the fetal liver

Stromal lineages continue to instruct HSPCs activity in the fetal liver during mid-gestation (12 to 16 days post-coitum in mice).[132] Once in the liver, hematopoiesis is supported by hepatic pericytes called *hepatic stellate cells*,[133] which derive from mesothelium progenitors.

Cxcl12 and Kit ligand mediate HSPCs homing into the fetal liver[134] and both of these factors are produced by hepatic stellate cells,[135-137] in addition to a collection of cytokines that regulate the immune cells fate.[138]

Hepatic stellate cells secrete insulin-like growth factor II (Igf2) which binds to its receptor Igf2r on HSPCs promoting their proliferation[136,139] while Igf2 reduction hampers fetal liver hematopoiesis.[140] Erythropoietin (Epo) is another cytokine secreted by hepatic stellate cells.[133,136] By signaling through its receptor (Epor) Epo triggers, the activation of several transcription factors that mediate erythroid maturation.[141] In the fetal liver, Epo deletion only prevents the appearance of terminally differentiated erythrocytes without affecting HSPCs numbers, suggesting that Epo specifically instructs the survival, proliferation, and maturation of erythroblasts.[142,143] Nonetheless, overexpression of Epor in HSPCs conferred a repopulating advantage over normal HSPCs in lethally irradiated mice,[144,145] suggesting that Epo signaling, mediated by hepatic stellate cells, enhances survival of HSPCs during their travel through the fetal liver. Similarly, Csf1 secreted by hepatic stellate cells[133,136] enhances

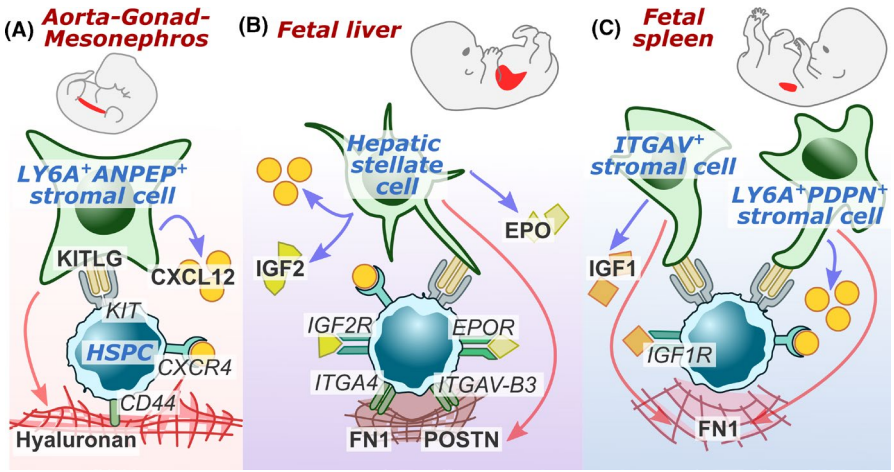

FIGURE 4 Stromal populations that accompany hematopoietic stem and progenitor cells during development. Stromal cells instruct HSPCs proliferation and long-term stemness from their inception in the (A) Aorta-Gonad-Mesonephros region, and during their passage through the (B) fetal liver and (C) fetal spleen. In the Aorta-Gonad-Mesonephros region, Ly6a^{+}Anpep^{+}stromal cells instruct HSPC through the Cxcl12 and Kit ligand cytokines, and by maintaining a hyaluronan-rich niche. In the fetal liver, hepatic stellate cells promote hematopoiesis by providing additional instructive signals, like Igf2 and Epo, in an Fn1- and Postndecorated extracellular matrix. In the fetal spleen, erythropoiesis and myelopoiesis are instructed by Itgav+and Ly6a^{+}Pdpn^{+}stromal cells by secreting Igf1 within an Fn1-enriched microenvironment. Stromal-produced ligands and extracellular matrix proteins are in bold and connected by blue and red arrows, respectively. Immune cell-expressed receptors are in italics

monocyte and macrophage progenitor proliferation through its receptor Csf1r.[146-148] Hepatic stellate cells also promote differentiation of dendritic cells and natural killer cells by secreting Csf2 and interleukin 15, respectively.[149,150]

