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Alteration of the Crypt Epithelial-Stromal Interface by Proinflammatory Cytokines in Crohn's Disease

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1. Introduction

The intestinal epithelium is a very dynamic tissue, being completely renewed over a 3-5 day period in the human. Epithelial cells in the intestine lie on a specialized layer of extracellular matrix material referred to as the basement membrane (BM). Intestinal epithelial cell interactions with BM molecules such as collagens, laminins, fibronectin and tenascin regulate crucial functions of the normal intestinal epithelial renewal process such as cell adhesion, migration, signalization and gene expression as well as anoikis. BM molecules can be secreted by epithelial cells but a number of them are exclusively synthesized and deposited by the subepithelial myofibroblasts. In this chapter, we will review alterations at the epithelial-stromal interface in Crohn's disease (CD) with a specific emphasis on epithelial cell and myofibroblast susceptibility to proinflammatory cytokines in the crypt region.

2. Epithelial BM molecules in the normal human intestine

The epithelial BM of the human intestine has been found to contain all the major components specific to most basement membranes as well as a number of non-exclusive BM components. There is good evidence that both types of BM components play an active role in intestinal epithelial cell biology through their interaction with specific cell membrane integrin and non-integrin receptors, which mediate cell adhesion, migration, cell cycle and gene expression. Current knowledge about epithelial BM composition in the normal human intestine is summarized below. More detailed information on BM molecules and their receptors in the intestine can be found elsewhere (Beaulieu 1997a, Beaulieu 2001, Lussier et al. 2000, Ménard et al. 2006, Teller&Beaulieu 2001).

2.1 Exclusive and non-exclusive BM components

As illustrated in Figure 1, exclusive BM components include the type IV collagens and laminins. These macromolecules are complex protein families composed of various sub-units. Detailed analysis of various genetic forms of type IV collagens and laminins revealed the presence of at least two distinct types of type IV collagen heterotrimers based on the expression of the α1(IV)/α2(IV) and α5(IV)/α6(IV) chains (Beaulieu 1992, Beaulieu et al.

1994, Simoneau et al. 1998) and the 4 main laminins, LM-111, LM-211, LM-332 and LM-511 (Beaulieu 1992, Beaulieu&Vachon 1994, Teller et al. 2007).
A second interesting feature of the intestinal epithelial BM is the presence of a relatively large number of non-exclusive BM components, such as fibronectin, tenascin-C, osteopontin and type VI collagen that have been found to be integral epithelial BM components (Aufderheide&Ekblom 1988, Beaulieu et al. 1991, Beaulieu 1992, Groulx et al. 2011, Simon-Assmann et al. 1990b) although they can be found also in the underlying interstitial matrix (Fig.1).

