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The extracellular matrix in IBD: a dynamic mediator of inflammation

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Abstract

Purpose of review—The extracellular matrix (ECM) is a frequently overlooked component of the pathogenesis of inflammatory bowel disease (IBD). However, the functional and clinically significant interactions between immune as well as non-immune cells with the ECM have important implications for disease pathogenesis. In this review, we discuss how the ECM participates in process associated with IBD that involves diverse cell types of the intestine.

Recent findings—Remodeling of the ECM is a consistent feature of IBD, and studies have implicated key ECM molecules in IBD pathogenesis. While the majority of prior studies have focused on ECM degradation by proteases, more recent studies have uncovered additional degrading enzymes, identified fragments of ECM components as potential biomarkers, and revealed that ECM synthesis is increased in IBD. These new studies support the notion that the ECM, rather than acting as a passive element, is an active participant in promoting inflammation.

Summary—New studies have offered exciting clues about the function of the ECM during IBD pathogenesis. The balance of ECM synthesis and turnover is altered in IBD, and the molecules involved exhibit discreet biological functions that regulate inflammation on the basis of specific cell type and matrix molecule.

Keywords

Inflammatory bowel disease; extracellular matrix; hyaluronan; fibronectin; collagen; Matrix-metalloproteinase

Introduction

The extracellular matrix (ECM) is a commonly overlooked component of all tissues, in both health and disease. Yet, this complex and dynamically remodeled collection of glycoproteins, proteins and glycosaminoglycans comprises the external environment of every cell during development and homeostasis, as well as during the processes of injury and repair [1]. The ECM controls the structure, organization and hydration of all tissues, and the individual ECM makeup of each organ provides unique biophysical properties, including

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Conflict of Interest

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elasticity and strength. The notion that ECM is merely a structural element is long outdated. Overall, connective tissue between cells provides cues to the cells in that environment through a variety of mechanisms including the interaction with mechanical receptors, for example integrins; acting as a reservoir for growth factors and cytokines that provide cell signals at appropriate times; and providing an environment that facilitates gas and nutrient exchange. The extensive battery of remodeling enzymes that are produced in the body biologically implies the importance of an appropriately formed ECM. The enzymes main physiologic function is to constantly remodel the deposited matrix so it can function appropriately, preventing build-up during homeostasis and initiating repair during injury. Families of metalloproteinases, proteases as well as glycolytic enzymes including heparanase, hyaluronidases and other glycanases, all contribute to homeostatic ECM turnover [1].

During injury and disease processes, matrix deposition and turnover can be highly altered from what occurs in the homeostatic composition [1]. Pathological matrix formation can be caused by increased, and sometimes altered, ECM production as well as by modification of expression and activation of matrix modifying enzymes.

ECM alterations in IBD

Common features of inflammatory bowel disease (IBD) (comprised of the chronic conditions of Crohn’s disease and ulcerative colitis) are tissue damage and alteration of the intestinal architecture due to chronic inflammation. Much of the tissue destruction is mediated by inflammatory leukocyte-derived and activated matrix metalloproteinases (MMPs), a family of zinc requiring proteolytic enzymes (MMPs) including MMPs 9, 2 (gelatinases). Goffin et at have recently shown the impact of selective MMP9 inhibition in animal models of colitis-associated fibrosis [2].

Recently, ECM remodeling, through expression of an unsuspected ECM cleaving enzyme, KIAA1199, that degrades the glycosaminoglycan hyaluronan was also associated with Crohn’s disease [3]. Degradation products of the HA matrix are considered damage associated molecular pattern (DAMP) molecules that are recognized by TLR receptors and initiate immune responses [4–6] including sterile inflammation [7]. Similarly, degradation products of collagen and laminin also have been shown to have biologic functions that the intact molecules do not trigger [1]. While function of these ECM fragments have yet to be directly investigated in IBD, circulating levels of the neo-epitopes of collagen, laminin and vimentin were found to correlate with subtypes of IBD, and may be useful for discriminating ulcerative colitis from Crohn’s Disease [2, 8, 9].

