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Chemokines and chemokine receptors in mucosal homeostasis at the intestinal epithelial barrier in inflammatory bowel disease

Noah P. Zimmerman, **Rebecca A. Vongsa**, **Michael K. Wendt**, and **Michael B. Dwinell***
Department of Microbiology and Molecular Genetics, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI 53226

Abstract

Chemokines, a large family of small chemoattractive cytokines, and their receptors play an integral role in the regulation of the immune response and homeostasis. The ability of chemokines to attract specific populations of immune cells sets them apart from other chemoattractants. Chemokines produced within the gastrointestinal mucosa, are critical players in directing the balance between physiological and pathophysiological inflammation in health, inflammatory bowel disease and the progression to colon cancer. In addition to the well-characterized role of chemokines in directed trafficking of immune cells to the gut mucosa, the expression of chemokine receptors on the cells of the epithelium makes them active participants in the chemokine signaling network. Recent findings demonstrate an important role for chemokines and chemokine receptors in epithelial barrier repair and maintenance as well as an intricate involvement in limiting metastasis of colonic carcinoma. Increased recognition of the association between barrier defects and inflammation and the subsequent progression to cancer in inflammatory bowel disease thus implicates chemokines as key regulators of mucosal homeostasis and disease pathogenesis.

Mucosal immunity

The healthy gastrointestinal mucosa is the largest repository of immune cells within the human body [1]. The constitutive presence and trafficking of immunocytes into the mucosal compartment has been termed physiologic inflammation and reflects production of chemokines by cells within the gastrointestinal mucosa [1-6]. The inflammatory bowel diseases (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), are chronic inflammatory diseases of the gastrointestinal tract that in genetically susceptible individuals are believed to arise out of fundamental dysregulation of the immune system in response to environmental triggers [7-9]. A growing body of work suggests that the chronic inflammation seen during IBD results from defects in the ability to properly regulate the immune system in response to the enteric microbiota [7;10-12]. These defects may include alterations in pattern

*Address Correspondence to: Michael B. Dwinell, Ph.D., Department of Microbiology and Molecular Genetics, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI 53226, Phone: (414) 456-7427 / FAX: (414) 456-6535, mdwinell@mcw.edu.

recognition receptors expressed by epithelial cells lining the gastrointestinal mucosal surface critical for identifying microorganisms [8;13-17]. In addition to recognition of the gut microbiota, disease pathogenesis may also reflect defects in immune regulation, increased influx of inflammatory cells, or diminished barrier integrity [18-23]. These factors are likely inter-related in that the additional influx of immune cells may elicit damage, resulting in epithelial and mucosal lesions, through increased production of an array of bioactive molecules. Alternatively, increased immunocyte trafficking may reflect a primary defect in barrier integrity, exacerbating pathogenesis of IBD by facilitating the entry of noxious luminal stimuli into the sub-epithelial mucosal and submucosal layers and thus leading to increased trafficking of inflammatory cells.

Further compounding IBD disease pathogenesis, patients with UC and CD are increasingly at risk for developing cancers of the colon and rectum [24-27]. Consistent with the model proposed by Itzkowitz and Yio [28] mucosal inflammation promotes the development of colon carcinoma through combinations of genetic and epigenetic mutations in an array of regulatory epithelial genes, further altering or exacerbating mucosal inflammation or mucosal wound healing responses [29;30]. The current model states that innate immune components, especially signaling through the pro-inflammatory NF-κB transcription factor, plays critical roles in connecting IBD to carcinoma development [31-33]. While these data are compelling, the causative cancer promoting genes dysregulated by these pathways in metaplastic epithelia remain to be fully established. Thus, regulation of host defense genes within the cells of the intestinal epithelial lining appears to play a key role in physiologic and pathophysiologic inflammation and may foster the progression to colon cancer in patients with unchecked mucosal immune responses.

The intestinal epithelium

Epithelial cells lining the mucosal surface of the gastrointestinal tract function in digestion and absorption of essential nutrients as well as the regulated secretion of electrolytes and macromolecules [34;35]. These cells also comprise a dynamic physical interface between the external luminal environment and the body's interior and thus represent a central mechanism of the innate immune system preventing or limiting the entry of food-and water-borne antigens and microbes [4]. The cells that comprise the mucosal barrier are a self-renewing system undergoing continuous replacement from pluripotent stem cells located near the base of the crypts of Lieberkühn. Daughters of these stem cells undergo terminal differentiation into absorptive enterocytes, Goblet cells or enteroendocrine cells as they migrate toward the crypt surface, or differentiate to Paneth cells as they migrate to the crypt base in the small intestine [36-41]. Intestinal epithelial cells migrate with increasing velocity along the basement membrane toward the small intestinal villus tip or colonic surface, whereupon those cells lose the ability to adhere to the basement membrane and undergo programmed cell death as they are subsequently shed into the intestinal lumen [37;42-44].

