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Intestinal Mesenchymal Cells

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Abstract

The non–white blood cell mesenchymal elements of the intestinal lamina propria are the myofibroblasts, fibroblasts, pericytes, stromal stem cells, muscularis mucosae, and the smooth muscle of the villus core associated with the lymphatic lacteal. We review the functional anatomy of these mesenchymal cells, what is known about their origin in the embryo and their replacement in adults, their putative role in intestinal mucosal morphogenesis, and the intestinal stem cell niche, and we consider new information about myofibroblasts as nonprofessional immune cells. Although our knowledge of the function of mesenchymal cells in intestinal disease is rudimentary, we briefly consider here their roles in cancer and intestinal inflammation.

Keywords

Myofibroblast; Muscularis mucosae; Stem cell niche; Mesenchymal stem cell; Fibrocyte; Pericyte; Stromal cell; Alpha smooth muscle actin; Mucosal immunology; Lymphatic lacteal; Intestinal immunity; Innate immunity; Adaptive immunity; Mucosal tolerance; Inflammation; Antigen presentation; Programmed cell death ligands; Regulatory T cell; Intestinal morphogenesis; Colorectal cancer; Cancer microenvironment; Inflammatory bowel disease; Intestinal inflammation

Introduction

The mesenchymal elements of the intestinal lamina propria, excluding white blood cells and endothelium, are the stromal cells (myofibroblasts and fibroblasts), the mural cells (pericytes) of the capillaries (which may be categorized as part of the intestinal stromal cell compartment), the bone marrow-derived stromal stem cells, the smooth muscle of the muscularis mucosae, and the smooth muscle bundles of the small intestinal villus core that are associated with the lymphatic lacteals. These mesenchymal cells possess similar marker molecules, origins, and coordinated biologic functions. This review addresses briefly the biology of these mesenchymal cells and recent studies demonstrating myofibroblasts act as nonprofessional immune cells. Their roles in diseases, especially gastrointestinal cancer and intestinal inflammation, are introduced. The reader is referred to recent excellent reviews of intestinal mesenchymal cells in health and disease [1•,2•,3••].

Identification Markers

Myofibroblasts are identified by their expression of the intracellular cytoskeletal microfilament α smooth muscle actin (α -SMA), intermediate filaments such as vimentin and desmin, and the absence of epithelial cytokeratins (Table 1) [4]. However, other mesenchymal elements of the lamina propria also express α -SMA: mural cells (pericytes) [5,6], bone marrow-derived stromal stem cells [6,7], the muscularis mucosae [4], and the smooth muscle of the small intestinal villus core that is associated with the lymphatic lacteal [8]. The muscularis mucosae and the smooth muscle of the villus core stain poorly with antibodies against vimentin, but react strongly to desmin antibodies, whereas the myofibroblasts and mural cells in uninflamed intestine do not stain for desmin [4,9,10].

The mesenchymal elements of the lamina propria are also identified by CD90, also known as thymocyte differentiation antigen 1 (Thy 1). Thy-1 is a 25–37 kDa, extracellular glycosylphosphatidylinositol-linked glycoprotein expressed by fibroblasts, myofibroblasts, mesangial cells, vascular pericytes, hematopoietic and mesenchymal stem cells, and activated endothelial cells. Its use in the mouse is limited because it is also expressed also by neurons and T cells [11].

Origin of Intestinal Stromal Cells

Embryonic Origin

Myofibroblasts are demonstrable as early as 21 weeks in the human embryo and in the mouse at E18.5 [12]. Neural crest cells have been shown to be the origin of a specialized myofibroblast within peripheral nerves [13], and as pericytes in the vessels of the thymus [14], but have not been well studied in the intestine. More compelling evidence has been presented that the serosal mesothelium is the common source of myofibroblasts and pericytes in the intestinal lamina propria [15].

