frontiers in Immunology

REVIEW
published: 15 May 2019
doi: 10.3389/fimmu.2019.01093

Coordination of Immune-Stroma Crosstalk by IL-6 Family Cytokines

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Stromal cells are a subject of rapidly growing immunological interest based on their ability to influence virtually all aspects of innate and adaptive immunity. Present in every bodily tissue, stromal cells complement the functions of classical immune cells by sensing pathogens and tissue damage, coordinating leukocyte recruitment and function, and promoting immune response resolution and tissue repair. These diverse roles come with a price: like classical immune cells, inappropriate stromal cell behavior can lead to various forms of pathology, including inflammatory disease, tissue fibrosis, and cancer. An important immunological function of stromal cells is to act as information relays, responding to leukocyte-derived signals and instructing leukocyte behavior in kind. In this regard, several members of the interleukin-6 (IL-6) cytokine family, including IL-6, IL-11, oncostatin M (OSM), and leukemia inhibitory factor (LIF), have gained recognition as factors that mediate crosstalk between stromal and immune cells, with diverse roles in numerous inflammatory and homeostatic processes. This review summarizes our current understanding of how IL-6 family cytokines control stromal-immune crosstalk in health and disease, and how these interactions can be leveraged for clinical benefit.

Keywords: stromal cells, cytokines, inflammation, fibrosis, immune

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Specialty section:
This article was submitted to Immunological Tolerance and Regulation, a section of the journal Frontiers in Immunology

Received: *28 February 2019*
Accepted: *29 April 2019*
Published: *15 May 2019*

Citation:
West NR (2019) Coordination of Immune-Stroma Crosstalk by IL-6 Family Cytokines. Front. Immunol. 10:1093. doi: 10.3389/fimmu.2019.01093

THE DIVERSE ROLES OF STROMAL CELLS IN IMMUNITY AND INFLAMMATION

The term "stroma" refers to the non-parenchymal components of tissues that form a supportive matrix in which parenchymal cells reside (1). While a confusingly broad array of cell types have been described as "stromal cells," in this review they are defined as non-hematopoietic, non-epithelial mesenchymal cells, including fibroblasts, myofibroblasts, bone marrow stromal cells, and the specialized fibroblast-like stromal cells of secondary lymphoid organs. Other mesenchymal populations such as endothelial cells, adipocytes, and muscle cells, while of great interest, are largely omitted from this discussion for the sake of brevity and clarity. Long considered to be mere structural entities without specialized functions, an explosion of data in the last two decades has established stromal cells as key regulators of both protective and pathological immune responses (2).

Regulation of immune function by stromal cells has been most extensively studied in the context of secondary lymphoid organs. First identified in 1992, podoplanin $(PDPN)^{+}$ fibroblastic reticular cells (FRC) form a dense reticular network in lymph nodes that facilitates leukocyte migration and antigen presentation (2–5). By producing soluble chemokines, cytokines, and other factors—such as CCL19 (C-C motif chemokine ligand 19), CCL21, and IL-7 (interleukin 7)—FRC are crucial for controlling leukocyte recruitment, survival, and proliferation. FRC-like stromal cells play similar roles in other lymphatic tissues, such as in tertiary lymphoid organs of the intestinal mucosa (6, 7).

In non-lymphoid tissues, stromal cells can exert similar effects to those of the secondary lymphoid organs by acting as scaffolds for leukocyte migration and by producing a diverse array of cytokines and chemokines (2).

