Cell

Leading Edge
Review

The Stromal Intervention: Regulation of Immunity and Inflammation at the Epithelial-Mesenchymal Barrier

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http://dx.doi.org/10.1016/j.cell.2016.11.040

SUMMARY

The immune system safeguards organ integrity by employing a balancing act of inflammatory and immunosuppressive mechanisms designed to neutralize foreign invaders and resolve injury. Maintaining or restoring a state of immune homeostasis is particularly challenging at barrier sites where constant exposure to immunogenic environmental agents may induce destructive inflammation. Recent studies underscore the role of epithelial and mesenchymal barrier cells in regulating immune cell function and local homeostatic and inflammatory responses. Here, we highlight immunoregulatory circuits engaging epithelial and mesenchymal cells in the intestine, airways, and skin and discuss how immune communications with hematopoietic cells and the microbiota orchestrate local immune homeostasis and inflammation.

Adopted from the fortune cookie realm, ''life is all about balance'' captures an underlying concept imperative for the normal function of tissues. A state of homeostatic equilibrium is maintained in multicellular organisms by the innate immune system, comprising a set of tissue-resident and circulating leukocytes primarily evolved to sense pathogens and tissue damage. The innate immune system acts to eliminate noxious sources by mediating inflammation, the process in which blood cells and plasma components are delivered to sites of perturbed tissue homeostasis, as in the case of infection or injury (Medzhitov, 2008; Nathan, 2002). Cells in various tissues, notably at barrier sites, are also constantly exposed to microbial and other environmental elements that may compromise tissue function, either by directly damaging cells or by excessive activation of inflammatory processes. The major challenge of the immune system is therefore to efficiently eliminate a noxious source without inflicting collateral damage that will perpetuate a chronic inflammatory cycle.

The inflammatory response follows four general consecutive phases: pathogen or damage recognition, recruitment of immune cells to the affected site, pathogen or damage elimination, and resolution of inflammation. Innate immune cell activation and inflammation are controlled autonomously through hard-wired receptor-mediated sensory mechanisms and production of inflammatory and immunosuppressive mediators. In concert with the hematopoietic immune system, recent studies demonstrate the central role of epithelial and mesenchymal cells in regulating the shape and intensity of localized immune responses, highlighting the contribution of these cells to immune homeostasis and inflammation. This nonimmune cell regulation of immune responses is pertinent to all phases of the inflammatory process, from promoting microbial symbiosis and immune homeostasis, to immune cell activation, recruitment, and suppression in case of pathogenic infection or injury.

Epithelial and mesenchymal cells line most organ surfaces and form barriers that enable physical separation and functional communication between the environment and the immune system. As the two prominent cell populations interacting with resident and recruited immune cells at barrier sites, both epithelial and mesenchymal cells are involved in dominant immunomodulatory mechanisms that if considered together, in our view, can provide an integrative understanding of barrier immunity and inflammation. Both cell types are able to modulate their environment by intricate immunological signaling that affect immune and nonimmune cells in the tissue, and at the same time, both cell types are responsive to environmental immune signals that modulate their own intrinsic function. While many parallels can be drawn between epithelial and mesenchymal immunoregulatory pathways, specific mechanisms are dependent on the unique cell identity and geographical positioning, even within sub-epithelial and mesenchymal populations. Moreover, while such imprinting immune signals are designated to promote homeostatic equilibrium, they can also drive pathological inflammation that perpetuates the original insult.

Other stromal elements such as endothelial, lymphatic, and neuronal cells are also pivotal in regulating immune functions at barrier sites; however, these cell types cannot be faithfully covered within the scope of this review. Here, we address basic principles and emerging roles of the epithelial-mesenchymal-immune crosstalk in immune homeostasis and inflammation,

focusing on immunomodulatory functions of epithelial and mesenchymal cells at barrier sites. We try to provide an integrative view on concerted mechanisms of epithelial and mesenchymal communication with immune cells and microorganisms that support tissue function or are subverted to propagate pathological inflammation.

Know Thy Neighbors—Immune Cell Interaction with the Gut Stroma and Epithelium

Immune cell function is greatly dependent on local cues derived from mesenchymal and epithelial cells that define the localization, activation state, immune phenotype, and survival of tissue hematopoietic cells. Unique microanatomical niches provided by mesenchymal and epithelial cells are illustrated by the remarkable immune cell diversity and compartmentalized distribution along the intestinal tract and across the various layers of the intestinal wall. This distribution is determined by mesenchymal-epithelial cellular and molecular gradients together with the interdependent microbial microenvironment, which collectively determine regional specificity.

Intestinal immune cells either cluster in the gut-associated lymphoid tissue (GALT) or disseminate throughout the intestinal lamina propria (LP) and overlying epithelium as individual effector cells. GALT is the primary intestinal reservoir of IgA-producing plasma B cells, consisting of Peyer's patches (PPs) in the small intestine and isolated lymphoid follicles (ILFs) in the small intestinal and colonic mucosa. PPs are formed following hematopoietic seeding of the embryonic gut, by local clustering of $CD11c^+$ dendritic cells (DCs) with $LT\beta R^+$ mesenchymal stromal cells, leading to stromal cell expression of cytokines (IL-7), chemokines (CXCL13, CCL19, CCL21), and adhesion molecules (VCAM-1, ICAM-1, MAdCAM-1) required for the attraction and retention of lymphoid-tissue inducer (LTi) cells in the developing PP (van de Pavert and Mebius, 2010). A reticular network of stromal cells serves as a conduit and substrate for lymphocyte migration and DC adhesion, following general organizing principles of secondary lymphoid organs (Mueller and Germain, 2009). DC distribution within PPs is also determined by expression of CCL20 (macrophage inflammatory protein 3 alpha [MIP3a]) by the dome epithelial cells, leading to migration of $CCR6^+$ immature DCs to the subepithelial dome region (Iwasaki and Kelsall, 2000). In contrast to PPs, ILFs originate in small cryptopatches that appear within the first 2 weeks after birth and develop to mature B cell follicles in response to antigens derived from commensal microorganisms with the transition to solid food (Bouskra et al., 2008). ILF formation is similarly dependent on the association of $LT\beta R^+$ stromal cells and $ROR\gamma t^+$ LTi cells, mediating recruitment of DCs and B cells in the presence of signals derived from the microbiota that further activate the stromal cells (Tsuji et al., 2008). Early embryonic and postnatal interaction between lamina propria stromal, epithelial, and hematopoietic cells is therefore imperative for GALT development.