Origin in Adults

The major source of myofibroblasts in the liver and pancreas is thought to be differentiation from stellate cells and this may occur in lung, skin, and presumably the intestine. Transforming growth factor β (TGF β) is considered to be the key inducer of myofibroblast differentiation [2•].

Epithelial to mesenchymal transition (EMT) occurs during embryonic development and during cancer tumorigenesis and metastasis [16]. In spite of a growing body of evidence incriminating EMT in tissue fibrosis, lineage tracing studies have failed to demonstrate EMT as a source of

liver or kidney fibrosis [17,18]. EMT has been suggested as a cause of persistent fistulae in Crohn's disease [19].

Using in situ detection of the Y chromosome in female humans and mice transplanted with male donor marrow, both subepithelial myofibroblasts and lamina propria mural cells can be shown to be replenished by bone marrow stem cells, especially following intestinal injury or neoplasia [20]. Mesenchymal stem cells (MSC) [21] and fibrocytes [6] are candidate intestinal stromal stem cells. MSCs are defined as CD45⁻ (pan-hematopoietic marker), CD34⁻ (hematopoietic stem cell/progenitor marker), α -SMA⁺ cells. The fibrocyte is a circulating α -SMA⁺, CD45⁺, CD34⁺ cell that is derived from a small subset of circulating CD14⁺ peripheral blood monocytes expressing immunoglobulin G (IgG) receptors. Fibrocytes, like MSCs, are found in inflamed tissue and in cancers [6]. Understanding these two bone marrow-derived cells and their abilities to induce or suppress immunity may be the key to stem cell therapeutics for gastrointestinal diseases [21].

Brown et al. [7] have reported a cyclooxygenase-2 (COX-2) expressing stromal cell in the lamina propria, which appears to be critical to epithelial repair in a dextran sodium sulfate (DSS) colitis model. These may be stromal stem cells in transit from the vasculature to become either pericytes or subepithelial myofibroblasts in the injured gut.

Mesenchymal-Epithelial Interactions

Intestinal morphogenesis is dependent on bidirectional instructive signals between the endoderm (epithelium) and mesoderm (mesenchymal cells) in the embryo and in the postnatal animal. Excellent and more detailed reviews are available of intestinal development/morphogenesis [12]. We focus briefly here on the role of epithelial-derived hedgehog (Hh) growth factors in the formation of the lamina propria mesenchymal cells and how these cells contribute to the epithelial stem cell niche.

Hedgehog (Hh) signaling is the most important factor in the development of the mesenchymal elements of the lamina propria [22]. The role of Indian Hedgehog (IHH) and Sonic Hedgehog (SHH) in intestinal morphogenesis has been examined in several transgenic or knockout murine models [10,23,24]. In all models, a disturbed epithelial to mesenchyme paracrine action results in myofibroblasts being mislocated throughout the villus, with disorganization or loss of smooth muscle fibers in the villus core and reduction or loss of the muscularis mucosae. Thus, decreased Hh signaling in the embryo results in failure of myofibroblasts to develop in an orderly subepithelial location, and failure of lamina propria smooth muscle elements to form properly. In two of the models there was early death (1–10 months) from varying degrees of villous atrophy, diarrhea, malabsorption and malnutrition [23,24]. The Hh knockout models are phenotypically similar to chronic small intestinal inflammatory diseases, especially celiac disease, where villus loss is a common histology. However, disorganization or the absence of small intestinal villous smooth muscle in this model suggests loss of lymphatic lacteal function, a condition called lymphangiectasia [25].

The Intestinal Stem Cell Niche

The intestinal epithelial stem cell niche is composed of epithelial cells, mesenchymal cells, basement membrane, and soluble and cell-associated growth and differentiation factors. The critical signaling molecule driving proliferation within the intestinal stem cell niche are the Wnts [26••]. Genes regulated by Wnt signaling are preferentially expressed within intestinal epithelial stem cells or immediate progenitors, and include *Lgr5* and *Olfm4*, which mark intestinal stem cells [26••]. The predominant cellular source of intestinal canonical Wnts (Wnts 3, 6, 9b) are the epithelial cells, whereas noncanonical Wnts (Wnts 2b, 4, 5a, 5b) and Wnt antagonists (SFRP-1, SFRP-2, Dkk-2, and Dkk-3) originate from the mesenchymal cells (Table

2) [26••]. Thus, one of the key functional roles of mesenchymal cells of the niche is to restrict Wnt/ β -catenin signaling to intestinal stem cells or early progenitor cells, and prevent any abnormal activity of this proliferative pathway in mature intestinal epithelial cells.