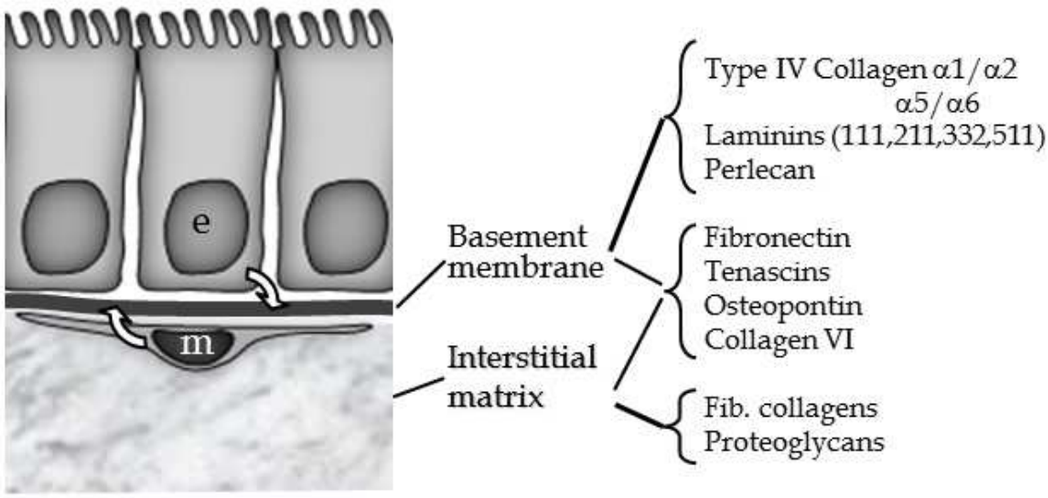

Fig. 1. The intestinal epithelial BM. The BM, which is located at the interface between the epithelial cells (e) and the subepithelial myofibroblasts (m), contains BM-specific macromolecules (e.g. type IV collagens and laminins) as well as non-exclusive BM components (e.g. tenascin-C and type VI collagen). Both types of components can originate from the epithelial cells and/or the subepithelial myofibroblasts (white arrows).

The third interesting phenomenon relative to the epithelial BM in the intestine is the dual tissular origin of the BM components. Indeed, while the type IV collagen α5(IV) and α6(IV) chains as well as type VI collagen are expressed at least in part by epithelial cells, the major type IV collagen chains α1(IV) and α2(IV) are exclusively of stromal origin (Beaulieu et al. 1994, Groulx et al. 2011, Simon-Assmann et al. 1990a, Simoneau et al. 1998, Vachon et al. 1993), presumably synthesized by the subepithelial myofibroblasts (Fig. 1). Analysis of the tissular origin of the laminins also revealed dual epithelial/stromal origin for laminins LM-111 and LM-332 (epithelial), LM211 (stromal) and LM511 (both) (Perreault et al. 1998, Teller et al. 2007).

2.2 Spatial and temporal BM microenvironments

Spatial and temporal patterns of expression for BM components in the intact intestinal epithelium have been very informative in evaluating the potential role of individual macromolecules in the regulation of cell functions, most notably cell growth and differentiation, under a normal environment. Indeed, during development, the process of endodermal differentiation into a functional epithelium coincides with the morphogenesis of the villi and the crypts in both the small and large intestines. In the mature intestine, the

epithelial renewing units consist of spatially well-separated proliferative and differentiated cell populations. Furthermore, the renewing units differ along the proximal-distal gradient, the crypt-to-villus axis of the small intestine being replaced by a gland-to-surface epithelial axis in the colon (Beaulieu 1997b, Ménard&Beaulieu 1994, Ménard et al. 2006) (Fig. 2).