Outside the GALT, the intestinal LP and epithelium are the immune effector sites hosting the largest pool of lymphoid and myeloid cells in the body. The journey of immune cells to and within the intestinal mucosa is instructed by epithelial and mesenchymal cells that impact the retention of immune cells within the gut mucosa. DCs imprint peripheral T cells with gut tropism by enhancing T cell expression of the gut-homing $\alpha4\beta7$ integrin and CCR9, a process driven by local metabolism of vitamin A to retinoic acid (RA) by intestinal stromal and epithelial cells (Hammerschmidt et al., 2008; Iwata et al., 2004; McDonald et al., 2012; Mora et al., 2003). Utilizing the intestinal-specific $\alpha4\beta7$-MAdCAM vascular address code, emigrating T cells are either distributed in the LP or are drawn toward the epithelium, which maintains a steady-state immune presence at the interface with the gut microbiota and food antigens. Intercalated within the epithelial layer, intraepithelial lymphocytes (IELs) represent the prominent immune subset that forms direct contact with enterocytes. IELs comprise a heterogeneous population of antigen-experienced T cells, the majority of which are $TCR\gamma\delta^+CD4^-CD8\alpha\beta^-$ cells induced in the thymus, or $TCR\alpha\beta^+$ cells expressing either CD4 or $CD8\alpha\beta$ that are induced in response to peripheral antigens (Cheroutre et al., 2011). IEL retention in the epithelium is mediated by transforming growth factor β (TGF-β)-driven expression of CD103 (integrin αE), a subunit of integrin $\alpha E\beta7$ that binds to epithelial E-cadherin. Further compartmentalization of immune cell subsets is mediated by additional epithelial factors, such as butyrophilin-like (BTNL) proteins that control specific localization of $\gamma\delta$ T cells (Di Marco Barros et al., 2016). IEL distribution varies considerably between the small and large intestines, owing in part to regional specificity in epithelial chemokine production (Mowat and Agace, 2014). Expression of CCL25 (thymus-expressed chemokine [TECK]) is restricted to epithelial cells in the small intestine, mediating specific recruitment of $CCR9^+$ lymphocytes to the small intestinal mucosa. Regional epithelial cytokine production may further regulate effector immune subsets, as localized production of IL-33 by epithelial cells in the proximal small intestine confers a regulatory phenotype with immunosuppressive properties on $ST2^+$ Th17 cells (Pascual-Reguant et al. in press). This is consistent with regional IL-17-dependent production of CCL20 by intestinal epithelial cells (IECs), which acts to recruit $CCR6^+$ Th17 cells to the proximal small intestine (Esplugues et al., 2011).

Environmental niches in the gut lumen cooperate with tissue-derived factors in instructing intestinal immune cell localization and function. The site-specific accumulation and activation state of Th17 cells is greatly affected by unique microbial niches, as for segmented filamentous bacteria (SFB) in the ileum, or by the local composition of dietary products such as trans fatty acids versus polyunsaturated fatty acids (Burkett et al., 2015). Induction of $ROR\gamma t$ in a population of colonic Treg cells by a specific array of commensal bacteria is required to limit inflammatory responses in colitis (Sefik et al., 2015). Alternatively, local microbiota-derived signals can promote the migration of LP Treg cells to the epithelium and induce their conversion to $CD4^+$ IELs (Sujino et al., 2016). Analogous mechanisms may control immunity at other barrier surfaces such as the skin, where colonization with specific commensal bacteria induces DC-dependent recruitment of IL-17A-expressing CD8 T cells to the epidermis, which enhance innate barrier immunity and limit pathogen invasion (Naik et al., 2015). Regional specificity in effector T cell subset localization is also evident in the skin, where subsets of $\gamma\delta$ T cells producing either interferon-γ (IFN-γ) or IL-17 occupy distinct niches in the outer and inner layers of the tissue

(Vantourout and Hayday, 2013). This hardwired niche residence is analogous to the segregation of intestinal IFN-γ-producing IELs from IL-17-producing γδ T cells in the LP. Regional gradients of epithelial, microbial and dietary products therefore impact both the localization and activation/differentiation state of immune cells at the barrier.

By expressing various tight junction proteins, mononuclear phagocytic macrophages/DCs can send dendrites through the epithelial monolayer to sample the intestinal lumen while replacing tight junctions between epithelial cells, thus preserving the integrity of the epithelial barrier (Rescigno et al., 2001). Expression of the transmembrane chemokine CX_3CL1 (fractalkine) on IELs directs the recruitment of resident CX_3CR1^+ macrophages/DCs to intraepithelial regions in the terminal ileum, providing them access to luminal microbiota (Niess et al., 2005). Trafficking of luminal bacteria to the gut draining mesenteric lymph nodes by CX_3CR1^{hi} phagocytes is, however, limited by a microbiota and MyD88-dependent mechanism that promotes tolerance toward commensal microbes (Diehl et al., 2013). Alternatively, LP $CD103^+$ DCs are mobilized to the epithelium in response to infection with luminal bacteria, possibly by chemokines produced downstream to MyD88/TLR signaling in epithelial cells (Farache et al., 2013). The DC-IEC interaction imprints a tolerogenic DC phenotype, dependent on epithelial-derived TGF-β and RA, which also increase CD103 expression (Iliev et al., 2009). A parallel interaction with RA-producing $Podoplanin^+$ stromal cells may further imprint RA production in $CD103^+$ DCs, which is dependent on stromal cell-derived GM-CSF (Vicente-Suarez et al., 2015). Taken together, these studies illustrate that local immune cell interactions with epithelial and stromal cells shape the homeostatic functions of the intestinal barrier by instructing regional specificity in immune cell distribution and phenotype.

Epithelial Immune Modules Controlling Intestinal Homeostasis

Epithelial cells have the capacity to function as immune rheostats by employing sensory mechanisms that induce an immunomodulatory output. Innate pattern recognition receptors such as Toll-like receptors (TLRs) and NOD-like receptors (NLRs) recognize damage- and pathogen-associated molecular patterns and activate effector responses that promote both tolerance and activation of immune responses (for recent reviews see Hooper, 2015; Peterson and Artis, 2014; Ramanan and Cadwell, 2016). In addition to these hardwired mechanisms, several cytokines and immune mediators are activated in epithelial cells in the steady-state and control immunomodulatory modules that are required for maintaining homeostasis. Many of these modules either activate, or are activated by, the major epithelial survival programs orchestrated by transducer and activator of transcription 3 (STAT3) and nuclear factor κB (NF-κB) (Figure 1).

Multiple independent signals converge on epithelial STAT3 activation to maintain intestinal immune homeostasis, collectively leading to containment of immune cell inflammatory profile. An important module through which epithelial STAT3 promotes immune homeostasis is mediated by IL-22, an IL-10 family member produced by ILCs, T cells, NK cells, DCs, and neutrophils. STAT3 activation by IL-22 is important for epithelial restitution, the process whereby epithelial cells migrate to reseal breached epithelial surfaces and directly promotes intestinal stem cell regeneration following injury (Lindemans et al., 2015; Pickert et al., 2009). The same signaling axis also mediates immunomodulatory functions enabling host-commensal symbiosis in the gut. SFB attachment to the microvilli of IECs induces IL-23-dependent IL-22 production by group 3 ILCs (ILC3), leading to STAT3 activation in IECs and production of serum amyloid A proteins 1 and 2 (SAA1/2), which then act directly on poised Th17 cells to amplify effector IL-17A production required for limiting extracellular pathogen infection (Atarashi et al., 2015; Sano et al., 2015). In a similar immune circuit, bacteria-dependent IL-23 production by intestinal DCs drives IL-22 production by ILCs, which again acts on the intestinal epithelium to upregulate fucosyltransferase 2 (*Fut2*) and protein fucosylation in IECs, which is in turn important to maintain commensalism and prevent infection (Goto et al., 2014; Pickard et al., 2014). Notably, polymorphism in the *STAT3* gene and in genes involved in its signaling pathway, including *IL23* and *FUT2*, has been associated with inflammatory bowel disease by genome-wide association studies (GWAS) (Jostins et al., 2012). Epithelial STAT3 signaling also regulates proximity-based mechanisms directly restricting inflammatory cell responses. Engagement of epithelial CD1d leads to STAT3-dependent expression of IL-10, heat shock protein 110 (HSP110), and CD1d itself, all of which elicit protective responses by restricting natural killer T (NKT) cell-mediated colitis (Olszak et al., 2014).