The mesenchymally derived bone morphogenetic proteins (Bmps) are members of the TGF β superfamily [27]. Bmps antagonize Wnt signaling along the crypt-villus axis, inhibiting stem cell expansion and promoting epithelial differentiation [27]. In the intestine, Bmp4 is synthesized by lamina propria stromal cells, whereas Bmp receptors are found on epithelial and stromal cells [10]. The reason why Bmp signaling is not active within the stem cell zone of intestinal crypts has recently been clarified by Kosinski et al. who found that myofibroblasts and muscularis mucosae cells located at the base of the crypts secrete the Bmp inhibitory molecules such as gremlin 1, gremlin 2, and chordin-like 1 [28•]. Thus, cryptal myofibroblasts and muscularis mucosae cells, via regional secretion of Bmp antagonists, create an environment in the stem cell niche where Wnt signaling proceeds unopposed. The Bmp tone increases lumenally generating an environment that promotes epithelial differentiation [28•].

In addition to regulating myofibroblast and smooth muscle development during ontogenesis, Hh signaling is also a primary determinant of stromal Bmp synthesis and, thus, contributes to establishment of the epithelial stem cell niche. As mentioned above, studies with transgenic animals have demonstrated that active Hh signaling within the stroma results in decreased epithelial proliferation and expansion of smooth muscle cells and myofibroblasts [29]. Mice engineered to exhibit attenuated Hh signaling show an opposite phenotype where intestinal myofibroblasts and smooth muscle cells are depleted and an expansion of the epithelial stem cell and progenitor pool occurs [10,23,24]. A similar phenotype is observed in transgenic mice overexpressing the Bmp inhibitor Noggin under the control of the villin or fatty acid binding protein promoter indicating the importance of Bmps as downstream mediators of Hh signaling [22,23]. Epithelial synthesis of Hh proteins in the adult gut is generally restricted to differentiated epithelial cells higher along the villus-crypt axis, further ensuring a lower level of Bmps within the proliferative zone at the base of the crypt [22].

Role of Myofibroblasts in Cancer

Although the genetic mutations that accumulate within epithelial cells lead to altered proliferation, resultant tumors are composed of various cell types. The importance of epithelial-mesenchymal interactions in both the initiation and progression of tumorigenesis are becoming increasingly more appreciated [30••]. Regulation of normal and carcinoma epithelial cell growth, migration and differentiation is dependent on microenvironmental cues. This microenvironment consists of extracellular matrix (ECM), mesenchymal cells (myofibroblasts, fibroblasts, smooth muscle cells, pericytes, endothelial cells, neutrophils, lymphocytes, and macrophages) and the basement membrane.

Differences in phenotypes, growth patterns, and migration have been noted between normal and tumor myofibroblasts and modification of the stroma during carcinoma formation is mediated, in part, via autocrine growth factor signaling in the stroma [30••]. The prevailing dogma is that epithelial cells amass genetic mutations that result in activation of fibroblasts into α -SMA⁺ expressing myofibroblasts [31]. The modified phenotype of these myofibroblasts is similar to fibroblasts associated with wound healing [5,31]. These activated myofibroblasts are known as peritumoral, reactive stromal, carcinoma-associated, or tumor-associated fibroblasts [31].