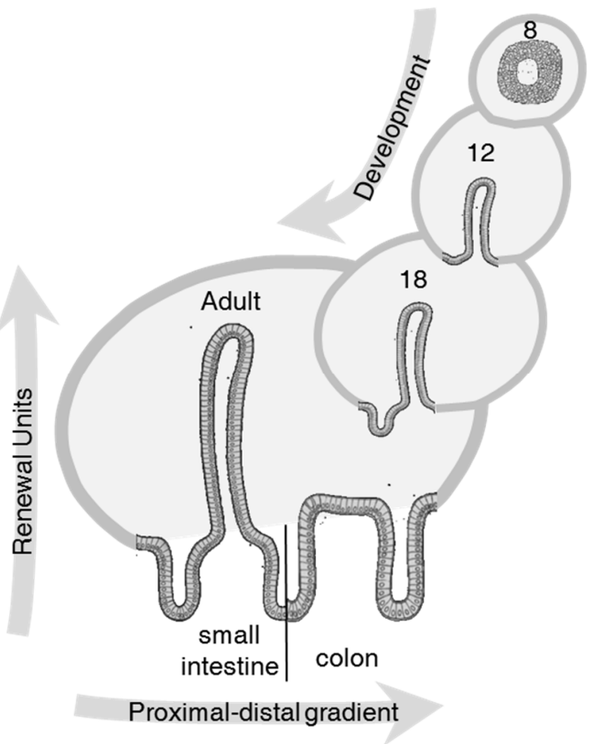

Fig. 2. Development and characteristics of the epithelium in the human small and large intestines. The human intestine develops relatively early during ontogeny. Villi develop between 9 and 11 weeks of gestation while crypts form around 16 weeks so that typical adult-like crypt-villus architecture is already established in the small intestine at mid-gestation (18 to 20 weeks). Similar crypt-villus architecture is transitorily present in the developing colon up to mid-gestation. However, at birth, the villi have disappeared and the typical adult gland-to-surface epithelial architecture has been established (proximal-distal gradient). At maturity, the proliferative cell populations responsible for the renewing of the epithelium are located in the lower ⅔ of the small intestinal crypts and the lower ½ of the colonic glands. The functional cells of these renewing units are located on the villus and the surface epithelium of the small and large intestines, respectively (Adapted from (Teller&Beaulieu 2001).

3. Alterations of epithelial BM composition in CD

Alterations of epithelial BM composition have been reported in various intestinal pathologies (Belanger&Beaulieu 2000, Teller&Beaulieu 2001). Although none of these alterations has yet been demonstrated to be the primary defect in any intestinal disease, they are not exclusively secondary to the disruption of the epithelial-stromal interface. In colorectal cancers for instance, laminin alterations are thought to play an active role in

invasion (Lohi 2001). Alteration in the distribution and/or expression of BM molecules were also observed in other intestinal pathologies such as tufting enteropathy (Goulet et al. 1995) and chronic inflammatory bowel conditions (Bouatrouss 1998). The alterations in the epithelial BM composition in the context of inflammatory bowel disease pathogenesis and as potential disease indicators will now be discussed.

3.1 BM components in the crypts of inflamed specimens from CD patients

Although clinically distinct, chronic inflammatory bowel diseases such as CD and ulcerative colitis share common histopathological features including mucosal inflammation, villous atrophy, crypt hypertrophy and epithelial cell injury (Chadwick 1991).

In CD, an important redistribution of laminins was observed at the epithelial-stromal interface of inflamed specimens as compared to non-inflamed specimens from the same patients (Bouatrouss et al. 2000). First, the crypt specific laminin, LM-211, was found to be essentially absent from the mucosa. Second, two other laminins, LM-332 and LM-511, remained strongly expressed in the epithelial BM of the atrophied and inflamed villi. However, a significant upregulation of both LM-332 and LM-511 expression was observed in the lower crypts of inflamed CD specimens. Furthermore, a significant reduction in the levels of tenascin-C was also observed in the crypt region of inflamed CD specimens (Francoeur et al. 2009). Incidentally, the intestinal mucosa is among the few sites where tenascin-C remains expressed in adulthood (Belanger&Beaulieu 2000). Interestingly, in ulcerative colitis, most of the epithelial BM surrounding the glands has been found to be devoid of immunoreactive laminin (Schmehl et al. 2000) and tenascin-C (Francoeur et al. 2009) in actively affected colonic tissues. Also, alterations in laminin and tenascin-C expression were not observed in celiac disease (Korhonen et al. 2000), an immune-mediated intestinal pathology that is also characterized by villus atrophy and crypt hyperplasia (Maki&Collin 1997), suggesting that the redistribution of laminins and tenascin-C in CD could be related to the chronic inflammatory condition.

From these studies, it can be concluded that important alterations in epithelial BM molecule expression occur in the intestinal mucosa of patients with inflammatory bowel diseases. The fact that these alterations appear to be mainly confined to the crypts in these diseases, as summarized for CD in Fig. 3, suggests that compositional changes in the crypt epithelial BM may be of functional importance in the pathogenesis of these afflictions.