Few recent reports analyzed which specific components of the ECM are modified during disease. Increased production of specific ECM components, such as hyaluronan (HA), has previously been associated with colitis and increased deposition of fibronectin and collagens associated with fibrotic complications and intestinal stricture formation in IBD. In this review, we discuss the role of the ECM within the unique and complex tissue microenvironments of the intestine during IBD.

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Intestinal epithelium

The intestinal epithelium sits on a specialized matrix, the basement membrane, that is more compact and differs in composition from the intracellular ECM. The basement membrane is rich in structural ECM elements, primarily collagens and laminins, as well as in heparin sulfate proteoglycans that bind to these components and sequester growth factors and cytokines. The architecture of the basement membrane, as revealed by dramatic electron microscopic analysis [10], consists of a dense filamentous mat with numerous, dynamically remodeled fenestrations that facilitate water and nutrient transport as well as connections between cells above and below the basement membrane. The intestinal epithelium is by design a highly turned over cell population and the constant sloughing epithelium represents a physical barrier mechanism that prevents infection of the underlying mucosal tissue.

The best known mechanisms of regulation of epithelial sloughing understandably involve matrix clipping of the basement membrane through increased expression and activation of MMPs. New reports have shown that: 1) MMP9 increases intestinal permeability in colitis through expression of myosin light chain kinase upregulation and phosphorylation [11]; and 2) that constitutive intestinal epithelial MMP9 increases epithelial apoptosis and loss of goblet cells during colitis, with accompanying inflammatory cytokine release [12]. Recently, O'Shea et al. have comprehensively reviewed the literature regarding specific MMPs and their role in IBD [13].

Endothelium

The vascular endothelium is a central mediator of the inflammatory process and the ECM is essential for all aspects of vascular function [14]. By altering the expression of ECM and cell adhesion molecules in response to pro-inflammatory molecules, endothelial cells (ECs) control the recruitment of circulating leukocytes to areas in which inflammatory cells are needed. In IBD, dysregulation of the vascular ECM has been demonstrated to promote adhesion and extravasation of leukocytes and platelets, and release of pro-inflammatory cytokines [15]. Cell adhesion molecules on the EC surface interact with components of the ECM, such as fibronectin, collagens, and laminin to regulate both the recruitment of circulating leukocytes and modulate intracellular signaling pathways , which control endothelial permeability. In response to inflammatory stimuli, microvascular ECs respond by upregulating cell adhesion and ECM molecules, and inflamed regions of endothelium of IBD patients promotes greater recruitment of leukocytes than non-inflamed tissue from the same patient [16]. Microvascular ECs isolated from patients with active IBD express high levels of E-selectin, intracellular adhesion molecule 1 (ICAM-1), and platelet endothelial cell adhesion molecule 1 (PECAM-1) [17]. In addition to leukocyte recruitment, cell adhesion molecule interactions with ECM ligands can also control intracellular events relevant to IBD. Binding of PECAM-1 to fibronectin or collagen initiates phosphorylation of cytoplasmic domains via outside-in signaling, leading to increased endothelial permeability and leukocyte transmigration [18, 19].

Endothelial ECM components, such as HA, have also been demonstrated to play a direct role in the recruitment of leukocytes in response to inflammatory stimuli. Under normal

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conditions, the HA is typically minimally adhesive for leukocytes. However, in IBD as well as other inflammatory diseases, HA is not only present in increased amounts but it is crosslinked with the heavy chains (HCs) of serum inter-α trypsin-inhibitor [20, 21]. This novel, inflammation-associated HC:HA complex is highly adhesive for leukocytes and promotes inflammatory cell recruitment. Following TNF-α treatment, microvascular ECs produce a HA-rich ECM which dramatically enhances recruitment of leukocytes via interaction with the HA receptor CD44 [20]. Murine models of colitis have demonstrated that deposition of HA precedes leukocyte infiltration into the submucosa, thereby promoting inflammation at early stages [22], and genetic disruption of HA synthesis reduces leukocyte recruitment [23].