Differences have been noted both in vivo and in vitro between tumor-derived myofibroblasts and myofibroblasts from normal tissue in their ability to stimulate epithelial proliferation and malignant transformation of immortalized epithelial cells [30••,31]. Employing a powerful model allowing recapitulation of stromal/epithelial interactions, Orimo et al. [32] have

demonstrated that co-injection of MCF-7 breast cancer cells with tumor associated myofibroblasts, as opposed to normal myofibroblasts or no myofibroblasts, into nude mice results in an enhanced tumor growth rate and tumor size. Similarly, deletion of the TGF- β receptor in stromal cells results in gastrointestinal epithelial malignancies in mice [33]. These studies demonstrate that myofibroblasts do not merely react to malignant epithelium, but rather that phenotypic alterations of myofibroblasts may, in and of themselves, induce the formation of premalignant and malignant tumors.

Through paracrine secretion of soluble factors and also through influencing extracellular matrix composition, myofibroblasts play a permissive role in colonic tumorigenesis [30••]. Myofibroblasts are a primary site of COX-2 expression in sporadic adenomatous polyps [5] and human myofibroblasts treated with PGE₂ release elevated levels of amphiregulin, HGF, and VEGF, which modify epithelial proliferation, epithelial migration, and neoangiogenesis, respectively [34]. Myofibroblasts also influence the progression of colorectal tumors by synthesis of other paracrine factors. These include abnormal basement membrane components, production of paracrine growth factors (IGF I and IGF II, HGF, EGF, VEGF, FGFs), and extracellularmatrix degrading enzymes such as metalloproteinases [31]. The ECM in the tumor microenvironment may serve as a barrier against tumor invasion, but it is also a reservoir of cell binding proteins and growth factors that affect tumor cell behavior. The ECM is substantially modified by proteases produced by tumor and stromal cells. As a result of the activity of these proteases, cell-cell and cell-ECM interactions are altered, new biologically active ECM molecules are generated, and the bioavailability and activity of many growth factors, growth factor receptors, and cytokines are modified [30••].

Convincing evidence has been presented in support of the Cancer Stem Cell Hypothesis, which states that tumors contain a subpopulation of cells similar to stem cells of normal tissues [26••]. Many of the same processes underlying maintenance of the intestinal epithelial stem cell niche are also important in maintaining the cancer stem cell niche within colorectal tumors. For example, mutations along the Wnt signaling axis occur in more than 80% of human colorectal cancer [26••]. Overexpression of Bmp antagonists has been noted in cancer-derived myofibroblasts, and mutations affecting Bmp signaling are frequently observed in juvenile polyposis syndromes [35]. Additionally, inappropriate expression of Hh proteins has been linked to the intestinal metaplasia associated with Barrett's esophagus [36].

Stromal Cells in Innate and Adaptive Immunity

The mucosal immune response of the gastrointestinal tract is characterized by a balance between immunity and tolerance. Epithelial cells interact with the intestinal microflora and dietary antigens, but the epithelial barrier is not sufficient to prevent these antigens from entering the lamina propria. Therefore, the professional and nonprofessional immune cells that reside just beneath the epithelial layer represent a second line of immune defense to "leaked" luminal antigens. Here, we summarize evidence that gut stromal cells act as nonprofessional immune cells to regulate innate and adaptive immunity.

Innate Immunity

Microbial products reaching the lamina propria may activate the innate immune response via pathogen associated molecular pattern-sensing toll-like receptors (TLRs). TLRs on professional antigen presenting cells (APCs) such as macrophages and dendritic cells regulate the efficiency of antigen presentation to T cells. However, CD90⁺ intestinal stromal cells [myofibroblasts and fibroblasts (MFs)], which comprise up to 30% of the lamina propria mononuclear cell population, also express TLRs [37]. TLR4 engagement on MFs leads to upregulation of expression of proinflammatory mediators (including interleukin [IL]-1 α , IL-1 β , IL-6, and IL-8) and adhesion molecules such as ICAM-1 [38], a process leading to the

migration of professional immune cells to the site of local gastrointestinal mucosal inflammation.