As highlighted in studies of IBD pathogenesis and colitis-associated cancer, epithelial cells actively participate as a dynamic front-line defense response to external stimuli, playing an integral role in innate and adaptive mucosal immunity [45-48]. Intestinal epithelial cells thus, participate in several distinct host defense mechanisms limiting pathogen or antigen entry

and the progression to colon cancer. Epithelial host defense functions include regulated secretion of electrolytes that are key to flushing noxious stimuli from the bowel lumen [35]. Alternatively, modulation of epithelial growth, apoptosis and differentiation function as repair mechanisms to maintain barrier integrity and limit entry of environmental luminal stimuli [6]. Further, the epithelium is a dynamic partner in mucosal immune responses through the regulated production of chemokines, cytokines, growth factors and antimicrobial molecules essential to mucosal inflammation and host defense [1;49-52].

Chemokines

Chemokines are a large family of small, 8-14kDa, secreted chemotactic cytokines with well-recognized roles in adhesion and directional homing of immune and inflammatory cells [53-55]. These molecules have been divided into four subfamilies based on the arrangement of highly conserved cysteine residues in the amino-terminus of the protein (Table 1). The largest chemokine subfamilies are the CXC chemokines in which the amino-terminal cysteines are separated by an intervening amino acid and the CC subfamily where the amino-terminal two cysteines are adjacent. Chemokines of the CXC subfamily can further be subdivided based on the amino-terminal presence or absence of a glutamate-leucine-arginine (ELR) amino acid motif which are potently chemoattractive for neutrophils and possess angiogenic properties [56]. Two additional subfamilies include XCL1/lymphotactin, which possess a single amino-terminal cysteine residue [57], and CX_3CL1/fractalkine in which three intervening amino acids separate the cysteines [58].

Chemokines have also been classified based on function and expression pattern into an inflammatory, or inducible, subfamily regulated by proinflammatory stimuli important in innate and adaptive immune responses. A homeostatic, or constitutive, chemokine subfamily plays a correspondingly key immune surveillance role in lymphocyte and dendritic cell trafficking between primary and secondary lymphatic tissues [59]. These molecules are highly basic proteins capable of adhering to glycosaminoglycans on cell surfaces further establishing localized foci of elevated chemoattractant concentrations [60]. In the vascular lumen, under elevated sheer stress from blood flow, endothelial-produced chemokines signal circulating leukocytes upon binding to the cognate chemokine receptor expressed by the target cells. Functionally, activation of the chemokine receptor results in increased affinity of leukocyte integrins for endothelial adhesion molecules as a first step in leukocyte diapedesis into the tissue space [61;62]. In addition, subsets of chemokines such as CX_3CL1 and CXCL16 possess transmembrane-domains that tether the chemokine ligand to the cell membrane thus further aiding the ability of those chemokines to establish focal regions of high ligand concentration and foster intimate contact with receptor expressing target cells [58;63].

Chemokine Receptors

Chemokines exert their actions through the binding and activation of specific 7 transmembrane G-protein coupled receptors located within the cell membrane of target cells [54]. Much like their ligands, chemokine receptors possess a conserved structure and possess 20-80% amino acid identity [64]. These receptors are largely linked to $G\alpha_i$

heterotrimeric G proteins and regulate cell migration [54]. Binding of the chemokine ligand to its cognate receptor activates the heterotrimeric G protein complex, resulting in the dissociation of the Gα subunit from the Gβγ subunits and establishing two distinct signaling modules capable of activating intracellular second messenger proteins. Increased flux in intracellular calcium and in turn chemotaxis of those cells is prominent amongst those signaling pathways activated by ligand engagement to chemokine receptors [53].

This shared biologic feature of chemokine signaling has classically been characterized by directed leukocyte and lymphocyte migration, and hematopoietic progenitor cell trafficking [53;54]. Within this generalized function, specificity is dictated by expression patterns of chemokine receptors on defined subsets of target cells and through temporal and spatial regulation of ligand expression. The prototypic role for chemokines in leukocyte activation and trafficking was expanded following the determination that subsets of chemokine receptors function as co-receptors for human immunodeficiency virus (HIV) infection [65;66].