In parallel to pro-survival programs induced by STAT3, nuclear factor κB (NF-κB) signaling enhances cell survival through induction of antiapoptotic and proliferative molecules, cytokines, and chemokines (Ben-Neriah and Karin, 2011). Epithelial NF-κB regulates important barrier functions required for establishing tolerance and immunity, including maintenance of the mucus layer and antimicrobial defense (Peterson and Artis, 2014). IL-18 is an IL-1 family proinflammatory cytokine constitutively expressed by IECs in the steady-state, that mediates type 1 immune responses upstream of NF-κB and downstream of inflammasome activation (Dinarello et al., 2013). IL-18 supports a healthy microbial configuration in the gut by mediating production of antimicrobial peptides, a process regulated by microbial activation of the epithelial NLRP6 inflammasome (Elinav et al., 2011; Levy et al., 2015). In addition, constitutive secretion of IL-18 from IECs inhibits Th17 differentiation and promotes Treg cell function, thus limiting local inflammation in the colon (Harrison et al., 2015). Intestinal Tregs are further regulated by the epithelial alarmin IL-33, another pleiotropic IL-1 family member. Epithelial production of IL-33 in response to inflammatory tissue damage promotes the function of colonic Treg cells, which preferentially express the IL-33 receptor subunit ST2, by enhancing Treg cell maintenance and accumulation in the inflamed tissue (Schiering et al., 2014). The proinflammatory cytokine IL-23 inhibits this regulatory mechanism by reducing Treg responsiveness to IL-33, providing a mechanistic link to the pathogenic role of IL-23 in colitis. In contrast, IEC apoptosis serves as a gauge limiting Treg proliferation in the intestine by inhibiting interferon-β (IFN-β) production in DCs through inhibitory CD300a association with phosphatidylserine exposed on

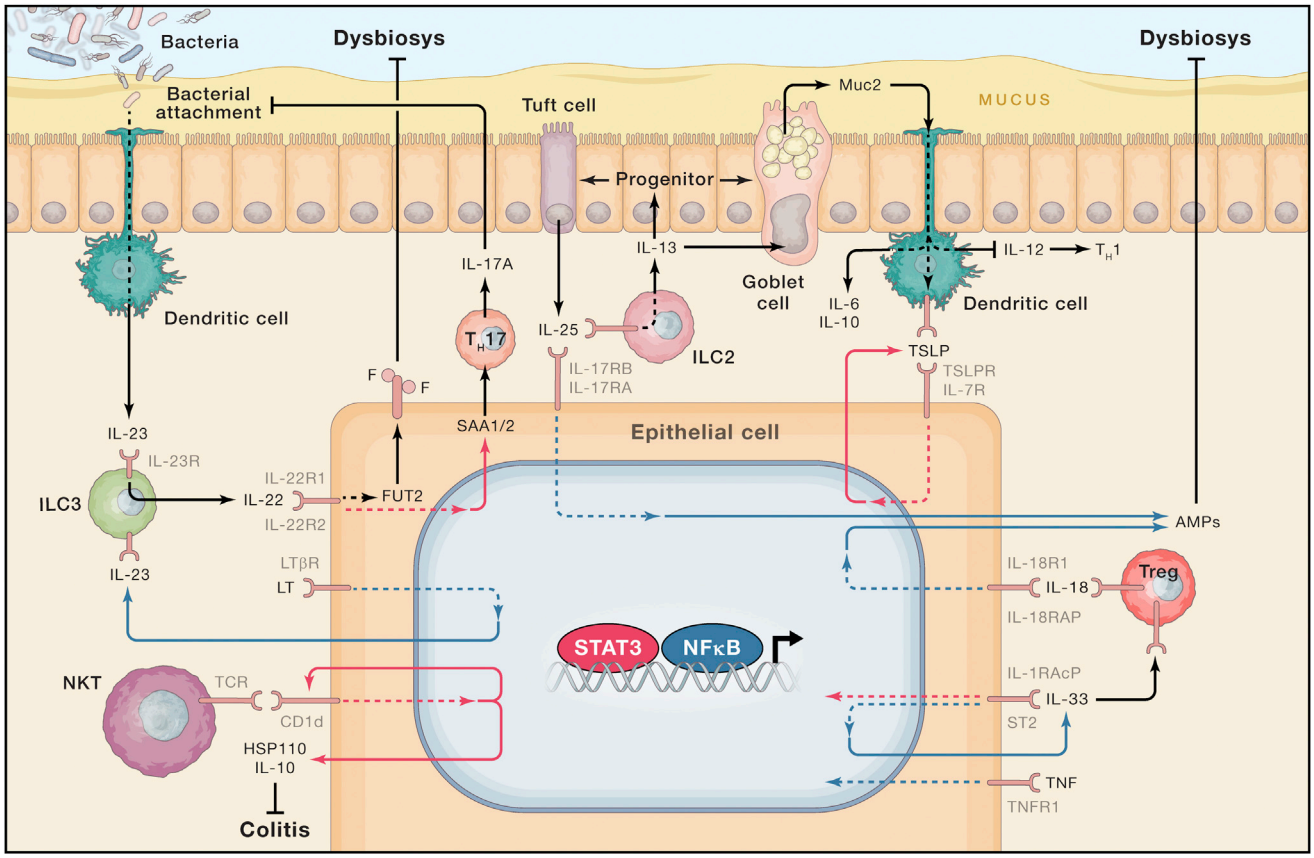

Figure 1. Epithelial Immune Modules Controlling Intestinal Homeostasis

Epithelial homeostatic immune modules and pro-survival signaling are integrated by STAT3 and NF-κB. IL-22 induces epithelial production of SAA1/2 and FUT2, leading to IL-17A production and protein fucosylation, respectively, which promote immunity and microbial symbiosis. Engagement of epithelial CD1d leads to production of CD1d, HSP110, and IL-10, limiting inflammatory NKT function. Autocrine TSLP and IL-33 amplification loops promote immunosuppressive DC and Treg functions. IL-18 signaling leads to production of antimicrobial peptides (AMPs), induction of Tregs, and amplification of IL-18 production. Tuft cell-derived IL-25 induces IL-13 in ILC2 cells, which promotes tuft and goblet cell differentiation. Goblet cell-derived MUC2 promotes immunosuppressive DC functions.

apoptotic epithelial cells (Nakahashi-Oda et al., 2016). Together, these studies underscore the importance of epithelial-immune interactions for maintaining immune homeostasis, as well as for conditioning immune cells to restore homeostasis by way of immunomodulatory signals derived from damaged epithelial cells.