Importantly, the immunological functions of stromal cells can vary substantially depending on their host organ and physiological context. For example, lymph node FRC recruit CCR7 (C-C chemokine receptor type 7)$^+$ T cells (naïve and central memory) and CCR7$^+$ dendritic cells (DC) to lymph nodes by producing the chemokines CCL19 and CCL21, as well as the pro-survival cytokines IL-7 and IL-15, thereby coordinating T cell activation and maintenance (4). In contrast, stromal cells in peripheral tissues generally lack expression of CCL19 and CCL21; accordingly, naïve and central memory T cells are infrequent in the periphery. However, expression of various pattern recognition and cytokine receptors by non-lymphoid tissue stromal cells allows them to sense microbial molecules and endogenous danger signals (1, 8, 9). In response, they produce chemokines [including CCL20 and CXCL10 (C-X-C motif chemokine ligand 10)] that attract effector T cells to sites of inflammation. Furthermore, inducible expression of leukocyte adhesion molecules including ICAM-1 (intercellular adhesion molecule 1) and VCAM-1 (vascular cell adhesion molecule 1) allows tissue-resident stromal cells to further influence the balance between leukocyte recruitment, retention, and recirculation (1, 2, 9). Finally, stromal cells contribute directly to immune response resolution and tissue repair, the latter being one of their best studied functions. Examples of "pro-resolution" factors produced by stromal cells include NOS2 (nitric oxide synthase 2) and NO (nitric oxide), which are released by lymph node FRC to constrain T cell proliferation (10–12), and IDO1 (indoleamine 2,3-dioxygenase 1) produced by peripheral stromal cells, which similarly limits T cell proliferation by depleting the critical T cell metabolite tryptophan (13, 14). Thus, stromal cells in different tissues collectively regulate the strength, quality, and duration of immune responses via diverse and complementary mechanisms.

As with most immunological processes, communication between stromal and immune cells is highly dependent on cytokines. Stromal cells bear receptors to a variety of biologically diverse cytokines that represent virtually all branches of innate and adaptive immunity, including innate inflammatory cytokines [e.g., TNF (tumor necrosis factor) and IL-1β], Th1 cytokines [e.g., IFN-γ (interferon gamma)], Th2 cytokines (e.g., IL-13), Th17 cytokines (e.g., IL-17A), and tolerogenic cytokines [e.g., TGF-β (transforming growth factor beta)] (7, 9, 15, 16). In turn, stromal cells can be prodigious producers of other cytokines and chemokines, such as IL-6 (1, 2, 7, 9). In recent years, cytokines of the IL-6 family have gained increasing attention for their roles in various homeostatic and pathological processes, which in many cases can be attributed to their ability to co-ordinate immune-stroma crosstalk. This review aims to provide a focused update on the contributions of IL-6 family members to immune-stromal interactions.

AN OVERVIEW OF THE IL-6 CYTOKINE FAMILY

The IL-6 family includes IL-6, IL-11, IL-27, IL-31, oncostatin M (OSM), leukemia inhibitory factor (LIF), ciliary neurotrophic factor (CNTF), cardiotrophin 1 (CT-1), and cardiotrophin-like cytokine factor 1 (CLCF1) (17, 18). With the exception of IL-27, which is a heterodimeric protein comprised of IL-27p28 and EBI3 (Epstein-Barr virus-induced gene 3) (19), IL-6 family members are compact 4-helix bundle cytokines made from a single polypeptide. Glycoprotein 130 (gp130, encoded by the *IL6ST* gene) is a crucial receptor subunit utilized by all members of the IL-6 family except IL-31. While gp130 expression is relatively ubiquitous in a wide variety of tissues and organs, cell-type specificity for different IL-6 family members is bestowed by the more restricted expression patterns of ligand-specific co-receptors, including IL-6R (IL-6 receptor), IL-11R (IL-11 receptor), IL-27Rα (IL-27 receptor alpha), OSMR (OSM receptor), LIFR (LIF receptor), and CNTFRα (CNTF receptor alpha). Three distinct forms of receptor-ligand complexes have been described (**Figure 1**). First characterized was that of IL-6, which engages IL-6R along with two subunits of gp130. Intriguingly, although this implies the formation of a trimeric complex, a series of cooperative interactions can ultimately produce an interlocked hexamer comprised of two subunits each of IL-6, IL-6R, and gp130 (20). A similar structure is likely formed in response to IL-11/IL-11R interaction (21, 22). In this arrangement, only gp130 drives signal transduction, due to an absence of intracellular signaling motifs in IL-6R and IL-11R. In contrast, OSMR, LIFR, and IL-27Rα form heterodimers with gp130 in the presence of their cognate ligands (23–28). Unlike IL-6R and IL-11R, OSMR, LIFR, and IL-27Rα are capable of driving signal transduction via their own suite of signaling motifs. Finally, CNTF and CLCF1 drive formation of a trimeric complex that includes gp130, LIFR, and CNTFRα (29–31). The gp130-independent outlier of the family, IL-31, engages a heterodimeric complex of IL-31Rα (previously known as gp130-like receptor) and OSMR (18). Notably, while mouse OSM binds with high affinity only to the gp130/OSMR heterodimer, human and rat OSM can bind with high affinity to either gp130/OSMR or gp130/LIFR heterodimers (32–34). Thus, in rats and humans, manipulation of LIFR would be expected to affect both OSM and LIF signaling (as well as CLCF1, CT-1, and CNTF), while manipulation of OSMR would influence OSM and IL-31 signaling. As a corollary, changes in human or rat OSM bioavailability would influence cells that express OSMR and/or LIFR, while changes in LIF or IL-31 would affect only LIFR- or IL-31Rα-expressing cells, respectively.