Subsequent analyses of the cell types expressing chemokine receptors lead to the description of even further functions, ascribing roles for specific subsets of chemokines in angiogenesis or angiostasis [67-69], immune and non-immune tissue development [70-75], recruitment of endothelial progenitor cells [76], and epithelial wound healing [77-81]. Redundancy of ligand for chemokine receptors is a key characteristic feature of this family of immune mediators. Thus, for several different chemokines, distinct ligands may bind to a single specific receptor, or alternatively, a single ligand may bind to separate chemokine receptors, leading to a high level of redundancy in chemokine receptor function, particularly in inflammatory responses [53;54]. Ligand-receptor selectivity may also determine the level of chemokine receptor desensitization by distinct chemokine ligand subsets, suggesting a hierarchical relationship in receptor signaling. These interactions may be of importance in elucidating the intricate multifactorial relationships that exist during immune and inflammatory responses as well as lymphoid organ development.

Chemokines in mucosal inflammation

Chemokines are ubiquitous mediators of inflammation and host defense with a central role in lymphocyte recirculation and immune surveillance as well as leukocyte trafficking. In addition, chemokines play a role in several diseases, from viral diseases, to cancer metastasis, to inflammation and autoimmune diseases [65;66;82-85]. Within the gastrointestinal mucosa, physiologic and pathophysiologic inflammation in the intestine reflects a network of inter-dependent relationships that is susceptible to inappropriate activation, despite multiple checks and balances and chemokine ligand-receptor redundancy. The diseases that comprise IBD are not simple inflammatory diseases. Instead, disease pathogenesis reflects an integrated activation of signaling events within and between components of the intestine including the epithelial cells, nervous system, immune cells and extracellular matrix. The relationship between intestinal epithelial cells and immune cells is an important factor in the intestinal immune response [6]. An array of cytokines and chemokines are upregulated during and likely playing key participatory roles in immunocyte infiltration into the pathologically inflamed gut mucosa [48;61].

As previously reviewed, several reports have established the current paradigm, schematically summarized in Figure 1A, for chemokines, especially those of the inflammatory/inducible group, in mucosal inflammation and their regulation in IBD [46;48;61;86]. Thus, an array of inflammatory chemokines including CXCL8, CCL2, CCL20, CCL5 amongst others, are elevated in human specimens from CD and UC patients and likely reflect mechanisms that result in increased trafficking and localization of monocytes, dendritic cells, natural killer cells, and T lymphocytes to the gut mucosa [48;61;87-94]. As a notable example, several reports link expression of the CCR6 ligand CCL20 to the cells of the intestinal epithelium *in vitro* and *in vivo* [94-96] with directing the trafficking of dendritic cells to the subjacent lamina propria and to the subepithelial dome of Peyer's patches [97-100].

Chemokines largely of the constitutive or homeostatic group, play key roles in lymphocyte and leukocyte recirculation and, more broadly have been shown to participate in development and organization of mesenteric lymph nodes, Peyer's patches, cryptopatches and establishment of the intraepithelial lymphoid compartment [99;101-104]. Following their development in primary lymph tissues, naïve antigen-inexperienced lymphocytes as well as leukocytes circulate through secondary lymphatic tissues sampling antigens and limiting entry of microbial pathogens [62]. The role for homeostatic chemokines and their receptors in mucosal lymphoid development and trafficking of immunocytes to the lamina propria in the gut has been extensively reviewed elsewhere [48;105]. Notably, expression of the chemokine receptor CCR7 plays a critical role in the organization of secondary lymphoid tissue, including Peyer's patches in the gastrointestinal tract [70;106]. Similarly, genetic deficiency of *CXCL13* or its receptor *CXCR5* results in impaired organization of intestinal Peyer's patches [75;107]. Those data are consistent with a role for this homeostatic chemokine in lymphoid organogenesis and organization within the gastrointestinal mucosa. Additionally, intestinal epithelial cells of the small intestine produce the chemokine CCL25, while those of the large intestine selectively secrete CCL28, with each regulating the trafficking of specific T cell subsets to the mucosa of those organs respectively [102;108;109]. Alterations in the receptors for those ligands, CCR9 and CCR10, are similarly associated with marked changes in lymphocyte recirculation into the gastrointestinal mucosa, impaired organization of Peyer's patches, and other mucosal-associated lymphoid tissue [103;110]. Development and organization of gastrointestinal mucosal lymphatic tissue is not solely regulated through signaling of members of the constitutive group of chemokines as genetic ablation of *CCR6* in knockout mice similarly leads to profound alterations in dendritic cell trafficking to the epithelial barrier as well as organization of isolated lymphoid follicles [98;100;111;112].