3.2 Effects of proinflammatory cytokines on human intestinal epithelial crypt cells

One of the landmarks of inflammatory bowel conditions such as CD is the chronic imbalance between immunoregulatory and proinflammatory cytokines (Bouma&Strober 2003, Fiocchi 1997a, MacDonald&Monteleone 2006, Sartor 2006). Among the cytokines most frequently found to be elevated in the inflamed CD mucosa are interleukin-1β and 6 (IL-1β and IL-6), tumor necrosis factor α (TNFα) and interferon γ (IFNγ). Because they represent the main component of the intestinal barrier, epithelial cells have been one of the nonimmune cell types most extensively studied in inflammatory bowel diseases. While morphological and functional alterations in epithelial integrity were described several years ago (Dvorak&Dickersin 1980, Hollander 1993), more recent work has provided evidence that these changes are primarily mediated by cytokines released from adjacent inflammatory cells as well as from the epithelial cells themselves (Abraham&Medzhitov 2011, Dionne et al. 1999, Fiocchi 1997b, McKay&Baird 1999, Podolsky 2000).

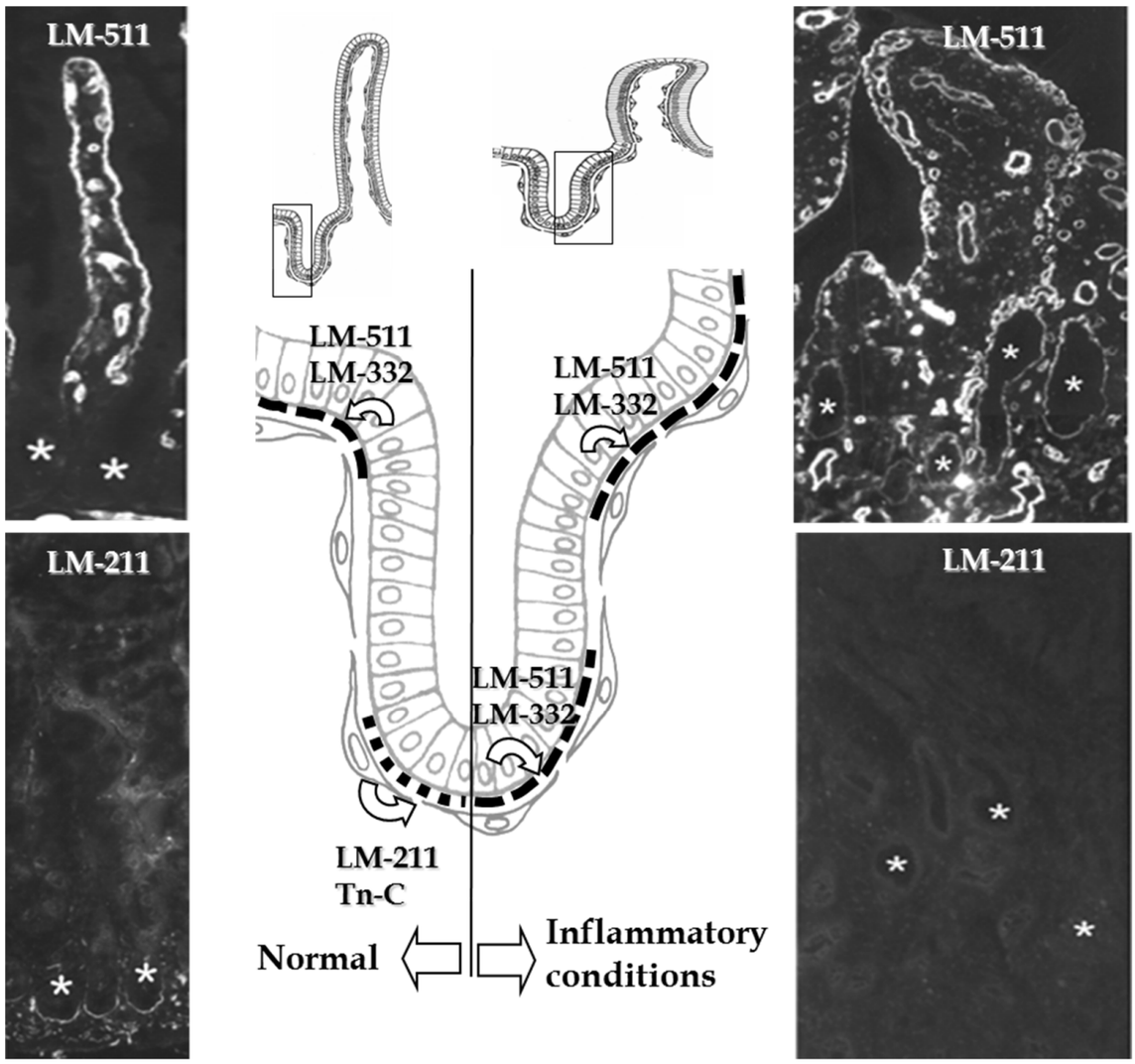

Fig. 3. Alterations of epithelial BM composition in the human intestinal mucosa under normal vs inflammatory conditions. In the normal small intestine (left), laminins LM-322 and LM-511 are found in the BM of the villus epithelial cells while laminin LM-211, is found in the BM of crypt epithelial cells. Tenascin-C (Tn-C) is found in the epithelial BM of both the crypts and villi. LM-332 and LM-511 of the epithelial BM are mainly produced by epithelial cells (E) while LM-211 and Tn-C are synthesized by the sub-epithelial myofibroblasts (SEMF). In inflamed CD specimens (inflammatory conditions), laminins LM-332 and LM-511 remain expressed by epithelial cells of the atrophied villi while in the crypts, the other laminin, LM-211, as well as most of the Tn-C at the epithelial BM are lost and replaced by the neo-expression of laminins LM-332 and LM-511. Functionally, these events are associated with pro-inflammatory cytokines which a) stimulate LM-332 and LM-511 production by crypt epithelial cells and b) induce apoptosis and de-differentiation of the sub-epithelial myofibroblasts (see sections 3.2 and 3.3 and Fig. 4 for more details).