Along these lines, constitutive epithelial production of thymic stromal lymphopoietin (TSLP) is required to maintain DCs in a noninflammatory state characterized by production of IL-10 and IL-6 (Rimoldi et al., 2005). Inactivation of IκB kinase-β (IKKβ) in IECs and promoter analyses identified TSLP as an NF-κB-regulated gene required to condition DCs toward type-2 anti-parasitic responses while limiting both DC and T cell type-1 proinflammatory cytokine production (e.g., IL-12, TNF, IFN-γ, IL-17) in the gut (Lee and Ziegler, 2007; Zaph et al., 2007). On the other hand, deletion of IKKα in IECs led to overproduction of TSLP by IECs, which inhibited IL-22 production by group 3 ILCs (ILC3s), resulting in impaired clearance of bacterial infection as well as increased colitis following intestinal damage (Giacomin et al., 2015). The pathological subversion of an otherwise protective cytokine function is also relevant to other NF-κB-regulated cytokines such as IL-18, as discussed below. Several members of the IL-17 cytokine family may further promote intestinal homeostasis through induction of epithelial NF-κB signaling (Korn et al., 2009). IL-17R signaling in IECs regulates α-defensins, Nox1, and Pigr expression, which control bacterial colonization in the small intestine (Kumar et al., 2016). An additional layer of IL-17 cross regulation is mediated by autocrine signaling of IL-17B and IL-17C, which are induced in epithelial cells following injury or infection and regulate pathogenic inflammation mediated by IL-25 and other inflammatory cytokines (Ramirez-Carrozzi et al., 2011; Reynolds et al., 2015). Constitutive epithelial cytokine production therefore regulates the microbial and inflammatory landscape of the barrier. Various epithelial immune modules are integrated by epithelial survival pathways, enabling the coupling of physical and functional barrier functions in controlling homeostatic symbiosis in the intestine (Figure 1).

Immune Regulation of Goblet Cells and the Mucus Layer

At mucosal barrier sites, goblet cells and surface secretory cells generate protective gel mucus layers by luminal secretion of mucin glycoproteins, forming a mesh of elongated polymers.

Goblet cell abundance in the gut is increased toward the distal colon, in concert with a parallel gradient of increased microbial load and expansion of the mucus layer. Normal mucus production is required for gut homeostasis, as depletion of the major secreted intestinal mucin, MUC2, leads to colitis and intestinal tumorigenesis (Van der Sluis et al., 2006; Velcich et al., 2002). Disrupted production of epithelial O-linked oligosaccharides (O-glycans)—a primary component of intestinal mucins—similarly results in spontaneous colitis due to excessive innate immune cell activation (Fu et al., 2011). At steady-state, mucus production is controlled by homeostatic pathways that involve autophagy, inflammasome assembly, and TLR signaling (Birchenough et al., 2016; Wlodarska et al., 2014). Owing to the central importance of the mucus layer to barrier functionality, inflammatory mediators produced under pathological conditions that affect goblet cell differentiation, maturation or function, are likely to have adverse effects on mucus layer integrity and the ability to control inflammation. In general, chronic inflammation associated with type 1 immune responses leads to goblet cell attenuation (in terms of both number and activity), whereas type 2 immune responses to parasitic infection and allergens mediate goblet cell induction. Recent studies have identified the role of epithelial cytokines, expressed in the steady-state and induced in response to an inflammatory challenge, in controlling goblet cell biology and function.

Mucus layer deficiency is a hallmark of ulcerative colitis, the prevalent chronic inflammatory disease of the lower intestinal tract (Pullan et al., 1994). A link between inflammatory IL-18 signaling and mucus layer deficiency was recently established in a mouse model of ulcerative colitis, showing that hyperactive IL-18 signaling in IECs promotes goblet cell and mucus layer depletion, leading to breakdown of the mucosal barrier and colitis (Nowarski et al., 2015). IL-18-mediated goblet cell dysfunction precedes clinical disease manifestation and is caused by a defect in goblet cell maturation through transcriptional regulation of the goblet cell differentiation program (Nowarski et al., 2015). Intestinal *Salmonella* infection also leads to goblet cell depletion and colitis driven by IFN-γ production by T-bet$^+$ ILCs (Klose et al., 2013). Intestinal DC-dependent production of IFN-γ by T cells establishes an epithelial immunosuppressive feedback mechanism by inducing epithelial production of IL-18 binding protein (IL-18BP), an IL-18 soluble decoy receptor, as well as the anti-inflammatory indoleamine 2,3 dioxygenase (IDO1) enzyme (Muzaki et al., 2016). It is therefore possible that different cellular sources of IFN-γ may differentially regulate goblet cell development and this may also be associated with dysregulated epithelial proliferation or differentiation. At the regulatory axis upstream of IL-18, IL-22 enhances IL-18 expression in IECs, which promotes bacterial clearance during infection, but increases inflammatory pathology in the case of parasitic infection (Muñoz et al., 2015). In *Il22*$^{-/-}$ mice, however, goblet cell hyperplasia and mucin production are inhibited following parasitic infection (Turner et al., 2013). These studies highlight two important principles in establishing protective immunity: the role of balanced cytokine expression and the role of the combinatorial cytokine milieu, both are dependent on the type of insult and affected cells (Figure 2).

Intestinal type-2 responses are initiated by epithelial production of IL-25, TSLP, and IL-33, which are released during tissue damage, parasitic pathogen recognition, or allergen exposure. Recent work identified the tuft cell, an obscure chemosensory cell subset of the small intestinal epithelium, as the major source of IL-25 in the naive gut and illuminated a response circuit to helminth infection involving epithelial remodeling (Gerbe et al., 2016; Howitt et al., 2016; von Moltke et al., 2016). Helminth infection increased IL-25 production by tuft cells, activating ILC2s to secrete IL-13, which then acted in an IL-4Rα-dependent manner to promote differentiation of epithelial crypt progenitors to tuft and goblet cells. Notably, IL-13 also enhances the production of goblet cell factors that mediate worm expulsion such as RELMβ, as well as increases autophagy-mediated mucus secretion (Dickinson et al., 2016; Peterson and Artis, 2014). The proximity to goblet cells or the mucus layer fosters immune communications that further shape immune cell function. In the small intestine, glycans associated with the goblet cell mucin MUC2 limit DC inflammatory cytokine production by transcriptional activation of β-catenin and inhibition of NF-κB in DCs (Shan et al., 2013). Furthermore, goblet cells were shown to mediate the passage of luminal low molecular weight antigens preferentially to tolerogenic CD103$^+$ DCs in the intestinal lamina propria, thus promoting immune homeostasis (McDole et al., 2012).

In contrast to the thick and adherent mucus layers in the gut, the airways mucus layer is thin and mobile. In the airways, mucociliary clearance (MCC) enables entrapment and elimination of inhaled particulate matter and pathogens along the respiratory surfaces. Ciliary movement is mediated by ciliated epithelial cells, while mucins are produced mostly by goblet and club secretory cells, together representing the two major epithelial cell classes that dominate the surface of the trachea, bronchi, and bronchioles (Whitsett and Alenghat, 2015). Airway epithelial secretion of MUC5B, one of the predominant pulmonary mucins, is required to maintain immune homeostasis in the lungs by preventing accumulation of material in the airways, which otherwise leads to bacterial infection, dysregulated macrophage function characterized by reduced phagocytosis and IL-23 production, and unresolved inflammation (Roy et al., 2014). In bronchial epithelial cells, MUC5B expression is induced by the inflammatory cytokines IL-1β and IL-17A downstream to NF-κB, which may promote excessive mucus production in chronic airway diseases (Fujisawa et al., 2011).