Besides cytokine secretion, hepatic stellate cells indirectly influence immune cells by modulating their microenvironment.[151] Hepatic stellate cells produce extracellular matrix components such as Fn1, Tnc, vitronectin (Vtn), and LAMs during in the fetal liver and decrease their expression once hematopoiesis takes place in the bone marrow.[136] Fn1 supports growth of HSPCs[152] via integrin receptors. In the fetal liver, expression of heterodimers of integrin beta 1 (Itgb1) in combination with several alpha integrins isoforms mediates Fn1-based adhesion of HSPCs.[153-156] Deletion of Itgb1 severely affects the homing of HSPCs into primary lymphoid organs after mid-term development, indicating that Fn1, deposited by stromal populations like hepatic stellate cells, is important for HSPC homing into the fetal liver.[157,158] Similarly, integrin alpha 4 (Itga4) deletion severely impairs progenitor migration and differentiation, both in the fetal liver and postnatally in the primary lymphoid organs.[159] Fn1-binding receptors are clearly at the hub of many processes and a complexity of responses between stromal and immune cells. Different integrin receptors also mediate a plethora of interactions between stromal cell-derived matrix proteins and HSPCs. For example, integrin alpha V-integrin beta 3 receptor mediates VTN binding by fetal liver-derived mast cells.[160] Signals through the same receptor ensure HSPCs long-lasting stemness by interacting with the extracellular matrix component periostin, which is present in the perivascular stroma of the fetal liver.[161,162]

In summary, hepatic stellate cells utilize a plethora of soluble and extracellular proteins to influence the adhesion, proliferation, migration, stemness, and differentiation of HSPCs during their transit through the fetal liver (Figure 4B).

4.4 | Mesothelial-derived stromal cells in the fetal and adult spleen

At late fetal stages, hematopoiesis switches from the fetal liver to other organs, such as the spleen in which specialized stromal populations promote macrophage and erythrocyte differentiation.[163,164] Alike hepatic stellate cells, stromal cell populations of the spleen derive from mesothelium progenitors.[97] *Integrin alpha V$^+$ stromal cells* in the fetal spleen enhance erythropoiesis via Kit ligand and Insulin-like growth factor 1 (Igf1) production.[164] Igf1 binding to its receptor (Igf1r) itself fails to sustain growth of HSPCs but in combination with Epo and Kit ligand enhance erythropoiesis.[165] As in the fetal liver, Itgb1 deletion also affects homing into the fetal spleen[158] suggesting that its extracellular matrix ligands, for example, Fn1, play also a role in fetal spleen hematopoiesis. Fetal spleen myelopoiesis is also supported by a splenic stromal population. Studies using immortalized splenic cell lines revealed the existence of a population that supports myelopoiesis in culture.[166] Later, a comparative study of fractionated splenic stromal populations at perinatal stages identified the *Ly6a$^+$Podoplanin$^+$ (Pdpn) stromal* subpopulation as being functionally equivalent to the immortalized cell line that supports myelopoiesis.[167] Therefore, in the fetal spleen, two stromal populations regulate hematopoiesis through cytokine production and the creation of a Fn1-rich niche (Figure 4C).

In adults, the spleen becomes an antigen-presenting site for lymphocyte activation as well as a supportive organ for extramedullary hematopoiesis under stress conditions such as blood loss. To accomplish these functions, the spleen organizes in an external red pulp around an internal white pulp, where erythrocyte- and lymphocyte-related functions take place, respectively. Within these compartments, distinct stromal cells derived from a common progenitor interact and regulate the activity of immune cells.[168,169]

When extramedullary hematopoiesis ensues, *perivascular stromal cells* in the red pulp express Kit ligand and Cxcl12 to attract circulating HSPCs and promote erythropoiesis.[170,171]

Inside the white pulp, three different stromal populations segregate into "B follicle" and "T zone" compartments to regulate the interactions between naïve lymphocytes and presenting cells. Cells arriving in the T zone encounter a network of *fibroblastic reticular cells* that express Cxcl12, C-C motif ligand 19, and 21 chemokines (Ccl19 and Ccl21) as well as interleukin 7 (Il7).[172,173] Both Ccl19 and Ccl21 signal through the C-C chemokine receptor type 7 (Ccr7), and deletion, of the ligands or the receptor, severely impairs homing of T-cell lymphocytes and dendritic cells into the spleen[172-174] while Il7 binding to its receptor (Il7r) promotes survival of T cells.[173,175] Thus, fibroblastic reticular cells mediate the interaction of antigen-presenting cells with naïve T-cell lymphocytes by facilitating their homing and survival within the T zones.