Considering that changes in BM composition under inflammatory conditions are mainly observed in the lower part of the crypt (Fig. 3), our laboratory investigated the effect of proinflammatory cytokines on laminin expression in human intestinal epithelial cells using the well-characterized human intestinal epithelial crypt (HIEC) cell line as an experimental cell model representative of the human intestinal lower crypt (Benoit et al. 2010, Pageot et al. 2000, Quaroni&Beaulieu 1997). Individually, all tested cytokines including IL-1β, IL-6, TNFα and IFNγ as well as transforming growth factor β (TGFβ) exerted relatively modest effects on laminin LM-332 and LM-511 production in HIEC cells. However in combination, a synergistic effect of TNFα and IFNγ was observed on both laminin LM-332 and LM-511 production at protein and transcript levels (Francoeur et al. 2004). TNFα and IFNγ synergy has also been reported in various intestinal epithelial cell models for chemokine production (Warhurst et al. 1998), alteration in epithelial barrier properties (Wang et al. 2006), and acquisition of susceptibility to Fas-induced apoptosis (Begue et al. 2006, Ruemmele et al. 1999). The TNFα/IFNγ combination was also found to synergistically induce caspase-dependent apoptosis in HIEC cells (Francoeur et al. 2004). Interestingly, caspase inhibitors completely prevented TNFα/IFNγ-induced apoptosis but did not influence the induction of laminin expression indicating that the two events occurred independently.

The contribution of TGFβ in the synergistic effects of TNFα/IFNγ on laminin production was investigated in light of the fact that levels of TGFβ have been reported to be elevated in the mucosa of CD patients (Babyatsky et al. 1996) and that this multifunctional cytokine can exert a crucial function on intestinal epithelial wound healing (Podolsky 2000), in part through its ability to stimulate extracellular matrix molecule expression (Verrecchia&Mauviel 2002). Indeed, in rodent intestinal crypt cells, the promotion of epithelial healing by specific cytokines such as IL-1β, IFNγ and TGFα was found to act under a bioactive TGFβ dependent mechanism (Dignass&Podolsky 1993). However, TGFβ was found to be significantly less potent than the TNFα/IFNγ combination in human intestinal crypt cells on laminin production suggesting a TGFβ-independent mechanism (Francoeur et al. 2004).