Goblet cell hyperplasia and mucus overproduction are defining features of airways hyperreactivity during allergic and Th2 responses and are directly induced by IL-13 signaling in AECs (Kuperman et al., 2002). Allergen-induced IL-13-mediated STAT6 activation leads to increased expression of SPDEF, required for differentiation of both pulmonary and intestinal goblet cells (Chen et al., 2009; Gregorieff et al., 2009). SPDEF expression in turn promotes feedforward IL-13 expression, goblet cell hyperplasia, and mucus production, as well as recruitment of DCs, ILCs, and eosinophils that exacerbate Th2 inflammatory responses to allergen challenge (Rajavelu et al., 2015). As mentioned above, one of the potent epithelial factors driving Th2 responses is IL-33, an IL-1 family member involved in allergic and inflammatory airway pathologies. Following exposure to allergen, IL-13 production by ILC2 cells is dependent on IL-33, leading to DC migration to draining lymph nodes and activation of Th2 cells (Halim et al., 2014). Alveolar epithelial cell

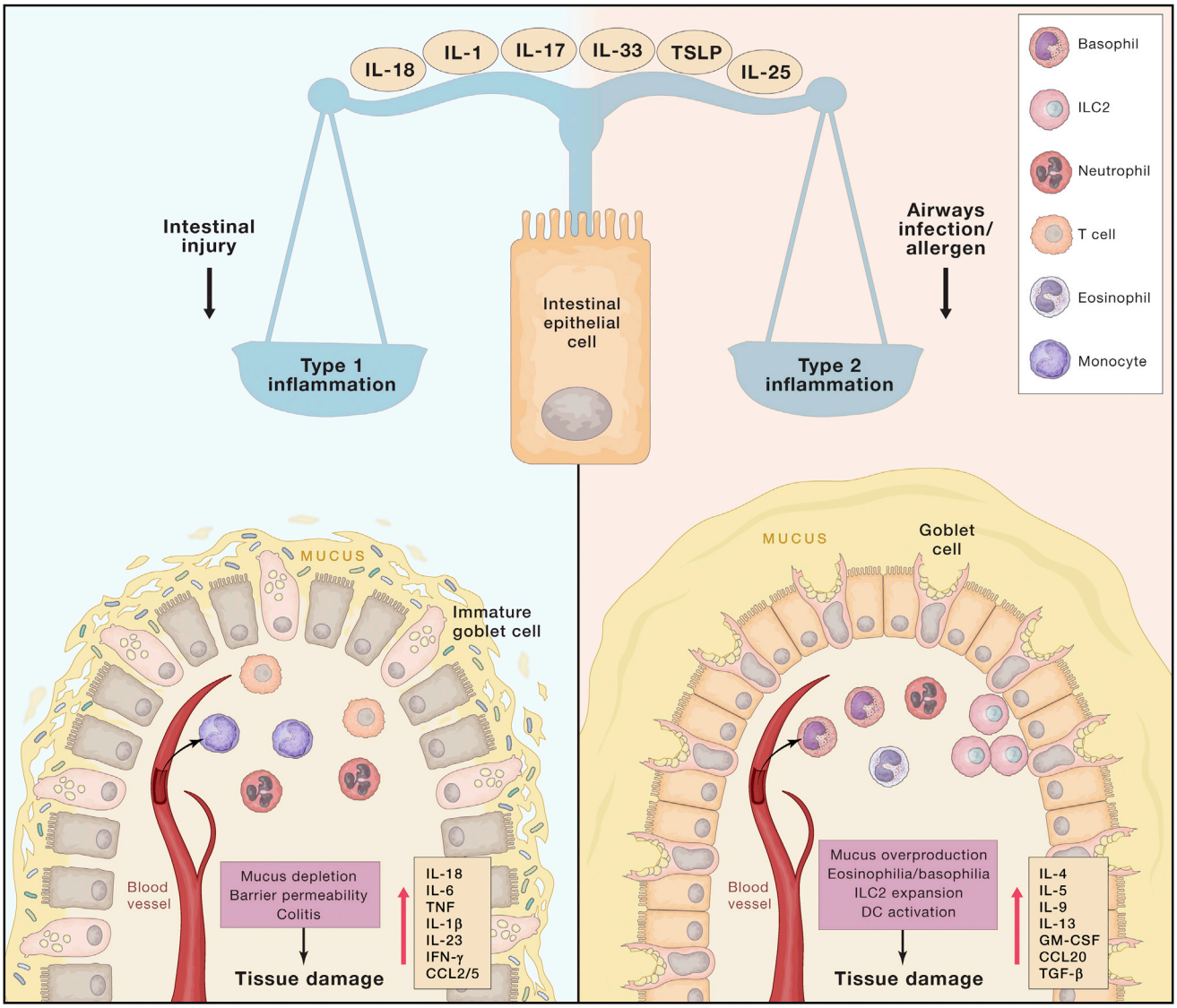

Figure 2. Subversion of Epithelial Homeostatic Immune Modules in Barrier Pathology

Homeostatic production of epithelial cytokines is imperative to control the type and intensity of inflammatory responses at mucosal barrier sites. This balance may be compromised following injury or infection, leading to dysregulated epithelial cytokine production that may exacerbate pathological inflammation and tissue damage. Excessive production of IL-18 following intestinal injury promotes depletion of mature goblet cells and the mucus layer, thus increasing barrier permeability and driving colitis. Recruited immune cells amplify type-1 responses that inflict tissue damage. Alternatively, excessive production of IL-33 or TSLP following airways infection or allergen exposure promotes goblet cell hyperplasia and mucus overproduction, together with amplification of type-2 responses by activated resident or recruited immune cells. In both cases, immune responses are shaped by the combinatorial effect of inflammatory mediators produced, which is in turn dependent on the nature of the tissue perturbation and the affected cells.

(AEC)-derived IL-33 and TSLP promote IL-9 autocrine signaling in ILC2s that leads to production of IL-13 and IL-5 (Mohapatra et al., 2016). These studies depict a Th2-propagating cycle involving epithelial IL-33 alarmin production that induces an IL-13-SPDEF feedforward loop, driving goblet cell hyperreactivity and Th2 inflammation in the airways (Figure 2).

Epithelial Immune Modules in the Airways

In analogy to the intestinal epithelium, immune homeostasis in the airways is dependent on the ability of epithelial cells to sense environmental signals and produce an immunomodulatory output. Aerobic respiration in the lungs requires consumption of ~20,000 L of air per day, potentially exposing a 100 m^2 epithelial surface to inhaled pathogens, particulates, and allergens (Weitnauer et al., 2016). Several mechanisms have therefore evolved in AECs which either increase tolerance to potentially inflammatory material or promote inflammatory responses. Dependent on A20 induction in AECs, exposure to farm dust and endotoxin reduces susceptibility to allergen challenge by limiting epithelial production of CCL20, GM-CSF, and IL-33, thus mitigating DC and eosinophil recruitment and Th2 inflammation (Schuijs et al., 2015). Similarly, Rac1 GTPase deletion in

bronchial AECs leads to decreased epithelial phagocytosis of apoptotic epithelial cells, leading to higher IL-33 and lower IL-10 expression and hyper-responsiveness to allergens (Juncadella et al., 2013). In contrast to allergy-restricting epithelial mechanisms, allergen-induced TLR4 stimulation in bronchial AECs leads to autocrine IL-1α signaling that increases epithelial production of GM-CSF and IL-33, attracting DCs and activating Th2 responses (Willart et al., 2012). Epithelial TGF-β1 was also identified as an inducer of allergic responses, as mice lacking epithelial-derived TGF-β1 were protected from the effects of allergen exposure and exhibited diminished airway inflammation that was associated with reduced ILC2 activation (Denney et al., 2015). The intensity of allergic responses in the airways is therefore regulated by the net effect of inflammation-limiting and inflammation-driving epithelial signals (Figure 2).