Although those data suggest a role for homeostatic/constitutive chemokines and their receptors in development of secondary lymphatic tissues within the gastrointestinal mucosa, their role in the pathogenesis of IBD is less clearly understood. Thus, changes in expression levels of homeostatic chemokines, including CCL19, CCL21, CCL25, CCL28 as well as CXCL12 and CXCL13 have been shown to be increased in pathologically-inflamed human small intestine or colon [113-117]. Given the role for these molecules in neo-lymphorganogenesis and lymphocyte recirculation expression of constitutive/homeostatic

chemokines may therefore participate in re-organization of peripheral lymphoid structures observed in the chronically inflamed mucosa of IBD patients [114;118].

CXCL12 and CXCR4

Due to its high degree of amino acid conservation and broad eukaryotic expression, CXCL12 has been termed a primordial homeostatic/constitutive chemokine [119]. Within the gastrointestinal tract, expression of CXCL12 has been noted by the cells of the human colonic and small intestinal epithelium [120]. These data, together with previous reports detailing the expression of its cognate receptor CXCR4 by those cells [92;121], suggests an autocrine/paracrine signaling arc between the cells of the mucosal epithelial barrier. In agreement with their concomitant expression in endothelial and epithelial tissues of the small and large intestine both CXCR4 and CXCL12 are similarly expressed in other mucosal epithelia including the liver and mammary gland [69;122;123]. In mice, CXCL12, initially termed stromal cell-derived factor-1, and CXCR4, initially termed fusin, appear to be the only chemokine or chemokine receptor critical for life, as genetic deficiency in either of those genes is embryonic lethal [71;72;124]. Phenotypic changes in *CXCR4* and *CXCL12* knockout embryos include marked defects in cardiac and gut vascular development and hematopoiesis [71;72]. The comparable phenotypic defects observed in those animals suggested this receptor and ligand comprised a monogamous signaling unit. Recent work, however, suggests CXCL12 is also capable of binding to the newly characterized chemokine receptor CXCR7 which is similarly necessary for life [125;126].

In addition, CXCL12 was among the first chemokines shown to inhibit HIV-1 entry through occupancy of the CXCR4 viral co-receptor expressed on T cells, and perhaps by cells of the intestinal epithelium [120;127]. Consistent with other members of the homeostatic/constitutive chemokine group, CXCL12 activation of CXCR4 regulates trafficking of hematopoietic stem cells, naïve lymphocytes and leukocytes [128;129] and has roles in cell-type specific mitogenesis [130-132], carcinoma metastasis [82;85;122], and rheumatoid arthritis [133]. Together, these findings implicate CXCL12 and CXCR4 in the broad regulation not only of lymphocyte recirculation, but also tissue morphogenesis, tumor metastasis and inflammatory disease.

Chemokine receptors at the epithelial barrier

Studies in chemokine receptor knockout mice assessed the roles for those receptors in modulating mucosal inflammation. Mice lacking the *CCR5* chemokine receptor appeared refractory to induction of colitis associated with addition of dextran sodium sulfate (DSS) to the drinking water [134]. Alternatively, blockade of CCR2, or a combinatorial approach blocking both CCR5 and CXCR3 using neutralizing antibodies similarly lead to decreased colitis in the DSS model [134]. However, mucosal protection in the DSS model of colitis reflected abrogation of leukocyte trafficking to the gut mucosa following the concomitant pharmacological blockade of the receptors CCR2, CCR5 and CXCR3 [135]. Broad expression of those receptors by monocytes and T lymphocytes, cells with a well known role in the pathogenesis of human IBD, were protective through modulation of immunocyte trafficking into the mucosa [135]. The conclusion that decreased trafficking of those cells is beneficial to

limiting disease pathogenesis was further strengthened in recent reports in which gut T lymphocytes were shown to exacerbate epithelial barrier defects, in turn worsening gut inflammation in a murine model of colitis [136;137].

While studies implicate regulated epithelial cell expression of chemokines with increased trafficking of immunocytes to the gastrointestinal mucosa in IBD and other inflammatory disorders, expression and functional analysis of chemokine receptors by those cells is more limited. Expression of chemokine receptors by intestinal epithelial cells was noted in conjunction with the prominence of chemokine ligand production by those cells [92;121]. Much like the analysis of the varying chemokine ligands, initial reports ascribed a limited functional role for chemokine receptors to the modulation of the intestinal epithelial inflammatory response through regulation of additional chemokines or expression of cellular adhesion molecules important in leukocyte transepithelial migration [92;121].