In addition to regulating the interaction of inflammatory cells with the endothelial surface, fragmentation of ECM molecules also contributes to the pathobiology of IBD. Fragmentation of ECM molecules by MMPs has been demonstrated to impair endothelial barrier integrity, which promotes transmigration of immune cells into the submucosal space [24]. Specific fragments of collagen generated by MMP-8 and -9 also function as chemo-attractants for neutrophils, which further induce MMP generation in IBD [25]. HA also contributes to ECM integrity in IBD, as degradation of HA by platelets results in small molecular weight HA fragments which can stimulate angiogenesis, chemotaxis, and cytokine expression [6, 26, 27]. Additionally, HA fragments also promote wound healing through enhanced fibroblast proliferation and myoblast differentiation which may contribute to fibrotic processes in IBD [28]. Elevated HA fragment deposition in the intestines is associated with inflamed IBD tissue [3], and may further perpetuate innate immune responses in IBD.

Submucosa

The submucosa is a dense network of connective tissue that consists of fibroblasts, smooth muscle cells, blood vessels, lymphatic vessels, and nerves which together acts to integrate the luminal mucosal layer and the external muscular layer. The submucosal ECM consists of a remarkable arrangement of diagonal collagen fibrils which provide the essential flexibility required during peristalsis [10]. The major collagen subtypes in normal tissue are type I (70%), Type III (20%), and type V (12%) [29]. However, during inflammation immune cells infiltrate the submucosa where they may release matrix-degrading enzymes and initiate a cycle of ECM degradation and synthesis. Chronic inflammation leads to dramatic alterations in both the cellular and molecular makeup of the submucosa. Tissue from IBD patients is characterized by an increase in total collagen, as well as increases in collagen type III and V, which may contribute to stiffening of the ECM and affect mechanotransduction [29–31]. Collagen degradation products produced by MMPs are released into the surrounding tissue, where these ECM fragments act as chemokines capable of enhancing neutrophil recruitment [25, 32]. MMP degradation products are also present in the serum of IBD patients at different levels in UC and CD, suggesting that ECM remodeling may be different in these disease states due to differences in leukocyte populations or MMP expression [8].

Fibronectin is another component of the submucosal ECM that regulates cellular behavior in IBD by mediating cell-matrix interactions. Fibronectin promotes fibroblast migration

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directly, and promotes proliferation by regulating the bioavailability of TGF-β. Fibronectin also binds to TNF-α, which promotes chemotaxis and MMP9 expression in monocytes [33, 34]. In IBD, fibronectin deposition is markedly increased and likely participates in the altered cellular makeup of the submucosa associated with the pathology of IBD [35, 36].

Intestinal smooth muscle cells and fibroblasts have been shown to produce increased levels of HA in IBD cells and tissues compared with healthy controls, and regions of inflamed submucosa contain high levels of HC:HA when compared with non-inflamed regions from the same IBD patient [21, 22]. Murine models of colitis have demonstrated that deposition of HA is an early event in inflamed intestinal tissue, preceding and promoting leukocyte infiltration, and that HA synthesis plays a crucial role in driving inflammation [22, 23].

Conclusion

Advances in our understanding of immune and non-immune cell interactions with the ECM in IBD have implicated several previously unsuspected mechanisms in disease pathogenesis. Previously, alterations of the ECM in IBD were viewed as a consequence of inflammation, but emerging evidence suggests that ECM remodeling (degradation and *de novo* synthesis) is an active participant in the inflammatory process in IBD pathobiology. By altering cellular processes and functioning to sequester cytokines, chemokines, and growth factors, the ECM acts as a dynamic regulator of disease progression in IBD. In the future, identifying cell-matrix interactions relevant to IBD and translating this knowledge into mechanistic studies will greatly enhance our ability to understand the manifestations of intestinal disease driven by the ECM and may lead to ECM-based therapeutic strategies.