Immunoregulatory Role in Adaptive Immunity

The majority of gastrointestinal peripheral CD4⁺ T cells exist as resting lymphocytes that can be quickly activated by presented antigens. CD4⁺ T cells are central to effective adaptive immunity, and their response is dictated by APCs. The capacity of intestinal stromal cells to regulate lymphocyte activation through major histocompatibility complex (MHC) class II expression is widely accepted. Moreover, we recently reported that human colonic MFs represent a major fraction of mucosal lamina propria MHC class II⁺ APCs in the uninfamed intestine and are capable of processing/presenting antigens to CD4⁺ T cells [39].

In order to sustain robust adaptive immune responses, T-cell activity is under strict immunoregulatory control. It has been proposed that a “tolerogenic,” antiproliferative effect is a fundamental characteristic of all mesenchymal stromal cells [40•]. Our findings support this notion. MFs isolated from normal mucosa express low levels of positive B7 type co-stimulators [39], but have a stronger expression of B7 negative co-stimulators PD-L1 and PD-L2 in vitro and in situ and are able to suppress activated CD4⁺ T cells [41•]. The suppressive mechanisms involve cell-contact and soluble mediators (see [2] for a more complete discussion). It was recently demonstrated that mesenchymal stromal cells can indirectly contribute to homeostatic immunoregulation via induction of regulatory T cells (Treg) [42]. Treg are a functionally distinct subset of lymphocytes that are actively involved in the maintenance of immunologic tolerance in the gastrointestinal tract. We conclude that an important function of MHC class II-expressing intestinal MFs may be to limit antigen-specific immune responses to luminal antigens.

Intestinal Inflammation

As discussed above, the colonic MFs express cell-associated ligands and soluble mediators (Table 2) that are involved in the regulation of professional immune cell responses during immunity and tolerance and, thus, likely play important roles in the immune defense mechanisms of the intestinal mucosa. Moreover, it seems likely that “these stromal cells can modify the quality, quantity and duration of the inflammatory response” [43••].

Acute Inflammatory Responses

As briefly discussed above under Innate Immunity, in response to microbial products and to immune mediators, intestinal MFs produce a number of soluble cytokines, chemokines, and growth factors that are key contributors to inflammatory responses (Fig. 1). Some of these soluble molecules (e.g., MCP-1, RANTES, IL-8) are essential in the attraction of professional immune cells to the site of the acute inflammation; others (e.g., IL-6, TGF- β , GM-CSF) are required for the activation/differentiation of the professional APCs and T cells. Moreover, these soluble proinflammatory mediators, as well the lymphocyte derived cytokines (e.g., IL-17, IL-22) that are produced during the active burst of inflammatory responses can lead to the amplification of the proinflammatory signaling program in mesenchymal stromal cells [1•, 44,45]. In summary, over the past decades it has been established that during acute inflammation, mesenchymal stromal cells in the peripheral and secondary lymphoid organs actively regulate the kinetics and nature of the inflammatory cells via cell contact-mediated interactions and by conditioning the local cytokine, chemokine, and growth factor milieu.

Resolution of Inflammation

It has been proposed that stromal mesenchymal cells contribute to the resolution or termination of acute inflammation (Fig. 1) by withdrawing survival signals and normalizing the

proinflammatory mediator gradients leading to either the apoptosis of infiltrated leukocytes and/or by allowing them to leave inflamed tissue through the draining lymphatics [43••]. Induction of apoptosis of activated hepatic stellate cells (a liver myofibroblast) is suggested as one mechanism contributing to the resolution of the inflammation in the liver [46]. Moreover, systemic administration of mesenchymal stem cells (MSC) significantly reduced systemic pulmonary inflammation induced by polymicrobial sepsis [47]. Interestingly, the MSC antiseptic effect has been associated with overall down-regulation of inflammation-related gene expression and promotion of the genes involved in phagocytosis and bacterial killing [47]. Moreover, we demonstrated that increased levels of interferon- γ , a cytokine associated with acute Th1-type inflammation, leads to upregulation of expression of the B7 negative co-stimulator PD-L1 on colonic myofibroblasts [2•]. As pointed out above, this cell-associated molecule is involved in the direct suppression of activated lymphocyte responses. Moreover, stimulation of the intestinal MFs with LPS and proinflammatory cytokines increases expression and secretion of PGE₂ [1•], an immunoregulatory molecule involved in the suppression of Th1 type responses, epithelial restitution and regeneration and epithelial chloride and water secretion. Intestinal secretion may directly contribute to the flushing of invading bacteria from the intestinal lumen.