All members of the IL-6 family drive signal transduction via receptor-associated Janus kinases (primarily JAK1 and JAK2), which phosphorylate a variety of conserved tyrosine residues in the cytoplasmic domains of signaling receptor subunits (gp130, OSMR, LIFR, IL-27Rα, and IL-31Rα) (17, 18, 35). Several downstream signaling pathways are activated in response, including signal transducer and activator of transcription

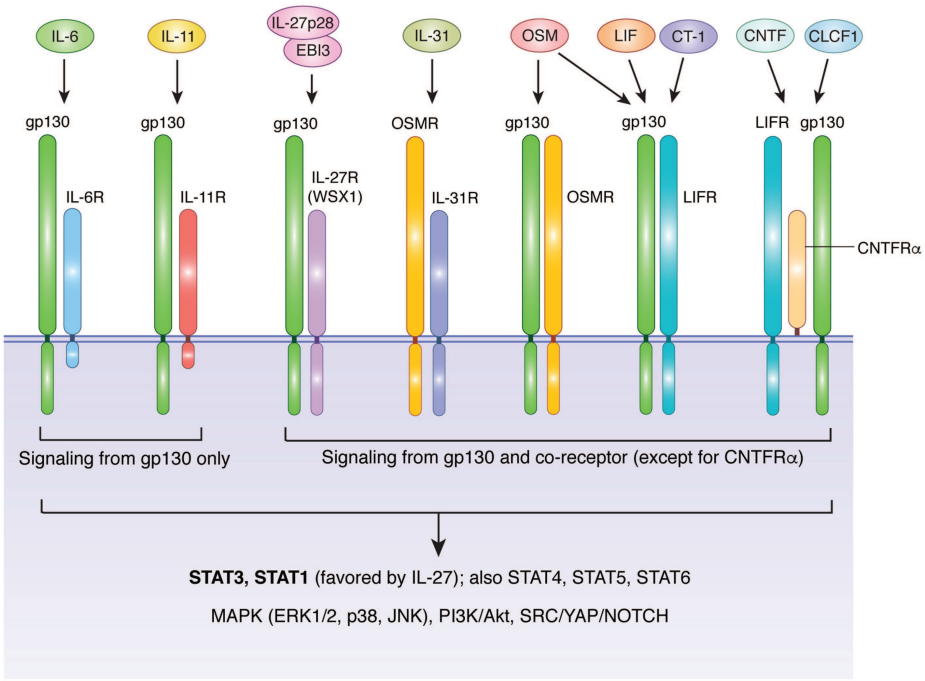

FIGURE 1 | Receptor usage of IL-6 family cytokines. With the exception of IL-31, IL-6 family cytokines transduce signals via receptor complexes that include gp130 and one or more additional ligand-specific subunits. IL-6 and IL-11 signaling requires IL-6R and IL-11R, respectively. The cytoplasmic domains of these receptor are short and lack signaling motifs, making gp130 the sole source of signal transduction downstream of IL-6 and IL-11. The heterodimeric cytokine IL-27 (comprised of IL-27p28 and EBI3) requires a complex of gp130 and IL-27RA. LIF and CT-1 use a heterodimeric complex of gp130 and LIFR, while CNTF and CLCF1 signal via a trimeric complex of gp130, LIFR, and CNTFRα, a GPI-anchored protein that does not directly contribute to signaling beyond facilitation of ligand binding. OSM displays species-specific receptor usage. In humans and rats, OSM signals via either gp130/OSMR or gp130/LIFR complexes, while in mice OSM is primarily recognized by OSMR. IL-31 does not require gp130, and instead uses a complex of OSMR and IL-31R. Aside from IL-6R, IL-11R, and CNTFRα, all receptors in the IL-6 family are capable of directly activating signal transduction in response to ligand binding. IL-6 family cytokines employ classical JAK-mediated signaling. Major downstream mediators include STAT3 (the main STAT for all except IL-27), STAT1 (activated preferentially by IL-27 and to a lesser extent by other IL-6 family members), additional STATs that depend on cell type and physiological context (including STATs 4, 5, and 6), the MAPK cascade, PI3K/Akt/mTOR signaling, and SRC/YAP/NOTCH signaling. Akt, protein kinase B; CLCF1, cardiotrophin-like cytokine factor 1; CNTF, ciliary neurotrophic factor; CT-1, cardiotrophin 1; EBI3, Epstein-Barr virus induced 3; ERK, extracellular signal-regulated kinase; gp130, glycoprotein 130, also known as IL-6 signal transducer; IL, interleukin; IL-6R, IL-6 receptor; IL-11R, IL-11 receptor; IL-27RA, IL-27 receptor; CNTFRα, CNTF receptor; LIF, leukemia inhibitory factor; LIFR, LIF receptor; MAPK, mitogen activated protein kinase; JAK, janus kinase; JNK, c-jun n-terminal kinase; mTOR, mammalian target of rapamycin; OSM, oncostatin M; OSMR, OSM receptor; PI3K, phosphatidylinositol-3-kinase; STAT, signal transducer and activator of transcription; SRC, Proto-oncogene tyrosine-protein kinase Src; YAP, yes-associated protein.