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References

1. Bonnans C, Chou J, Werb Z. Remodelling the extracellular matrix in development and disease. Nat Rev Mol Cell Biol. 2014; 15:786–801. [PubMed: 25415508]
2. Goffin L, Fagagnini S, Vicari A, Mamie C, Melhem H, Weder B, Lutz C, Lang S, Scharl M, Rogler G, et al. Anti-MMP-9 Antibody: A Promising Therapeutic Strategy for Treatment of Inflammatory Bowel Disease Complications with Fibrosis. Inflamm Bowel Dis. 2016; 22:2041–2057. [PubMed: 27542125]
3. Soroosh A, Albeiroti S, West GA, Willard B, Fiocchi C, de la Motte CA. Crohn's Disease Fibroblasts Overproduce the Novel Protein KIAA1199 to Create Proinflammatory Hyaluronan Fragments. Cell Mol Gastroenterol Hepatol. 2016; 2:358–368. e354. [PubMed: 27981209]
4. Termeer C, Benedix F, Sleeman J, Fieber C, Voith U, Ahrens T, Miyake K, Freudenberg M, Galanos C, Simon JC. Oligosaccharides of Hyaluronan activate dendritic cells via toll-like receptor 4. J Exp Med. 2002; 195:99–111. [PubMed: 11781369]
5. Jiang D, Liang J, Fan J, Yu S, Chen S, Luo Y, Prestwich GD, Mascarenhas MM, Garg HG, Quinn DA, et al. Regulation of lung injury and repair by Toll-like receptors and hyaluronan. Nat Med. 2005; 11:1173–1179. [PubMed: 16244651]