A second population of splenic stromal cells, referred as *follicular dendritic cells*, secretes C-X-C motif chemokine 13 (Cxcl13).[176] Deletion of the Cxcl13 receptor, Cxcr5, impairs the transit of B cells into the B follicles,[177] highlighting the role of follicular dendritic cells to direct the migration of B cells into their specialized niches inside the spleen. Covering the B follicles and bordering the red pulp, a third stromal population, termed *marginal reticular cells*, secretes the tumor necrosis factor ligand superfamily member 11 (Tnfsf11).[178] Deletion of the Tnfsf11 receptor, Tnfrsf11a, reduces the number of B cells but not T cells in the spleen and increases the extramedullary hematopoiesis in the red pulp.[179] Marginal reticular cells thus have multiple roles in easing the transit of B cells into the B follicles and restricting erythropoiesis in the red pulp.

Besides cytokine secretion, splenic stromal cells, particularly fibroblastic reticular cells, exert their influence on the immune cell function by altering their niche.[180-182] Lymphocyte interactions with fibroblastic reticular cells stimulate the production of extracellular matrix components such as LAMs, Fn1, collagens, and Tnc, resulting in the construction of a reticulated stroma that physically limits the access of leukocytes into the white pulp.[183-185] In the red pulp, deletion of integrins that mediate the recognition to several extracellular matrix components, severely impairs HSPCs migration and extramedullary erythropoiesis.[157,159,186] At the marginal zone of the B follicles, where marginal reticular cells reside, a specialized basement

membrane composed of laminin alpha 5 promotes survival of B cells via interactions with the Itga6-Itgb1 receptor.[187] Hyaluronan present in the white pulp increases the stickiness of lymphocytes via expression of the receptor for hyaluronic acid-mediated motility or Rhamm,[188] further denoting the relevance of immune cell interaction with extracellular matrix components in the splenic stroma. Thus, specialized splenic stromal cells not only mediate tissue-specific immune cell functions in the spleen by secreting cytokines, but also generate and maintain unique extracellular matrix microenvironments that fuel these immunological processes.

4.5 | Other immuno-supportive stromal niches

Similar to splenic stromal populations, lymph nodes also possess resident stromal cells that exert a major influence on their immunological functions.[189,190] These stromal populations, collectively called *fibroblastic reticular cells*, include six to nine functionally distinct stromal cell subsets.[189,191] The origin of this plethora of stromal populations traces back to a single lineage of perivascular progenitors near the lymph node anlagen during mid-term development. These progenitors proliferate locally, generating regional clones that differentiate into multiple stromal populations.[192] As in the spleen, fibroblastic reticular cells generate a reticulated stroma in the lymph nodes[184] that works as a filtering mesh that permits the sensing of soluble antigens. During the adaptative immune response, lymph nodes expand, and the reticulated matrix becomes transiently disrupted granting access to myeloid subsets that support antigen recognition.[182]

The adult bone marrow works as the final residence of HSPCs and is the most extensively characterized stromal niche.[193] As in other stromal niches, Cxcl12 and Kit ligand exerts major influences on HSPCs in the bone marrow.[194-198] Two main sources for Cxcl12 and Kit ligand in the bone marrow include *periarteriolar pericytes*, which reside on larger blood vessels, and *perisinusoidal stromal cells*, which inhabit the smaller capillaries.[125,199-201] Periarteriolar pericytes also support the maintenance of B-cell progenitors[202] via Il7 expression[203] and, via Csf1 expression,[204] induce osteoclast differentiation to preserve endosteal niche fitness.[205] Perisinusoidal stromal cells are dedicated cytokine secretors that also produce Csf1 and Il7.[200,204,206] Recent single-cell RNA sequencing studies further expanded this stromal population heterogeneity with potentially different immune regulatory functions.[207]