Thus, prior reports largely ascribe a limited role for chemokines in the directed infiltration of damage-provoking or, alternatively damage-exacerbating, immune cells into the gut mucosa in IBD. However, recent evidence from our laboratory, and others, endorse expanding that model and assign a role for chemokine receptor signaling in the maintenance of the epithelial barrier by stimulating the migratory repair process, termed restitution, of wounded epithelium [79;81;138]. Specifically, in addition to CXCL8, studies in cell culture systems, as modeled in Figure 1B, demonstrate that CXCL12 binding to CXCR4 regulates epithelial cell restitution, which is critical for repair of the barrier subsequent to inflammatory injury [79;81].

Epithelial wound healing

Limitations in epithelial barrier integrity have long been associated with IBD. Consistent with the morphoregulation hypothesis of Edelman [139] epithelial wound repair mechanisms parallel those important in barrier morphogenesis and require the spatial and temporal integration and coordination of epithelial migration, proliferation and maturation [140-144]. Mucosal architecture and integrity rely upon regulated epithelial migration out of the crypt toward the lumen surface [37]. The process of epithelial migration is chemotactic locomotion and does not reflect ‘pressure’ generated from continually dividing stem cells in the crypt [139;145;146]. It has been shown that deletion of extracellular mediators profoundly alters mucosal structure and epithelial maturation in transgenic mice, leading to inflammation and adenoma formation [40;147-151]. Restitution, defined as the rapid migration of epithelial cells over the site of injury independent of proliferation, is a key step in mucosal repair [140;142;144;152]. Epithelial cells surrounding the injury subsequently initiate proliferation and differentiation gene programs to complete the repair and repolarize into a mature enterocyte. Epithelial restitution and repair processes are of vital importance to homeostatic turnover characteristic of the healthy mucosa and is an essential function within normal epithelial migration [153].

Within the gastrointestinal tract several growth factors, cytokines, hormones, neuropeptides, and polyamines [154;141;143;146;149;155;156] as well as luminal peptides and probiotics have been shown to participate in epithelial restitution *in vitro* and *in vivo* [142;157;158]. The inflammatory chemokine CXCL8 was shown to stimulate epithelial carcinoma cell

migration [138;159] and the cytokine TGFβ_1 has been shown to participate both in restitution and also constitutive barrier formation [149]. TGFβ_1 and its receptor, TGFβRII, share many features in common with the homeostatic chemokine CXCL12 and its cognate receptor CXCR4. Namely, both ligand and receptor are widely expressed by a multiplicity of cellular targets *in vivo* and both of these receptor-ligand pairs have been shown to mediate cell type specific signaling of differentiation, migration, extracellular matrix formation, and immune responsiveness [65;72;160].

Restitution is dependent largely upon Rho-mediated modifications to the actin cytoskeleton [147;161-166]. Deficiencies in specific F-actin regulatory signaling pathways leads to aberrant epithelial migration and differentiation *in vitro* and *in vivo* [41;161;163;167-171]. In contrast to TGFβ_1 directed epithelial migration, the chemokine receptor CXCR4 is coupled to heterotrimeric G-proteins and, in specific target cell subsets, directly activates the monomeric RhoA GTPase to initiate actin polymerization, and in turn leukocyte migration [82;129].

The signaling pathways regulated by chemokine receptors upon ligand engagement parallel, in part, those intracellular effectors of the epithelial restitution pathway. Thus, *in vitro* assays of restitution using wounded monolayers of intestinal epithelial cells indicate epithelial sheet migration across the denuded barrier is dependent upon activation of the Rho GTPase and in turn formation of F-actin filaments at the leading edge [152;161;164]. The importance of these signaling pathways in healing of micro-ulcers *in vivo* has recently been shown in mouse models of restitution [172] and support not only the relevancy of data from the cell culture systems but also the key role for the canonical Rho-ROCK/MLCK-actin signaling module in epithelial restitution and barrier integrity. As the role for chemokines as cardinal mediators of directed cell movement in epithelial restitution had not been established, our laboratory has begun investigating the function of chemokine receptors expressed at the mucosal epithelial cell surface. Studies using cell culture systems indicate that, much like TGFβ_1, engagement of CXCL12 to CXCR4 elicits a rapid increase in epithelial restitution via activation of the RhoGTPase and the downstream polymerization of F-actin in accordance with the known epithelial migration paradigm [79;81]. Moreover, we noted that this homeostatic chemokine not only was capable of directing sheet migration across wounded epithelial monolayers but was a potent chemotactic signal for single cell suspensions of human intestinal epithelial cells. In support of those data, a report examining the functions of CCR6 indicate that ligand stimulation modulates p130Cas of the focal adhesion complex, suggesting chemokines may have broader impact on epithelial cell adhesion and migration [173]. Together, these data parallel the function of chemokines in leukocytes and suggested that CXCL12 and CXCR4 might play a role in movement of metastatic carcinoma cells out of the gastrointestinal mucosa.