(STAT) proteins (including STAT1, STAT3, STAT4, STAT5, and STAT6), the mitogen-activated protein kinase (MAPK) cascade, the phosphatidylinositol-3-kinase (PI3K)/Akt pathway, and the SRC/YAP/NOTCH pathway (**Figure 1**). While signal transduction by individual IL-6 family members is broadly similar, the relative strength of activation of specific pathways can differ depending on the cytokine, cell type, and physiological context. For example, unlike gp130, OSMR efficiently recruits the adapter protein SHC, allowing OSM to drive more potent activation of the MAPK pathway than IL-6, which signals via SHP-2 bound to gp130 (35, 36). Similarly, although STAT3 is generally considered to be the dominant STAT protein activated by the IL-6 family, IL-27 preferentially activates STAT1 (37). Further complexity is provided by the capacity of IL-6, IL-11, and CNTF to signal via soluble receptor forms in a process known as *trans* signaling. In this process, soluble versions of IL-6R, IL-11R, or CNTFRα are produced either through proteolytic cleavage of membrane-bound receptors, or via expression of alternatively spliced mRNA; in either case, the soluble receptor form can dimerize with its cognate ligand in solution, and subsequently produce a functional signaling complex in association with membrane-bound gp130 (18, 38–40). Cells thus require only gp130 to be sensitive to *trans* signaling, which allows many cell types that lack IL-6R, IL-11R, or CNTFRα to respond to these cytokines. In the case of IL-6, *trans* signaling is thought to be a critical mechanism by which IL-6 promotes disease pathogenesis, particularly arthritis and colorectal cancer (18, 41, 42). Thus, while many similarities exist between IL-6 family cytokines, differences in their receptor usage, signal transduction profiles, and patterns of receptor expression collectively foster a substantial degree of functional pleiotropy. Indeed, IL-6 family members influence cell survival, proliferation, differentiation, metabolism, and migration, thus contributing to a plethora of physiological processes that are critical for both homeostasis and pathology.