In summary, the two proinflammatory cytokines TNFα and IFNγ synergistically induce the expression of the specific BM molecules, laminin LM-332 and LM-511, in human intestinal crypt cells. The synergistic effect of the TNFα/IFNγ combination on laminin production was found to be independent of the effect of these cytokines on cell apoptosis and appears to be controlled by an apparent TGFβ-independent mechanism.

3.3 Effects of proinflammatory cytokines on human pericryptal subepithelial myofibroblasts

Along with the epithelial cells, myofibroblasts are another important nonprofessional immune mucosal cell type for which evidence supports a participation in the pathogenesis of inflammatory bowel diseases (Fiocchi 1997b, Macdonald&Monteleone 2005). The myofibroblast is an intermediate cell type between the smooth muscle cell and the fibroblast that is characterized by alpha smooth muscle actin (αSMA) and vimentin expression (Gabbiani 2003). While there is evidence that intramucosal myofibroblasts can be involved in CD (Vallance et al. 2005), it is the intestinal subepithelial myofibroblasts present immediately subjacent to the epithelial BM (Powell et al. 2005) in the form of a pericryptal sheath that have been the primary focus of attention in the pathogenesis of inflammatory bowel diseases. Because of their vicinity to the basal surface of epithelial cells, they are potential targets for

bacteria and their products deposited in the subepithelial compartment when the epithelial barrier is disrupted. In turn, when stimulated, myofibroblasts can release various cytokines and chemokines (Fiocchi 1997b, Powell et al. 1999, Powell et al. 2005) and extracellular matrix molecules (Riedl et al. 1992) suggesting that intestinal subepithelial myofibroblasts can participate in the innate immune response (Otte et al. 2003, Saada et al. 2006). Furthermore, the subepithelial myofibroblast represents a key component of epithelial-stromal interactions in the intestine (Ménard et al. 2006, Powell et al. 2005), which can regulate both basic and healing epithelial cell functions through the secretion of paracrine factors such as the Wnts, BMPs, and TGFβ, which target epithelial cells (Ménard et al. 2006, Powell et al. 2005), the release of proteinases (Kruidenier et al. 2006, McKaig et al. 2003) and the production of extracellular matrix molecules that contribute to the epithelial BM such as laminin LM-211 and tenascin-C (Beaulieu 1997a, Perreault et al. 1998, Riedl et al. 1992, Teller et al. 2007, Vachon et al. 1993).

Analysis of subepithelial myofibroblast characteristics in inflamed small intestinal mucosa of CD patients revealed a number of alterations in the crypt region (Francoeur et al. 2009). First, a disappearance of αSMA positive cells was observed in a large proportion of the crypts while in others, the αSMA cellular staining was abnormally thick and co-stained by desmin suggesting a reorganization/redifferentiation into smooth muscle cells. Characterization of the pericryptal myofibroblastic sheath in the colonic mucosa from patients with various pathologic conditions including CD, ulcerative colitis, acute infectious colitis and noninfectious colitis confirmed the disappearance of αSMA positive cells (also desmin negative) in the inflamed mucosa from inflammatory bowel diseases but not in other pathological conditions. Analysis of the expression of tenascin-C, which is exclusively produced by the myofibroblasts and muscle cells of the human intestine (Belanger&Beaulieu 2000) in the crypt epithelial BM revealed a close correlation between myofibroblast disappearance (loss of normal αSMA staining) and loss of tenascin-C staining (Francoeur et al. 2009). The significant reduction of αSMA positive cells in the pericryptal region concomitant with a disappearance of tenascin-C (Francoeur et al. 2009) and laminin LM-211 (Bouatrouss et al. 2000) suggested that pericryptal myofibroblasts are lost in the inflamed mucosa of CD patients.