Tumor metastasis

Among the most serious complications of IBD is the increased risk of colon cancer and its associated malignancy. Given their well defined roles in leukocyte trafficking, it was intuitive that chemokine receptor expression on carcinoma cells could aid in their metastasis to sites of constitutive as well acute inflammatory sites of high chemokine ligand

production. Indeed, in accordance with our studies [79] there is increasing evidence implicating several chemokine signaling networks in directed metastasis of colorectal carcinoma. Specifically, CXCR3 and CCR7 expression on the surface of colorectal carcinoma cells appears to aid in the specific homing of those cells to regional lymph nodes while CXCR4 and CCR6 seem to be more specific to liver metastasis where expression of the specific CXCL12 and CCL20 ligands, respectively, are readily abundant [174;175]. Thus, differential chemokine receptor expression by metaplastic carcinoma cells may play key roles in the sequential steps of primary tumor growth, invasion, vascular entry, cell homing and exit at ectopic tissues [85]. Consistent with that notion, we have shown that expression of an array of chemokine receptors of the inflammatory group is extensive and variable amongst a battery of colonic carcinoma cell lines [92].

Cancer is a hyperproliferative disorder that involves morphological cellular transformation, dysregulation of apoptosis, uncontrolled cellular proliferation, invasion, angiogenesis, and metastasis [176]. Clinical and epidemiologic studies have suggested a strong association between chronic infection, inflammation, and cancer [32;33;177;178]. Several chemokines are known to be prominently regulated by inflammatory mediators such as the transcription factor NF-κB, and have dysregulated expression patterns in IBD as well colorectal carcinoma. A large majority of research has focused on the role of chemokines in the pathologic recruitment of immune and vascular cells into chronically inflamed mucosa and tumors. Given the identification of chemokine receptor expression on normal intestinal epithelium as well as in colorectal carcinoma, these cells are not only producers of chemokine ligands, but are also targets of chemokine signaling. For example, CXCL8, a chemokine ligand known to upregulated in colitis and carcinoma, signaling through CXCR1 has been linked to the epithelial-mesenchymal transition in colonic carcinoma [179].

In addition to chemokines of the inflammatory group, the homeostatic primordial signaling axis CXCR4-CXCL12 has been shown to be the major chemokine network pathologically hijacked by metastasizing carcinoma cells [82;122;123;180-183]. These data are strengthened by studies showing increased CXCR4 expression in colorectal carcinomas correlated with increased metastasis and decreased clinical prognosis [184;185]. Similarly, CXCL12 stimulation of mammary cancer cells via CXCR4 and CXCR7, the newly identified receptor for CXCL12 and CXCL11, has been shown to promote tumor cell proliferation and survival [186;187]. However, recent work from our laboratory indicates CXCL12 is epigenetically silenced in colorectal cancer and that constitutive over-expression of CXCL12 in carcinoma cells increased caspase activity and decreased tumor growth and metastasis [188]. Similar findings were obtained in mammary carcinoma, implying that pathological silencing of CXCL12 is not confined to colorectal cancer [123]. Aberrant loss of homeostatic chemokine expression may thus facilitate disease progression and worsening disease prognosis by abolishing the autocrine/paracrine signaling arc of the healthy gastrointestinal epithelium (Figure 1C). Moreover, pathologic silencing of CXCL12 has been detected in ulcerative colitis samples (unpublished observations) suggesting that that small subset of cells may be at a selective advantage for metastasis in colitis-related carcinoma even though an overall modulation of CXCL12 has not been noted in UC [189]. Further studies are needed to elucidate the full importance of non-chemotactic roles for

chemokines in IBD and colitis-associated carcinoma, especially how paracrine and autocrine chemokine signaling networks are modulated in the epithelial compartment.

Future Directions

Inflammatory bowel disease, radiation injury, colorectal cancer as well as infectious enterocolitis and therapeutic drugs have long been associated with defects in epithelial integrity. Therefore, factors that contribute to wound healing are of clinical importance as possible therapeutic modality to restore barrier homeostasis. While additional work is needed, especially in *in vivo* models of colitis, the information from cell culture systems implicate chemokines as equally-potent in stimulating restitutive migration as the prototypical trefoil factors and growth factors. Chronic dysregulation of chemokines and/or chemokine receptors appears to aid in the latter steps of disease progression including *de novo* establishment of mucosa-associated lymphoid tissue, as well as carcinoma cell metastasis. Studying the genetic, epigenetic and immunological mechanisms modulating expression of chemokines and chemokine receptors will shed light on the critical roles for those molecules in the progression from physiologic to pathophysiologic inflammation and neoplasia in the human colon.