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6. Scheibner KA, Lutz MA, Boodoo S, Fenton MJ, Powell JD, Horton MR. Hyaluronan fragments act as an endogenous danger signal by engaging TLR2. J Immunol. 2006; 177:1272–1281. [PubMed: 16818787]
7. Taylor KR, Yamasaki K, Radek KA, Di Nardo A, Goodarzi H, Golenbock D, Beutler B, Gallo RL. Recognition of hyaluronan released in sterile injury involves a unique receptor complex dependent on Toll-like receptor 4, CD44, and MD-2. J Biol Chem. 2007; 282:18265–18275. [PubMed: 17400552]
8*. Mortensen JH, Godskesen LE, Jensen MD, Van Haaften WT, Klinge LG, Olinga P, Dijkstra G, Kjeldsen J, Karsdal MA, Bay-Jensen AC, et al. Fragments of Citrullinated and MMP-degraded Vimentin and MMP-degraded Type III Collagen Are Novel Serological Biomarkers to Differentiate Crohn's Disease from Ulcerative Colitis. J Crohns Colitis. 2015; 9:863–872. This study highlights the potential utility of ECM fragments as biomarkers for IBD. [PubMed: 26188349]
9. Heikius B, Niemela O, Niemela S, Karttunen TJ, Lehtola J. Elevated serum PIIINP and laminin in inflammatory bowel disease indicate hepatobiliary and pancreatic dysfunction. Hepatogastroenterology. 2002; 49:404–411. [PubMed: 11995461]
10. Komuro T, Hashimoto Y. Three-dimensional structure of the rat intestinal wall (mucosa and submucosa). Arch Histol Cytol. 1990; 53:1–21.
11*. Nighot P, Al-Sadi R, Rawat M, Guo S, Watterson DM, Ma T. Matrix metalloproteinase 9-induced increase in intestinal epithelial tight junction permeability contributes to the severity of experimental DSS colitis. Am J Physiol Gastrointest Liver Physiol. 2015; 309:G988–997. Using a mouse model of colitis, the authors demonstrate the role of MMP9 as a regulator of epithelial barrier function and inflammation. [PubMed: 26514773]
12. Liu H, Patel NR, Walter L, Ingersoll S, Sitaraman SV, Garg P. Constitutive expression of MMP9 in intestinal epithelium worsens murine acute colitis and is associated with increased levels of proinflammatory cytokine Kc. Am J Physiol Gastrointest Liver Physiol. 2013; 304:G793–803. [PubMed: 23471340]
13. O'Shea NR, Smith AM. Matrix metalloproteases role in bowel inflammation and inflammatory bowel disease: an up to date review. Inflamm Bowel Dis. 2014; 20:2379–2393. [PubMed: 25222664]
14. Davis GE, Senger DR. Endothelial extracellular matrix: biosynthesis, remodeling, and functions during vascular morphogenesis and neovessel stabilization. Circ Res. 2005; 97:1093–1107. [PubMed: 16306453]
15. Hatoum OA, Heidemann J, Binion DG. The intestinal microvasculature as a therapeutic target in inflammatory bowel disease. Ann N Y Acad Sci. 2006; 1072:78–97. [PubMed: 17057192]
16. Binion DG, West GA, Volk EE, Drazba JA, Ziats NP, Petras RE, Fiocchi C. Acquired increase in leucocyte binding by intestinal microvascular endothelium in inflammatory bowel disease. Lancet. 1998; 352:1742–1746. [PubMed: 9848350]
17. Koizumi M, King N, Lobb R, Benjamin C, Podolsky DK. Expression of vascular adhesion molecules in inflammatory bowel disease. Gastroenterology. 1992; 103:840–847. [PubMed: 1379955]
18. Woodfin A, Voisin MB, Nourshargh S. PECAM-1: a multi-functional molecule in inflammation and vascular biology. Arterioscler Thromb Vasc Biol. 2007; 27:2514–2523. [PubMed: 17872453]
19. Rijcken E, Mennigen RB, Schaefer SD, Laukoetter MG, Anthoni C, Spiegel HU, Bruewer M, Senninger N, Krieglstein CF. PECAM-1 (CD 31) mediates transendothelial leukocyte migration in experimental colitis. Am J Physiol Gastrointest Liver Physiol. 2007; 293:G446–452. [PubMed: 17510197]
20. de La Motte CA, Hascall VC, Calabro A, Yen-Lieberman B, Strong SA. Mononuclear leukocytes preferentially bind via CD44 to hyaluronan on human intestinal mucosal smooth muscle cells after virus infection or treatment with poly(I.C). J Biol Chem. 1999; 274:30747–30755. [PubMed: 10521464]
21. de la Motte CA, Hascall VC, Drazba J, Bandyopadhyay SK, Strong SA. Mononuclear leukocytes bind to specific hyaluronan structures on colon mucosal smooth muscle cells treated with polyinosinic acid:polycytidylic acid: inter-alpha-trypsin inhibitor is crucial to structure and function. Am J Pathol. 2003; 163:121–133. [PubMed: 12819017]

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22. Kessler S, Rho H, West G, Fiocchi C, Drazba J, de la Motte C. Hyaluronan (HA) deposition precedes and promotes leukocyte recruitment in intestinal inflammation. Clin Transl Sci. 2008; 1:57–61. [PubMed: 20443819]

23*. Kessler SP, Obery DR, de la Motte C. Hyaluronan Synthase 3 Null Mice Exhibit Decreased Intestinal Inflammation and Tissue Damage in the DSS-Induced Colitis Model. Int J Cell Biol. 2015; 2015:745237. This study demonstrates a direct role for hyaluronan synthase-3 in inflammatory disease progression. [PubMed: 26448758]

24. Faveeuw C, Preece G, Ager A. Transendothelial migration of lymphocytes across high endothelial venules into lymph nodes is affected by metalloproteinases. Blood. 2001; 98:688–695. [PubMed: 11468168]

25. Koelink PJ, Overbeek SA, Braber S, Morgan ME, Henricks PA, Abdul Roda M, Verspaget HW, Wolfkamp SC, te Velde AA, Jones CW, et al. Collagen degradation and neutrophilic infiltration: a vicious circle in inflammatory bowel disease. Gut. 2014; 63:578–587. [PubMed: 23525573]