EXPRESSION OF IL-6 FAMILY CYTOKINES BY STROMAL CELLS

Although some members of the IL-6 family are produced primarily by hematopoietic cells (notably OSM and IL-27), stromal cells can be important sources of several others, including IL-6, IL-11, and LIF. Diverse factors appear to regulate the expression of these cytokines by stromal cells, including microbial sensing, detection of endogenous alarmins, stimulation by other cytokines (including those within the IL-6 family itself), and cell stress (**Figure 2**). Although these inputs are known drivers of cytokine production, the critical drivers *in vivo*, particularly under physiological conditions, are rarely well defined.

In response to infection or an inflammatory challenge, IL-6 production is rapidly increased by stromal cells. Depending on their location and the nature of the challenge, this could be due to direct sensing of danger signals, responses to other inflammatory cytokines, or both. As an NF-κB (nuclear factor kappa B) response gene (43), IL-6 is induced by stromal cells downstream of several pattern recognition receptors including, but probably not limited to, toll-like receptor (TLR)2, TLR4, and NOD2 (nucleotide binding oligomerization domain 2) (44–46). The NF-κB activating cytokines IL-1β, IL-17A, and TNF (tumor necrosis factor alpha) are also potent inducers of stromal IL-6 production, and can do so in synergy with one another (43, 47–54). Although NF-κB is thought to be the dominant driver of IL-6 production downstream of these cytokines, contributions by MAPK signaling have also been observed. Indeed, signaling by alternative pathways such as the MAPK and PI3K cascades may underlie the ability of cytokines like OSM (55, 56), IL-4 (49), and TGF-β (54, 57) to promote stromal IL-6 expression, since these are not classical activators of NF-κB. Beyond cytokines and danger signals, cadherin-11 (CDH11), a mesenchymal cadherin that engages in homophilic interactions between adjacent cells, has also been shown to drive IL-6 production via NF-κB and MAPK signaling (53). Indeed, blockade of CDH11 attenuates inflammation in mouse models of arthritis, an effect that may be due in part to reduced IL-6 production by $CDH11^+$ synovial fibroblasts (53). Finally, IL-6 is a well-known product of the senescence-associated secretory phenotype (SASP) in fibroblasts, a feature associated with aging and cancer (58). Indeed, IL-6 produced by prostate tumor fibroblasts in response to metabolic stress has been proposed to mediate malignant progression (59).

Less is known about the regulation of LIF and IL-11 expression by stromal cells, but the mechanisms involved may be similar