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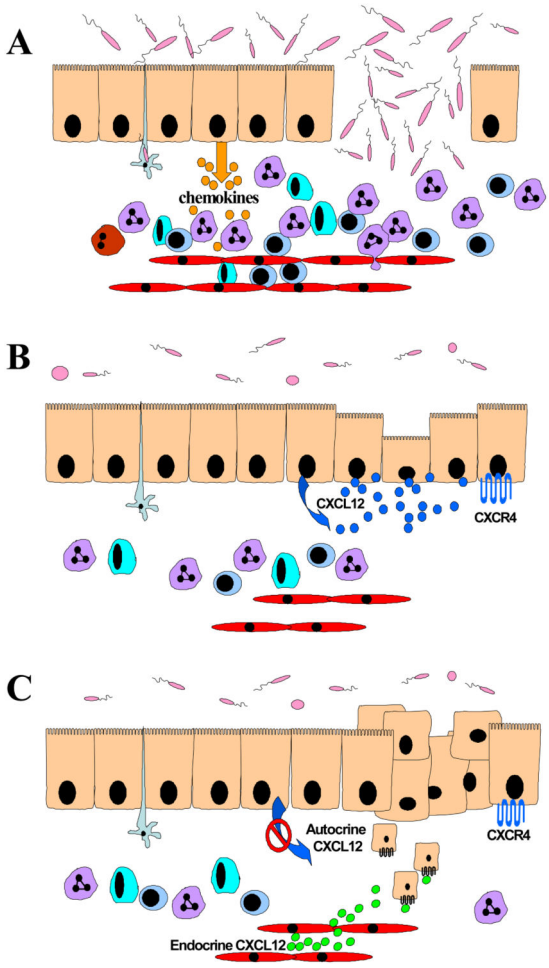

Figure 1. Expanded role for epithelial-derived chemokines in mucosal inflammation, wound healing, and carcinogenesis

A. Chemokines likely regulate immune cell trafficking in the inflammatory bowel diseases. Increased expression and production of chemokines by epithelial cells in the damaged or intact mucosal barrier direct the elevated trafficking of leukocytes and lymphocytes of the innate and adaptive immune response to the gastrointestinal mucosa. **B.** Potential roles for chemokines in repair of the epithelial barrier. The homeostatic chemokine CXCL12 is constitutively expressed in the cells of the human intestinal epithelium. In culture model systems CXCL12 activates the canonical restitutive epithelial migration signaling pathway and aids in increased closure of wounded epithelial monolayers. **C.** Chemokines differentially participate in the progression from dysplastic epithelium to frank tumor and metastasis. Epigenetic silencing of CXCL12 in the colonic carcinoma cells confers metastasis-proficient phenotype to those cells, allowing them to respond to endocrine chemokine gradients (green circles).

Table 1

Nomenclature and characteristics of chemokines and chemokine receptors.[1]