Chronic Inflammation

Intestinal MFs may contribute to chronic inflammatory gastrointestinal diseases such as Crohn's disease (CD), ulcerative colitis (UC), celiac disease, and food allergy via alteration of matrix deposition, upregulation of proinflammatory cytokine production, disruption in the balance of mucosal inflammatory cells, and changes in the menu of secreted, soluble immunoregulatory molecules and mediators. Thus, it seems likely that mucosal MFs may prevent the resolution of acute inflammation, leading to chronic inflammation (Fig. 1). Intestinal MFs taken from chronically inflamed tissues display a fundamentally altered phenotype compared with cells extracted from normal tissues at the same anatomic site [1•]. Increased collagen secretion by inflammatory bowel disease (IBD)-derived fibroblasts in response to the profibrogenic factors (PDGF, bFGF, and TGF β 1) has been noted [48]. Studies in our laboratory demonstrated that UC-derived MFs have enhanced expression of PD-L1, the immunosuppressive molecule discussed above, whereas myofibroblasts derived from CD showed decreased expression of this molecule when compared to normal controls (I.V. Pinchuk, unpublished observation). This alteration in stromal cell PD-L1 expression may contribute to the imbalance in Th1/Th2 immune responses observed during chronic inflammation associated with IBD.

Switch from Acute to Chronic Inflammation

It remains unclear if, and in what manner, the immunoregulatory function of the intestinal stromal cells changes during the switch from acute to chronic inflammation. A transient appearance of activated MFs is accompanied by resolution of acute inflammatory activity. This is usually accompanied by a balanced repair process. However, the persistence of these cells in an activated, α -SMA⁺ myofibroblast form is proposed to have a stronger proinflammatory effect [45], and is suggested to promote tissue fibrosis and chronic inflammation [1]. In an animal model of intestinal inflammation, an increase in activated α -SMA⁺ stromal cells is noted in colonic mucosa in the earlier stage of chronic inflammation [1•,20]. In murine models of colitis it has been demonstrated that bone marrow-derived cells contribute to the increase in the number of α -SMA⁺ (activated) intestinal stromal cells in inflamed regions when compared with noninflamed regions of mucosa [20]. Both increases [1•] and decreases [49] in subepithelial myofibroblasts have been reported in human IBD tissue. There appears to be an increased sensitivity to apoptosis [50] by MFs isolated from IBD tissue. This dichotomy in the number of cells expressing α -SMA may be explained by the stage of tissue repair being observed in the model or during the human inflammatory disease, since we know that during

the normal healing process, α -SMA⁺ myofibroblasts may increase and then decrease [5]. Also, it is possible that at some point during ongoing inflammation, several different populations of α -SMA⁺ activated mesenchymal stromal cells may be present in the mucosa: 1) myofibroblasts derived from locally activated “normal” fibroblasts that contribute to tissue repair and will then undergo apoptosis to resolve the inflammatory process, as described for hepatic stellate cells [46]; or 2) myofibroblasts acutely derived from bone marrow precursors that arrive at the site of ongoing inflammation where the inflammatory milieu might alter their immunoregulatory molecular expression pattern during differentiation into myofibroblasts. The imbalance between these two possible scenarios might define the appearance of a persistent proinflammatory phenotype of the intestinal stromal cells that perpetuates chronic inflammation (Fig. 1).