26. de la Motte C, Nigro J, Vasanji A, Rho H, Kessler S, Bandyopadhyay S, Danese S, Fiocchi C, Stern R. Platelet-derived hyaluronidase 2 cleaves hyaluronan into fragments that trigger monocyte-mediated production of proinflammatory cytokines. Am J Pathol. 2009; 174:2254–2264. [PubMed: 19443707]

27. McKee CM, Penno MB, Cowman M, Burdick MD, Strieter RM, Bao C, Noble PW. Hyaluronan (HA) fragments induce chemokine gene expression in alveolar macrophages. The role of HA size and CD44. J Clin Invest. 1996; 98:2403–2413. [PubMed: 8941660]

28. Webber J, Meran S, Steadman R, Phillips A. Hyaluronan orchestrates transforming growth factor-beta1-dependent maintenance of myofibroblast phenotype. J Biol Chem. 2009; 284:9083–9092. [PubMed: 19193641]

29. Graham MF, Diegelmann RF, Elson CO, Lindblad WJ, Gotschalk N, Gay S, Gay R. Collagen content and types in the intestinal strictures of Crohn's disease. Gastroenterology. 1988; 94:257–265. [PubMed: 3335305]

30. Stallmach A, Schuppan D, Riese HH, Matthes H, Riecken EO. Increased collagen type III synthesis by fibroblasts isolated from strictures of patients with Crohn's disease. Gastroenterology. 1992; 102:1920–1929. [PubMed: 1587410]

31. Johnson LA, Rodansky ES, Sauder KL, Horowitz JC, Mih JD, Tschumperlin DJ, Higgins PD. Matrix stiffness corresponding to strictured bowel induces a fibrogenic response in human colonic fibroblasts. Inflamm Bowel Dis. 2013; 19:891–903. [PubMed: 23502354]

32. Xu X, Jackson PL, Tanner S, Hardison MT, Abdul Roda M, Blalock JE, Gaggar A. A self-propagating matrix metalloprotease-9 (MMP-9) dependent cycle of chronic neutrophilic inflammation. PLoS One. 2011; 6:e15781. [PubMed: 21249198]

33. Vaday GG, Hershkoviz R, Rahat MA, Lahat N, Cahalon L, Lider O. Fibronectin-bound TNF-alpha stimulates monocyte matrix metalloproteinase-9 expression and regulates chemotaxis. J Leukoc Biol. 2000; 68:737–747. [PubMed: 11073115]

34. Franitza S, Hershkoviz R, Kam N, Lichtenstein N, Vaday GG, Alon R, Lider O. TNF-alpha associated with extracellular matrix fibronectin provides a stop signal for chemotactically migrating T cells. J Immunol. 2000; 165:2738–2747. [PubMed: 10946305]

35. Dammeier J, Brauchle M, Falk W, Grotendorst GR, Werner S. Connective tissue growth factor: a novel regulator of mucosal repair and fibrosis in inflammatory bowel disease? Int J Biochem Cell Biol. 1998; 30:909–922. [PubMed: 9744082]

36. Burke JP, Ferrante M, Dejaegher K, Watson RW, Docherty NG, De Hertogh G, Vermeire S, Rutgeerts P, D'Hoore A, Penninckx F, et al. Transcriptomic analysis of intestinal fibrosis-associated gene expression in response to medical therapy in Crohn's disease. Inflamm Bowel Dis. 2008; 14:1197–1204. [PubMed: 18452219]

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Key Points

- Alteration of the ECM is a characteristic of IBD throughout the structure of the intestine
- Changes in the composition of the ECM lead to altered cellular behavior, including promoting and sustaining inflammatory processes
- The timing of ECM remodeling likely varies by matrix component. Some molecules, such as HA, precede inflammatory disease progression
- Fragments of ECM molecules can be biomarkers of disease activity and may represent useful therapeutic targets in the future