Systematic Name	Common synonym [2]	Class/Expression	Receptor	Cells Attracted
CXCL1	GROα	ELR$^+$, Inducible	CXCR2, CXCR1	neutrophils
CXCL2	GROβ	ELR$^+$, Inducible	CXCR2	neutrophils
CXCL3	GROγ	ELR$^+$, Inducible	CXCR2	neutrophils
CXCL4	PF4	ELR$^-$, Inducible	?[3]	fibroblasts, endothelial cells
CXCL5	ENA-78	ELR$^+$, Inducible	CXCR2	neutrophils
CXCL6	GCP-2	ELR$^+$, Inducible	CXCR2	neutrophils, macrophages
CXCL7	NAP-2	ELR$^+$, Inducible	CXCR2	neutrophils
CXCL8	IL-8	ELR$^+$, Inducible	CXCR1, CXCR2	neutrophils, macrophages
CXCL9	Mig	ELR$^-$, Inducible	CXCR3	Th1 T cells, NK cells
CXCL10	IP-10	ELR$^-$, Inducible	CXCR3	Th1 T cells, NK cells
CXCL11	I-TAC	ELR$^-$, Inducible	CXCR3	Th1 T cells, NK cells
CXCL12	SDF-1	ELR$^-$, Constitutive	CXCR4, CXCR7	CD34$^+$ progenitor cells and most hematopoietic cell types
CXCL13	BCA-1	ELR$^-$, Constitutive	CXCR5	naive B cells, CD4$^+$ T cells
CXCL14	BRAK	ELR$^-$, Constitutive	?	monocytes, immature dendritic cells, NK cells
CXCL16	SR-PSOX	ELR-, Constitutive	CXCR6	naïve CD8$^+$ T cells, subsets of activated memory CD4$^+$ T cells, NK-T cells
CCL1	I-309	Inducible	CCR8	monocytes, T cells, B cells
CCL2	MCP-1	Inducible	CCR2	monocytes, T cells, NK cells, immature dendritic cells
CCL3	MIP-1α	Inducible	CCR1, CCR5	monocytes, macrophages, NK cells, T cells, Th1 T cells, Th2 T cells, immature dendritic cells
CCL4	MIP-1β	Inducible	CCR5, CCR8	monocytes, macrophages, T cells, Th1 T cells, immature dendritic cells
CCL5	RANTES	Inducible	CCR1, CCR3, CCR5	monocytes, macrophages, eosinophils, NK cells, T cells, Th1 T cells, immature dendritic cells
CCL7	MCP-3	Inducible	CCR1, CCR2, CCR3	monocytes, macrophages, NK cells, T cells, immature dendritic cells
CCL8	MCP-2	Inducible	CCR3	eosinophils, basophils, mast cells, Th2 T cells
CCL11	Eotaxin	Inducible	CCR3	eosinophils, basophils, mast cells, Th2 T cells
CCL13	MCP-4	Inducible	CCR2, CCR3	monocytes, T cells, NK cells, immature dendritic cells, eosinophils, basophils, mast cells, Th2 T cells
CCL14	HCC-1	?	CCR1	monocytes, macrophages, NK cells, T cells
CCL15	HCC-2	?	CCR1, CCR3	monocytes, macrophages, NK cells, T cells, eosinophils, basophils, mast cells, Th2 T cells
CCL16	HCC-4	?	CCR1	monocytes, macrophages NK cells, T cells

Systematic Name	Common synonym [2]	Class/Expression	Receptor	Cells Attracted
CCL17	TARC	Inducible/constitutive	CCR4	Th2 T cells, macrophages
CCL18	PARC	Constitutive	?	T cells
CCL19	MIP-3β/ELC	Constitutive	CCR7	T cells, B cells, mature dendritic cells
CCL20	MIP-3α/LARC	Inducible/Constitutive	CCR6	T cells, B cells, immature dendritic cells
CCL21	SLC	Constitutive	CCR7	T cells, B cells, mature dendritic cells
CCL22	MDC	Inducible/Constitutive	CCR4	Th2 T cells, macrophages
CCL23	MPIF1		CCR1	
CCL24	Eotaxin-2	Inducible	CCR3	eosinophils, basophils, mast cells, Th2 T cells
CCL25	TECK	Constitutive	CCR9	thymocytes, T cells
CCL26	Eotaxin-3	Inducible	CCR3	eosinophils, basophils, mast cells, Th2 T cells
CCL27	CTACK	Constitutive	CCR10	T cells, monocytes, B cells, immature dendritic cells
CCL28	MEC	Constitutive	CCR10, CCR3	T cells
XCL1	lymphotactin	?	XCR1	T cells, natural killer cells
CX_3CL1	fractalkine	Inducible/Constitutive	CX_3CR1	T cells, monocytes, neutrophils

[1] CXCL15, CCL6, CCL9/CCL10, and CCL12 represent the mouse chemokines lungkine, C10, MRP-2, and MCP-5 for which the human orthologs have yet to be identified.

[2] abbreviations used: BCA, B cell-activating chemokine; BRAK, breast and kidney chemokine; CTACK, cutaneous T cell-attracting chemokine; ENA, epithelial neutrophil attractant; ELC, Epstein-Barr virus-induced receptor ligand chemokine; GCP, granulocyte chemoattractant protein; GRO, growth-related oncogene; HCC, hemofiltrate CC-chemokine; IP, γ-interferon-induced protein; I-TAC, interferon-inducible T cell α chemoattractant; LARC, liver and activation-related chemokine; MCP, monocyte chemoattractant protein; MDC, macrophage-derived chemokine; MEC, mucosa-associated epithelial chemokine; MIG, monokine induced by γ-interferon; MIP, macrophage inflammatory protein; NAP, neutrophil activating protein; PARC, pulmonary and activation-regulated chemokine; PF, platelet-factor; RANTES, regulated on activation normal T cell expressed and secreted; SDF, stromal cell-derived factor; SLC, secondary lymphoid tissue chemokine; SR-PSOX, scavenger receptor for phosphatidylserine and oxidized lipoprotein; TARC, thymus and activation related chemokine; TECK, thymus expressed chemokine.

[3] Question mark indicates unknown receptor or regulation pattern.