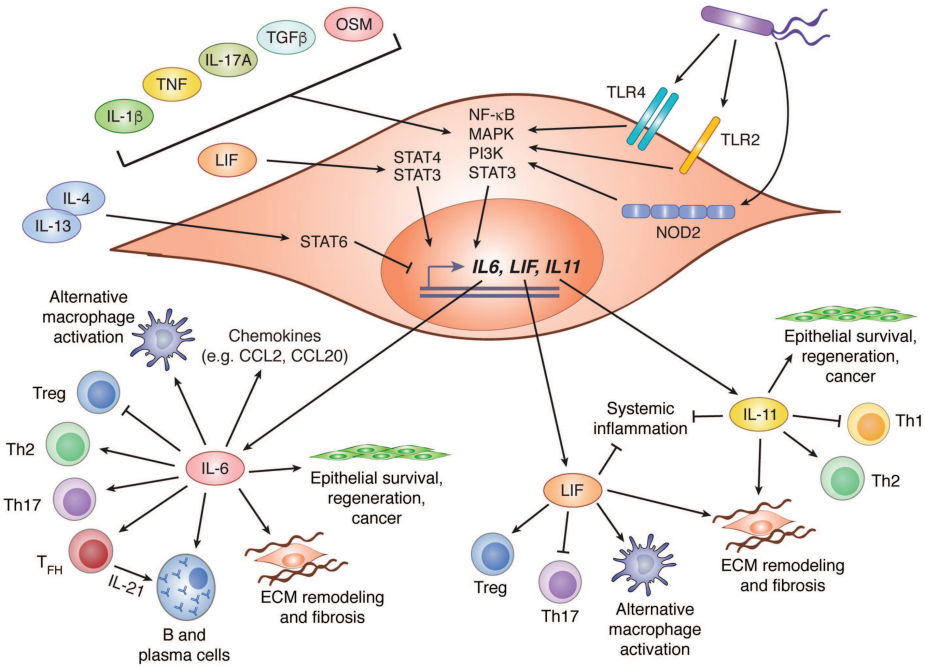

FIGURE 2 | IL-6 family cytokine production by stromal cells and their biological effects. Stromal cells are important contributors to production of three members of the IL-6 family: IL-6, LIF, and IL-11. Expression of these cytokines is regulated by various stimuli including recognition of bacterial products via TLR2, TLR4, or NOD2, and diverse cytokines that drive activation of NF-κB, MAPK, PI3K, and STAT3. LIF has been shown to promote IL-6 expression via STAT4 signaling, while IL-4 and IL-13 can suppress LIF and IL-11 expression through activation of STAT6. Following production by stromal cells, IL-6, LIF, and IL-11 can influence diverse biological processes including $CD4^+$ T cell polarization, regulation of chemokine production, promotion of alternative macrophage differentiation, and tissue remodeling through effects on stromal and epithelial cells. In this figure, arrows indicate stimulatory effects, and capped lines indicate inhibitory effects. All processes illustrated are described further in the main text. CCL, C-C motif chemokine ligand; ECM, extracellular matrix; IL, interleukin; LIF, leukemia inhibitor factor; MAPK, mitogen activated protein kinase; NF-κB, nuclear factor kappa B; NOD2, nucleotide-binding oligomerization domain-containing protein 2; OSM, oncostatin M; PI3K, phosphatidylinositol-3-kinase; STAT, signal transducer and activator of transcription; T_{FH}, T follicular helper cell; TGFβ, transforming growth factor beta; Th, T helper; TLR, toll-like receptor; Treg, regulatory T cell.

to those of IL-6. Like IL-6, LIF and IL-11 expression by stromal cells can be induced by IL-1β, TNF, and TGF-β (60–64). Notably, induction of both IL-11 and LIF in response to TGF-β stimulation of cancer-associated fibroblasts is thought to promote tumor progression (61, 62). Intriguingly, IL-4 and IL-13 were shown to counteract TNF and IL-1β-induced expression of LIF and IL-11, but not IL-6, by gingival fibroblasts (64). This effect was dependent on STAT6, and provides a potential mechanism for selective modulation of individual IL-6 family members.

RESPONSIVENESS OF STROMAL CELLS TO IL-6 FAMILY CYTOKINES

Stromal cells express the necessary receptor subunits to respond to the majority of gp130-dependent IL-6 family cytokines. In general, gp130 and OSMR are ubiquitously expressed by stromal cells from essentially all anatomical locations studied thus far. OSM is therefore a major activating factor of stromal cells, as well as various other mesenchymal populations including endothelial cells, muscle cells, adipocytes, and osteoblasts (34, 56, 65). Expression of other ligand-specific receptor subunits is more variable and depends on the cell type, anatomical location, and physiological context. IL-6R, for example, tends to be expressed at relatively low levels, and stromal cells are correspondingly less sensitive to classical IL-6 signaling than OSM. Indeed, expression of OSMR mRNA in human colon fibroblasts is roughly 10x higher than that of IL-6R (55). However, inflammatory conditions that yield soluble IL-6R can increase stromal cell sensitivity to IL-6 due to *trans* signaling. Responsiveness of stromal cells to LIF appears to vary widely depending on anatomical location. For example, LIF induces contractile and inflammatory phenotypes in dermal and synovial fibroblasts, respectively, but has little effect on colon fibroblasts (55, 62, 63, 66). Sensitivity of stromal cells to IL-11 and IL-27 has also been documented (67–73). In contrast, IL-31Rα does not seem to be expressed by most stromal cells at physiologically relevant levels (74, 75).