Beyond regulation of allergic responses, AECs control the magnitude of immune responses in the steady state and following infection or injury by regulating immune cell recruitment and function. Circadian glucocorticoid hormone expression leads to rhythmic CXCL5 expression in bronchial cells that modulates pulmonary antibacterial responses by controlling neutrophil recruitment (Gibbs et al., 2014). In addition, increased neuropeptide and cytokine production from pulmonary neuroendocrine cells that fail to cluster during development leads to increased macrophage recruitment and heightened inflammation that result in disruption of alveolar structure (Branchfield et al., 2016). As discussed above, reciprocal communication with recruited or resident immune cells is an important determinant in the tissue response to infection and injury. Production of IL-18 and IL-33 during influenza virus-induced lung injury promotes secretion of amphiregulin (AREG) from Treg cells that promotes AEC repair (Arpaia et al., 2015). This crosstalk, therefore, enables the establishment of a protective feedback mechanism to resolve tissue damage, as was also demonstrated in other tissues such as skeletal muscle (Burzyn et al., 2013).

Reciprocal modulation of epithelial cells by immune cells is also important to fortify the barrier in both the airways and the intestine by enhancing cell-cell contacts and reducing barrier permeability. Tight junction formation between alveolar macrophages and alveolar epithelial cells through connexin43 is immunosuppressive and reduces LPS-induced neutrophil recruitment and inflammation (Westphalen et al., 2014). In the gut, IL-17A production by γδ T cells following intestinal epithelial injury induces the tight junction protein occludin that limits excessive epithelial permeability and maintains barrier integrity (Lee et al., 2015a). Several other cytokines, including IFN-γ, TNF, and IL-13, were shown to modulate epithelial tight junction proteins and the permeability of the mucosal barrier (Turner, 2009). In summary, constitutive and inducible epithelial immune modules initiate protective immune responses by sensing tissue damage, microorganisms and their products, inhaled particulates or allergens, and immune cell-derived signals. In parallel, epithelial cells directly limit the inflammatory potential of immune cells by enhancing production of immunosuppressive cytokines, restricting recruitment and propagation of inflammatory cells, and supporting propagation and survival of immunosuppressive cells (Figure 1). These homeostatic modules can, however, promote tissue pathology when exacerbated in response to injury or infection (Figure 2).

The Mesenchymal Barrier in Regulation of Immune Homeostasis

The connective tissue underlying the epithelial barrier is composed of mesenchymal cells and extracellular matrix (ECM) that provide the structural support for epithelial, vascular, lymphatic, and neuronal organization, as well as serves as a conduit for migration of immune cells. The connective tissue thus facilitates close and dynamic interactions between resident mesenchymal and immune cells, enabling proximity-based mechanisms of immune modulation through cellular and ECM interactions. The major connective tissue mesenchymal cell subsets can be generally classified as fibroblasts, α-smooth muscle actin (α-SMA)-expressing myofibroblasts, and perivascular pericytes, although each subset is likely to include multiple functionally distinct cell populations, and no subset can be uniquely identified by specific marker expression (Armulik et al., 2011; Powell et al., 2011). Mesenchymal cells are endowed with a remarkable ability to sense and respond to environmental signals triggered by injury or infection and regulate the local immune landscape by shifting between inflammatory and immunosuppressive states, analogous to the macrophage polarization paradigm (Bernardo and Fibbe, 2013). This plasticity enables dynamic regulatory communication with the overlying epithelium and the various immune cells populating the connective tissue.

Most connective tissues are heterogeneous with respect to resident mesenchymal populations, owing to the tissue architecture, multiple mesenchymal developmental origins, and a range of activation and differentiation states. This directly affects organ-to-organ immunomodulatory heterogeneity due to differential regulation of immune mediator expression by resident mesenchymal cells. For example, RA production is activated in intestinal fibroblasts but attenuated in skin fibroblasts, respectively regulating DC or mast cell function (Kurashima et al., 2014; Vicente-Suarez et al., 2015); $AOC3^{+}$ intestinal myofibroblasts and skin fibroblasts are characterized by distinct transcriptional programs and responsiveness to TGF-β (Hsia et al., 2016). The remarkable diversity of fibroblast subsets even within the same tissue is exemplified in the dermis, the connective tissue underlying the skin epidermis, where papillary and reticular fibroblasts are found in two different layers that differ in fibroblast density and ECM composition (Driskell and Watt, 2015). Gene expression analysis of human skin fibroblasts from different anatomical sites revealed distinct transcriptional programs regulating ECM production, metabolism, and differentiation, and suggested that *HOX* genes may direct topographic differentiation and positional memory in fibroblasts (Chang et al., 2002). A similar layered architecture and marked fibroblast diversity characterize the intestinal connective tissue, where a layer of pericryptal myofibroblasts lie in the basement membrane directly under the epithelial layer, while an inner network of fibroblasts, myofibroblasts, and pericytes is organized around blood vessels and lymphatic lacteals in the lamina propria and the muscularis mucosa (Powell et al., 2011).

Mesenchymal cells are endowed with innate sensory mechanisms, akin to innate immune cells, and can actively modulate

immune cell behavior by adjusting the local cellular and cytokine microenvironment. In the skin, activation of Notch/CSL signaling in dermal mesenchymal cells is required to prevent inflammation and tissue atrophy that precedes epithelial tumorigenesis by reducing c-Jun and c-Fos expression, thus limiting production of inflammatory cytokines and growth factors (Hu et al., 2012). Similarly, activation of Notch signaling in epidermal keratinocytes by the metalloproteinase ADAM17 is required to prevent inflammation by inhibiting c-Fos and keratinocyte production of TSLP and GM-CSF (Murthy et al., 2012). Skin fibroblasts express high levels of the RA-degrading enzymes CYP26A1 and CYP26B2, thus limiting inflammatory activation of mast cells by RA-dependent upregulation of $P2X_7$ (Kurashima et al., 2014). Dermal adipocytes share a common developmental origin with reticular fibroblast and are layered in the hypodermis underlying the reticular dermis (Driskell and Watt, 2015). Dermal adipocytes were recently shown to protect against Staphylococcus aureus bacterial infection in the skin, which induces adipocyte cell expansion and production of cathelicidin antimicrobial peptide that has bactericidal activity (Zhang et al., 2015). This adds a mesenchymal dimension to the innate immune sensing mechanisms operating in the skin. In adipose tissue, type 2 cytokines derived from ILC2s and eosinophils regulate adipocyte precursor numbers and fate and stimulate beige fat biogenesis via IL-4Rα signaling in PDGFRα$^+$ bipotential adipocyte precursors, promoting their proliferation and subsequent commitment to the beige fat lineage (Lee et al., 2015b). IL-33 was found to be critical for the maintenance of ILC2s in white adipose tissue (WAT) and in limiting adiposity in mice by increasing caloric expenditure, a process associated with recruitment of beige adipocytes in WAT involving ILC2 production of methionine-enkephalin peptides (Brestoff et al., 2015). It is therefore plausible that IL-33 produced by infected or damaged epithelial cells promotes immunity through regulation of adipocyte homeostasis.