Conclusions

Alpha smooth muscle positive stromal cells are replenished in the adult intestine by bone marrow stem cells, and understanding their function is the key to the future of stem cell therapy of intestinal diseases. Lamina propria mesenchymal cells are critical to the instruction of intestinal morphogenesis and regulation of epithelial proliferation and differentiation in the stem cell niche. These processes are subverted by cancer to enhance carcinogenesis, tumorigenesis, and metastasis. The understanding of the immune function of intestinal stromal cells is far from complete. Studies of intestinal stromal cells and those in other parenchymal organs allow us to propose that these cells are appropriately “licensed” to be active participants in innate immunity and in the regulation of professional immune cells during active immunity or tolerance. Thus, lamina propria stromal cells are part of a sophisticated immune network throughout the mammalian body and play important roles in intestinal inflammatory diseases.

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Fig. 1.

Role of intestinal stromal cells (myofibroblasts and fibroblasts [MF]) in resolving acute and perpetuating chronic inflammation. In response to microbial products and dietary peptides that cross the epithelial barrier, intestinal MFs may be activated to produce proinflammatory mediators and molecules that may either down regulate inflammation or lead to chronic inflammation. Recent research has provided insights to the immunosuppressive function of MFs. However, little is known about the mechanisms whereby MFs cause sustained inflammation. We postulate that myofibroblasts derived from epithelial to mesenchymal transition (EMT) and/or bone marrow (BM) stem cell migration may do this through yet unknown processes and factors

Table 1

Mesenchymal stromal cell markers

Cell type	Myofibroblasts	Fibroblasts	Pericytes	Stromal stem cells	Muscularis mucosae	Lymphatic lacteal-associated smooth muscle
Markers						
α -SMA	+	-	+	+	+	+
Desmin	-	-	$\pm$	-	+	+
Vimentin	+	+	+	+	-	-
CD90	+	+	+	+	$\pm$	+

α -SMA α smooth muscle actin

Table 2

Cytokines, growth factors, and other mediators secreted by intestinal stromal mesenchymal cells

Cytokines	Growth factors	growth factors	Chemokines	Other mediators
IL-1	Amphiregulin	KGF	Eotaxin	CO
IL-6	BMP	NGF	Gro-1 α	H ₂ O ₂
IL-11	BMP antagonists	NPP1	IL-8	HETE
IL-13	BDNF	PDGF-AA	MCP-1	IDO
IL-15	CSF-1	PDGF-BB	MIF-1	PGE ₂
IL-23	FGF 2,7, 13	SCF	MIP-1 α	Prostacyclin
LIF	bFGF	SDF	MIP-2	Retinoic acid
TNF- α	GM-CSF	TGF- β	RANTES	
	HGF	VEGF		
	IGF-I	Wnts		
	IGF-II	Wnt antagonists		

BDNF brain-derived neurotrophic factor, *BMP* bone morphogenetic proteins, *CSF* colony-stimulating factor, *FGF* fibroblast growth factor, *GM-CSF* granulocyte-macrophage colony-stimulating factor, *HETE* hydroxyeicosatetraenoic acids, *HGF* hepatocyte growth factor, *IDO* indoleamine 2,3-dioxygenase, *IGF* insulin like growth factor, *IL* interleukin, *KGF* keratinocyte growth factor, *LIF* leukemia inhibitory factor, *MCP* monocyte-chemoattractant protein, *MIF* macrophage migration inhibitory factor, *MIP* macrophage inflammatory protein, *NGF* nerve growth factor, *NPP* nucleotide pyrophosphatase/phosphodiesterase, *PDGF* platelet-derived growth factor, *PGE₂* prostaglandin E₂, *RANTES* regulated on activation normal T-cell expressed, and secreted, *SCF* stem cell factor, *SDF* stromal cell-derived factor, *TGF* transforming growth factor, *TNF* tumor necrosis factor, *VEGF* vascular endothelial growth factor

(Adapted from Powell et al. [51], with permission.)