To test this hypothesis, we used various preparations of myofibroblastic cells isolated from the human intestinal mucosa (Pinchuk et al. 2007, Teller et al. 2007, Vachon et al. 1993) as experimental cell models. Myofibroblasts are known to respond to various inflammatory signals (Otte et al. 2003, Saada et al. 2006) and have been shown to be altered in inflammatory bowel diseases (Fiocchi 1997b, Powell et al. 1999, Powell et al. 2005). For instance, mesenchymal cells isolated from the inflamed mucosa show higher levels of collagen production than their normal counterparts. We thus investigated the possibility that a loss of pericryptal myofibroblasts occurs in the inflamed regions of CD mucosa by testing myofibroblast susceptibility to the same panel of proinflammatory cytokines used above for epithelial cells (section 3.2). Individually, IL-1β, IL-6, TNFα and IFNγ as well as TGFβ exerted little or no effect on the growth and survival of intestinal myofibroblasts. However, cytokine combinations containing TNFα and IFNγ induced significant caspase-dependent apoptosis, suggesting that this mechanism may account for the loss of myofibroblasts in the inflamed CD mucosa. While not yet reported for myofibroblasts, the synergistic effect of TNFα/IFNγ on various functions has been described in other cell types, namely intestinal epithelial cells (Begue et al. 2006, Francoeur et al. 2004, Ruemmele et al. 1999, Wang et al. 2006, Warhurst et al. 1998).

Interestingly, the pro-apoptotic effect of pro-inflammatory cytokines was only observed with myofibroblasts isolated from normal mucosa, myofibroblasts isolated from inflamed

mucosa being apoptosis-resistant (Francoeur et al. 2009). Distinct intrinsic properties of myofibroblasts isolated from inflammatory bowel disease vs non-inflammatory bowel disease patients remains to be elucidated but is not without precedent (Lawrance et al. 2001). The contribution of bone marrow-derived myofibroblasts in the regenerative process in inflammatory bowel disease (Andoh et al. 2005, Brittan et al. 2007) may explain the resistance to cytokine-mediated apoptosis.

The high levels of TGFβ in the inflamed mucosa may need to be further investigated considering its anti-inflammatory effect in inflammatory bowel diseases (Fiocchi 2001) and its promoting effect on myofibroblast differentiation (Simmons et al. 2002). Indeed, although not directly tested on myofibroblasts for apoptosis, TGFβ was found to significantly enhance αSMA expression in intestinal myofibroblasts while all other cytokines reduced αSMA expression. Interestingly, TGFβ completely reversed the down-regulation of αSMA expression triggered by individual proinflammatory cytokines but failed to prevent the αSMA down-regulation induced by the TNFα/IFNγ combination, suggesting a dedifferentiation mechanism (Francoeur et al. 2009).

In summary, these studies showed that the myofibroblasts of the intestinal pericryptal sheath are a target for proinflammatory cytokines in active inflammatory bowel diseases. The disappearance of laminin LM-211 and tenascin-C in the pericryptal region of the inflamed CD mucosa appears to be a direct consequence of the alteration of the myofibroblastic sheath. While proinflammatory cytokines appear to be responsible for the net reduction of the number of pericryptal myofibroblasts, the mechanisms involved include caspase-dependent apoptosis and dedifferentiation toward a fibroblastic phenotype.