Intestinal mesenchymal cells serve as resident sentinels and a source of chemokines and cytokines that regulate immune homeostasis, but also mediate recruitment, retention, and modulation of immune cells at sites of infection or injury. CD90$^+$ connective tissue fibroblasts express a range of TLRs, as well as HLA-DR/MHC-II molecules, and can therefore sense microbial patterns and modulate T cell function (Owens, 2015). Following allogeneic bone marrow transfer, MHC-II$^+$ myofibroblasts serve as antigen-presenting cells and promote alloreactive donor T cell expansion within the gastrointestinal tract (Koyama et al., 2011). Infection with the enteric bacterium *Citrobacter rodentium* induces NOD2-dependent expression of CCL2 (monocyte chemotactic protein 1 [MCP-1]) in stromal intestinal cells that is important for recruitment of inflammatory monocytes and pathogen clearance (Kim et al., 2011). Intestinal myofibroblasts also regulate cytokine and growth factor availability through IGFBP5, COX2, and Epimorphin, thus directly controlling epithelial proliferation and repair (Brown et al., 2007; Chivukula et al., 2014; Roulis et al., 2014; Shaker et al., 2010) (Figure 3).

The Mesenchymal Barrier in Inflammation

Several pathways involving mesenchymal homeostatic mechanisms of tissue repair may be subverted to drive pathological inflammation in the intestine. Constitutive deletion of IKKβ in colVI-lineage$^+$ intestinal mesenchymal cells reduces susceptibility to colitis and colitis-associated cancer (CAC) by reducing proinflammatory IL-6 expression and STAT3 activation (Koliaraki et al., 2015). Intriguingly, inducible deletion of IKKβ in col1a2-lineage$^+$ intestinal mesenchymal cells increases susceptibility to CAC by inducing TGF-β and HGF secretion, promoting colonic tumor growth (Pallangyo et al., 2015). Whether these contrasting results reflect the heterogeneity of intestinal mesenchymal populations or perhaps confounding developmental factors remains to be determined. Production of epiregulin (EREG) by FSP1$^+$ intestinal fibroblasts was also shown to drive tumor growth in CAC (Neufert et al., 2013). Consistent with both protective and pathogenic inflammatory potential, IL-36 induction in IECs following injury promotes mesenchymal proliferation and expression of GM-CSF, CXCL1, and IL-6, mediating immune cell infiltration, but also epithelial proliferation and production of antimicrobial peptides (Scheibe et al., 2016). As in the case of epithelial cells, excessive activation of otherwise homeostatic NF-κB and STAT3 signaling in intestinal mesenchymal cells may induce pathogenic production of inflammatory mediators such as TNF, neutralization of which is a frontline therapy in inflammatory bowel disease (Neurath, 2014).

The mesenchymal immunomodulatory capacity not only substantiates the role of tissue mesenchymal cells in the initiation of immune responses, but also places mesenchymal cells at the junction of reparative and pathological inflammation (Figure 3). Reparative inflammation depicts inflammatory signaling that mediates activation of both epithelial and connective tissue progenitors to promote expansion of the tissue structural components (Karin and Clevers, 2016). As a result of chronic injury or inflammation, however, excessive activation of fibroblasts and myofibroblasts may lead to accumulation of collagen-rich ECM and result in fibrosis. Many of the signals that induce fibroblast activation originate in damaged epithelium and include direct immune modulators such as TGF-β, IL-1, transglutaminase 2 (TG-2), and TNF, as well as immune modulators that act indirectly through immune cell activation, such as TSLP, IL-25, and IL-33 (Wynn and Ramalingam, 2012). TGF-β is expressed by multiple cell types during inflammation and is one of the most prominent drivers of fibrosis. In a multitude of organs, including the lung and kidney, the pathology mediated by TGF-β involves local fibroblast mobilization, proliferation, and differentiation into active ECM-secreting myofibroblasts, as well as recruitment of pericytes, fibrocytes, and inflammatory hematopoietic cells, resulting in excessive ECM deposition and inflammation. In the case of antigen-driven pulmonary inflammation, epithelial TGF-β promotes COX2 production in lung fibroblasts, which exacerbates chronic airway inflammation by inducing fibroblast proliferation and collagen generation, as well as mucus secretion (Sun et al., 2015). Lung injury also promotes IL-1α production by damaged AECs, which can induce inflammatory cytokines and chemokines in lung fibroblasts and promote neutrophilia and collagen deposition, exacerbating inflammatory tissue damage (Suwara et al., 2014). Induction of TG-2 signaling in alveolar epithelial cells and fibroblasts following lung injury leads to epithelial IL-6 production and activation of inflammatory responses