Bone marrow stromal cells also regulate immune cell behavior by altering the extracellular matrix landscape within the bone marrow. Fn1, LAMs, and collagens are major components of the bone marrow stroma.[208] Receptors for Fn1 and LAMs are required for HSPCs migration from the fetal liver into the bone marrow.[209] Fn1 binding restricts proliferation of HSPCs,[210] while blocking its binding hampers the homing capacity of HSPCs[211-213] and the survival of B-cell progenitors.[214] Higher expression of the Fn1 receptors also correlates with a higher homing capacity of B-cell progenitors to the bone marrow niche,[215] indicating that the Fn1-rich niche favors B-cell progenitor sustenance. On the other hand, myeloid progenitors adhere preferably to LAMs via its receptor,[209,216] indicating that stromal cells can modulate the adhesion of different progenitors in potentially specialized lymphoid versus myeloid niches.

Mutant bone marrow stromal cells, uncapable of supporting HSPCs, downregulate several collagen genes, particularly collagen IX.[217] Analogously, collagen IX knockout mice had impaired myelopoiesis.[218] This suggested that bone marrow stromal cells produced collagen IX regulates myeloid populations. Collagens I, VI, and XIV also promote adhesion of myeloid cells,[219-222] whereas hyaluronan favors adhesion of monocytes via the CD44 receptor.[223,224] This indicates that collagen- and hyaluronan-rich niches are preferred docking sites for myeloid and monocytic progenitors, respectively.

Tnc produced by bone marrow stromal cells also supports hematopoiesis.[225] Blocking or deleting Tnc from stromal cells reduce their HSPCs-maintenance potential in culture[226,227]; conversely, removing Tnc from the bone marrow niche favors T-cell differentiation and mobilization of HSPCs.[228] Interestingly, Tnc-null mice present normal bone marrow hematopoiesis but recover poorly after myeloablation,[229] indicating that Tnc has passive and active HSPCs-regulation functions by enhancing adhesion in homeostasis and promoting proliferation under immunosuppressive conditions.

5 | FUTURE RESEARCH

In the past, most studies on stromal-immune cell interactions have been focused on stromal-produced paracrine and juxtacrine factors that instruct immune cell behavior. There are also increasing examples of matrix components, deposited by stromal cells, impacting cell physiology. This is altering the perception of these molecules from just structural components to important regulators of immunological processes. Consequently, future studies focused on the activity of immune cells will also need to consider the composition and changes in the tissue niches produced and maintained by particular stromal populations. Particularly, emerging evidence showing the capacity of stromal cells to actively mobilize immunologically active niches to sites of injury further expands the recruitment strategies implemented by stromal cells beyond chemokine secretion. We envision the discovery of similar and more diverse niche rearrangement mechanisms by stromal cells, which meaningfully impact the immune system function.

Understanding the aforementioned venues of communication with immunological agents will require a profound insight into the full heterogeneity of the stromal populations within each organ. Informative new technologies, such as single-cell RNA sequencing, have been and will continue to be fundamental to discover new stromal cell populations and potential novel forms of interaction with immune cells. Coupling these findings with genetic lineage-tracing, cell type-specific cell ablation and gene knockouts, organoids, and more complex co-culture methods will continue to enrich our knowledge on the synergy between stromal

and immune communities that occur over our lifetime and in every tissue of the human body.

These specialized stromal populations and their particular niches represent valuable candidates for directed therapies in multiple diseases. Treatments focused on altering the direct (paracrine/juxtacrine factors) or indirect (extracellular matrix composition and dynamics) venues of communication between dedicated stromal to different immune cells, to elicit a desired immune response, will have a major impact when treating cancers, fibrosis, autoimmune, and chronic diseases.

ACKNOWLEDGEMENTS

YR is supported by the Human Frontier Science Program Career Development Award (CDA00017/2016), the German Research Foundation (RI 2787/1-1 AOBJ: 628819), the Fritz–Thyssen–Stiftung (2016-01277), the Else-Kröner-Fresenius-Stiftung (2016_A21), and the European Research Council Consolidator Grant (ERC-CoG 819933).

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

D. C-G. and D. J. performed the literature research and figure preparation. YR coordinated the review's narrative.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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How to cite this article: Correa-Gallegos D, Jiang D, Rinkevich Y. Fibroblasts as confederates of the immune system. *Immunol Rev*. 2021;00:1–16. https://doi.org/10.1111/imr.12972