CONTROL OF INFLAMMATION AND ADAPTIVE IMMUNITY BY THE IL-6-STROMA AXIS

Exposure of stromal cells to factors such as microbial ligands or inflammatory cytokines can drive IL-6 production during both acute and chronic inflammation. Following infection of mice by *Toxoplasma gondii*, for example, IL-6 expression was shown to be elevated in a population of bone marrow stromal cells characterized by high VCAM-1 and low CD146 expression, and stroma-derived IL-6 was required for the increased myelopoiesis that occurs as part of the host response to infection (76). Bone marrow stromal cells also induce IL-6 in response to viral infections such as CMV (cytomegalovirus) (77). During *Helicobacter hepaticus*-driven colitis in mice, non-hematopoietic stromal cells are the dominant intestinal producers of IL-6, with expression levels that substantially exceed those of MHC-II$^+$ myeloid cells (55). Interestingly, IL-6 expression may be a feature of specific intestinal stromal cell subsets with distinct ontogeny or activation states. For example, human OSMR^{high} intestinal stromal cells were found to be enriched in IL-6 expression relative to their OSMR^{low} counterparts (55), consistent with the well-established ability of OSM to induce IL-6 expression in mesenchymal cells (78–86). Single-cell RNA-sequencing has similarly revealed substantial heterogeneity in the intestinal stromal cell compartment. High IL-6 expression is enriched in a stromal cell subset that is rare in healthy individuals, but dramatically expanded in patients with inflammatory bowel disease (IBD) (87). Notably, these cells were further characterized by expression of a variety of additional immunostimulatory molecules, including IL-33 and the FRC-associated chemokines CCL19 and CCL21, implying a specialized role in immune regulation (87). Notably, a disease-associated single nucleotide polymorphism (SNP) in the human *IL6* promoter was shown to control production of IL-6 by fibroblasts, but had no effect on IL-6 expression by CD14$^+$ monocytes, suggesting that host genetics can also play an important role in determining stromal IL-6 output (88).

Following initiation of acute inflammation, IL-6 can act on several cell types to shape the quality of the ensuing immune response. For example, IL-6 controls the balance between inducible regulatory T cell (Treg) and Th17 differentiation following activation of naïve CD4$^+$ T cells (41). Although stromal cells have not conclusively been demonstrated to contribute to this process, FRC-derived IL-6 has been suggested to support the development and maintenance of B cell responses. Medullary FRC were shown to be important regulators of plasma cell homeostasis, in part by producing the plasma cell survival factor IL-6 (89, 90). IL-6 is also necessary for the differentiation of follicular helper T cells (T_{FH}), which drive the maturation of B cells and the generation of protective antibody responses (91, 92). Importantly, IL-6 induces production of IL-21 by T_{FH} cells, which is critical for both T_{FH} maintenance and plasma cell differentiation in germinal centers (93, 94). Publicly available data provided by the ImmGen project suggest that FRC constitutively express IL-6, and do so at levels that far exceed those of other lymph node-resident cell types (95). Thus, FRC-derived IL-6 is likely to be a central linchpin in the regulation of both T cell and B cell responses in secondary lymphoid organs.

In inflamed peripheral tissues, IL-6 controls the temporal switch from recruitment of granulocytes to preferential recruitment of mononuclear cells by modulating chemokine and cytokine production in local mesenchymal cells, including the suppression of TNF and IL-1β production, possibly via STAT3-mediated repression of NF-κB signaling (96, 97). IL-6 promotes the differentiation of monocytes into macrophages rather than dendritic cells *in vitro*, but genetic IL-6 deficiency does not affect dendritic cell frequencies *in vivo* (98–101). However, IL-6 appears to mediate alternative macrophage differentiation *in vivo* and inhibits inflammatory cytokine production and microbicidal activity by macrophages (102–105). IL-6 can also promote survival and regeneration of damaged epithelia during inflammatory challenges, a feature that can be subverted to promote cancer progression (106). Thus, while IL-6 is important for initiation of immune responses, it also promotes resolution

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