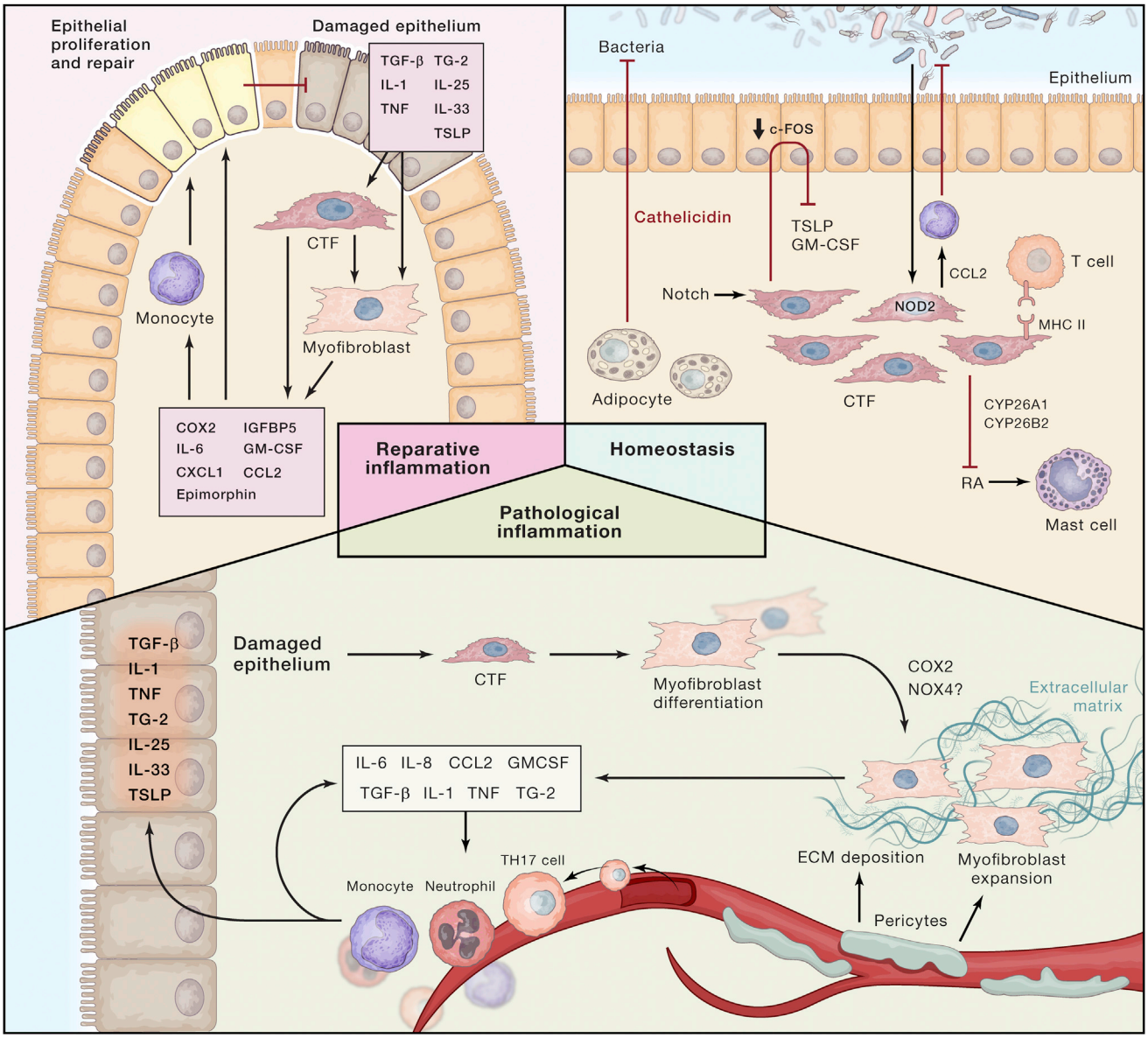

Figure 3. Mesenchymal Cells at the Crossroads of Reparative and Pathological Inflammation

Mesenchymal mechanisms controlling immunity in the skin and intestine include direct bactericidal activity and recruitment of inflammatory monocytes, as well as homeostatic regulation of epithelial inflammatory mediators and immune cell activation (top right). Following injury, epithelial-derived cytokines promote reparative inflammation by induction of cytokines and growth factors in connective tissue fibroblasts (CTFs) and myofibroblasts, promoting epithelial proliferation and repair either directly or through immune cell recruitment (top left). Chronic tissue damage or inflammation may drive the conversion of activated CTFs and vascular pericytes to ECM-producing myofibroblasts, leading to fibrosis, recruitment of inflammatory cells, and excessive production of inflammatory mediators, thus driving pathological inflammation that exacerbates tissue damage (bottom).

associated with increased Th17 differentiation and fibrosis (Oh et al., 2011).

Whereas the full spectrum of mesenchymal populations responsible for lung fibrosis remains to be established, two mesenchymal cell populations that contribute to fibrotic tissue formation following injury include FOXD1 progenitor-derived lung pericytes and collagen 1-expressing fibroblasts (Hung et al., 2013). A recent study also identified activated perivascular fibroblasts as a source of fibrosis during repeated lung injury, dependent on macrophage-mediated induction of Notch signaling (Cao et al., 2016). The dominant role of pericytes in fibrosis is consistent with identification of Gli1-expressing perivascular cells with stem cell-like characteristics as mediators of injury-induced fibrosis in various organs (Kramann et al., 2015). Regardless of its source, the fibrotic ECM itself can further induce a pro-fibrotic phenotype in lung fibroblasts (Parker et al., 2014). This may be associated with TGF-β induction of NADPH oxidase (NOX)-4 in lung fibroblasts, as its product hydrogen

peroxide is required for myofibroblast differentiation, ECM production, and contractility (Hecker et al., 2009). Similar mechanisms were described in other models such as obstructive renal fibrosis, where the injured tubular epithelium releases TGF-β that directly induces pericyte-myofibroblast transition, as well as induces epithelial growth factors that drive pericyte proliferation (Wu et al., 2013). Signals derived from the injured mucosa can therefore act on diverse resident mesenchymal cell subsets to activate myofibroblast differentiation and proliferation programs that lead to excessive ECM production and prevent resolution of tissue damage and inflammation (Figure 3).

In addition to their role in fibrosis, perivascular mesenchymal cells are important for recruitment and retention of inflammatory cells in affected tissues. In response to inflammatory mediators such as TNF or *N*-formyl-methionyl peptide (fMLP), pericytes associated with capillaries and arterioles upregulate intercellular adhesion molecule 1 (ICAM-1) and macrophage migration-inhibitory factor (MIF), which are required for interstitial migration of recruited monocytes and neutrophils to subcutaneous sites of sterile inflammation (Stark et al., 2013). Vascular inflammation induced by the vasodilator angiotensin leads to IL-6 production by aortic adventitial fibroblasts and CCL2-mediated recruitment and adventitial accumulation of inflammatory monocytes (Tieu et al., 2009). Pulmonary vascular adventitial fibroblasts isolated from humans with severe pulmonary hypertension downregulate miR-124 expression, which normally inhibits CCL2, thus providing a molecular link to excessive CCL2 production by these cells (Wang et al., 2014). Another general recruitment-retention mechanism is mediated by the CXCL12 (stromal-derived factor 1 [SDF1])/CXCR4 interaction, which promotes inflammatory cell recruitment in multiple inflammatory disorders. The same interaction is utilized by pericytes in the steady-state to retain hematopoietic progenitors in the bone marrow. Inflammatory mediators therefore condition perivascular mesenchymal cells to promote site-specific accumulation of inflammatory cells in affected tissues.

Future Directions

The concept of a non-hematopoietic immune system proxy required for establishing immunity and inflammation has been firmly substantiated in recent years, but many of the cellular players and their immunomodulatory contributions remain elusive. It is likely that research in the upcoming years will yield a more comprehensive understanding of homeostatic and inflammatory immune modules activated in specialized differentiated epithelial populations at barrier sites, together with the associated question of how inflammation regulates epithelial differentiation and wound healing. Still very little is known about the mesenchymal makeup of the barrier connective tissue, and studies expanding the structural framework of mucosal and barrier tissues will help illuminate novel cellular interactions and immunomodulatory functions. Understanding site-specific and compartmentalized microbial effects is also key in determining the full spectrum of the immunomodulatory signals operating in the barrier.

The functional heterogeneity of tissue-specific epithelial cells, fibroblasts, myofibroblasts, and pericytes, together with their ontogenic relationships and plasticity potential, need to be better understood in order to elucidate mechanisms of inflammation and develop specific and effective targeting strategies to inflammatory disease. Such mechanistic investigations would greatly benefit from the development of novel cell-type-specific genetic tools. Elucidation of epithelial and mesenchymal immunomodulatory functions may also shed light on fundamental processes in cancer initiation and progression associated with epithelial-to-mesenchymal transition (EMT) and mesenchymal-to-epithelial transition (MET), as well as immune signaling in cancer-associated fibroblasts (CAFs). Defining immune communications with other non-hematopoietic tissue constituents, including endothelial, neuronal, and lymphatic elements, is an area of intensive investigation likely to further illuminate fundamental immunoregulatory functions. While these studies will inevitably enable integration of immunological principles across barrier sites, they will also provide sub-anatomical contexts for unique and specialized immune responses. As the complex immunological circuitry within tissues unravels, the barrier to understanding the barrier is gradually being lifted.

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