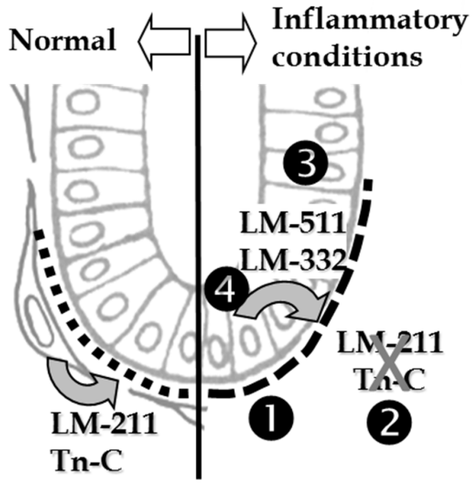

Fig. 4. Functional alterations of human intestinal epithelial-stromal components resulting from the synergistic effects of TNFα and IFNγ. The TNFα/IFNγ combination was found to trigger myofibroblast caspase-dependent apoptosis and myofibroblast dedifferentiation, which results in the disappearance of a significant portion of the pericryptal sheath (1) and, concomitantly, the loss of two extracellular matrix molecules specifically synthesized by these cells: laminin LM-211 and tenascin-C (Tn-C) (2). The TNFα/IFNγ combination was found to also elicit caspase-dependent apoptosis in epithelial crypt cells (3) as well as induction of the expression of the laminins LM-332 and LM-511 (4), two laminins normally not expressed in the lower crypt. Expression of LM-511 may compensate for the disappearance of LM-211.

4. Conclusions

It is becoming more and more evident that under inflammatory conditions, the intestinal immune response relies on a complex interplay between immune and nonprofessional immune cells (Fiocchi 1997b, Macdonald&Monteleone 2005). Proinflammatory cytokines, namely TNFα and IFNγ in combination, were shown to induce human intestinal crypt epithelial cell apoptosis and altered expression and distribution of laminins LM-332 and LM-511 in the crypts (Francoeur et al. 2004), two events that contribute to the disruption of epithelial cell homeostasis (Bouatrouss et al. 2000, Teller&Beaulieu 2001). As summarized in Fig. 4, the proinflammatory conditions that prevail in the intestinal mucosa of patients affected with inflammatory bowel diseases also disrupt the pericryptal sheath, as shown by the loss of myofibroblasts and altered expression of laminin LM-211 and tenascin-C (Francoeur et al. 2009). Taken together, these data suggest that the entire epithelial-stromal interface is affected in the intestine under proinflammatory conditions.

5. Acknowledgements

The authors wish to thank the other members of the laboratory for discussion, namely Drs Caroline Francoeur and Yamina Bouatrouss who were particularly involved in the original work and Elizabeth Herring for proofreading the manuscript.
The work was supported by grants from the Canadian Institutes for Health Research. JFB holds the Canadian Research Chair in Intestinal Physiopathology and is a member of the FRSQ-funded Centre de Recherche Clinique Etienne-LeBel of the CHUS.

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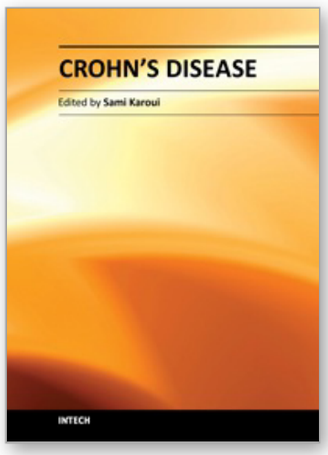

Crohn's Disease
Edited by Dr. Sami Karoui

ISBN 978-953-307-811-3
Hard cover, 210 pages
Publisher InTech
Published online 13, January, 2012
Published in print edition January, 2012

In this book, several important points regarding Crohn's disease are discussed. In the first section, we focus on etiopathogeny of Crohn's disease and the recent advances in our overall understanding of the disease - specifically, the role of the gut epithelium, alterations of the epithelial crypts, and the roles of the different cytokines in the pathophysiology of Crohn's disease. In the second section, a diagnosis of Crohn's disease is discussed. Another particular area of focus is in the diagnosis of intestinal tuberculosis, and the role of mycobacterium avium in Crohn's disease. In the third and final section, the management of Crohn's disease is discussed, with a focus on recent evidence-based medicine recommendations.

How to reference
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Amira Seltana, Manon Lepage and Jean-François Beaulieu (2012). Alteration of the Crypt Epithelial-Stromal Interface by Proinflammatory Cytokines in Crohn's Disease, Crohn's Disease, Dr. Sami Karoui (Ed.), ISBN: 978-953-307-811-3, InTech, Available from: http://www.intechopen.com/books/crohn-s-disease/alteration-of-the-crypt-epithelial-stromal-interface-by-proinflammatory-cytokines-in-crohn-s-disease

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