

# Mucosal Architectural Rearrangement in Coeliac Disease

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**Abstract** Celiac disease (CD) is the most common autoimmune enteropathy in the western world caused by the intolerance to gluten in genetically predisposed individuals. CD is characterized by a remarkable rearrangement of the mucosal architecture, in which process myofibroblasts play a crucial role. Myofibroblasts (intestinal subepithelial myofibroblasts and interstitial cells of Cajal) are the most represented mesenchymal cell types in the gut mucosa and are involved in a broad range of biological processes including growth, mucosal protection, repair, inflammation and fibrosis. Myofibroblasts actively contribute to the mucosal changes in CD due to their ability to produce an excessive amount of extracellular matrix and basement membrane components (e.g. collagens, fibronectin, and specific enzymes including tissue transglutaminases) and through the expression of matrix metalloproteinases (MMPs) and tissue inhibitors of matrix metalloproteinases (TIMPs). The enhanced production of ECM components and MMPs and the altered shape and motility of myofibroblasts in the duodenal mucosa of patients with CD suggest that myofibroblasts may play an essential role in the pathogenesis of CD.

**Keywords:** celiac disease, myofibroblast, extracellular matrix, tissue transglutaminase, matrix metalloproteinase

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## 1. Introduction

Celiac disease (CD) is an autoimmune enteropathy characterized by villous atrophy, crypt hyperplasia and rearrangement of the mucosal architecture resulting in two to three-fold increased depth of the lamina propria [34]. In genetically susceptible individuals inflammation is triggered by dietary gluten and related prolamins present in wheat, rye and barley [4,12,31]. The chronic inflammation leads to injury of the epithelial barrier thus facilitating the entry of dietary antigens into the lamina propria [32]. Intestinal myofibroblasts were shown to influence the recruitment and activation of immune cells and repair mechanisms through their ability to produce chemokines, cytokines and extracellular matrix components [1]. In the present review we give an overview about the mucosal architectural rearrangement in CD with special focus on the role of intestinal myofibroblasts.

## 2. Intestinal Myofibroblasts

Intestinal fibroblasts and myofibroblasts are the most represented mesenchymal cell types in the gut mucosa [24]. Definitely myofibroblasts are spindle or stellate-

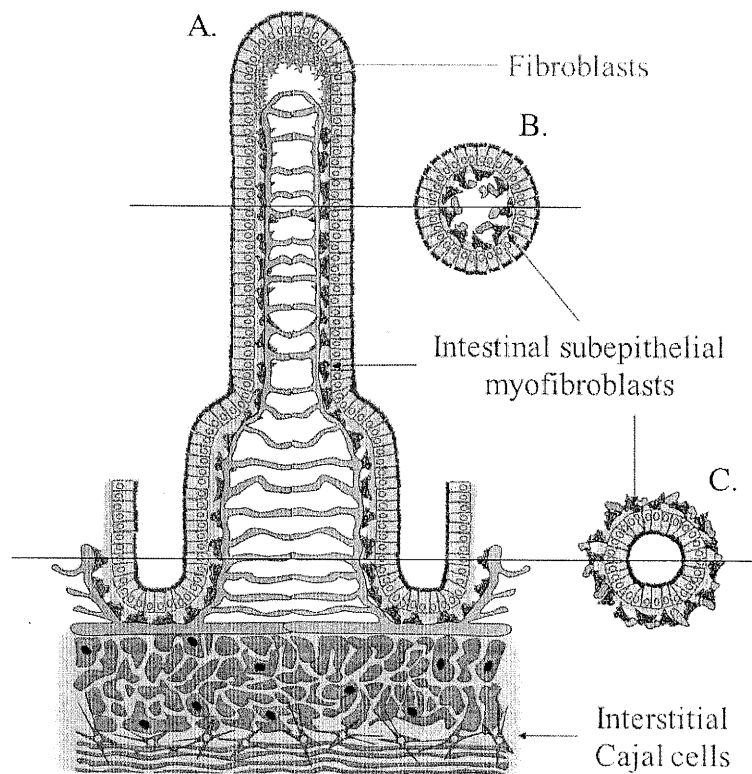
shaped cells that are positive for  $\alpha$ -smooth muscle actin ( $\alpha$ -SMA), vimentin, desmin and fibronectin and lack of the epithelial markers, such as cytokeratins and are considered as activated fibroblasts [7,11].

In the intestinal lamina propria there are two distinct populations of myofibroblasts, the interstitial cells of Cajal and the intestinal subepithelial myofibroblasts (SEMFs) [23]. Interstitial cells of Cajal are located in an intramuscular space between the submucosa and muscularis propria [27] (Figure 1). They serve as pacemakers, which generate slow electrical waves and stimulates smooth muscle cells leading to their contraction [26]. Furthermore interstitial cells of Cajal were shown to be involved in the regulation of neurotransmission as well [15].

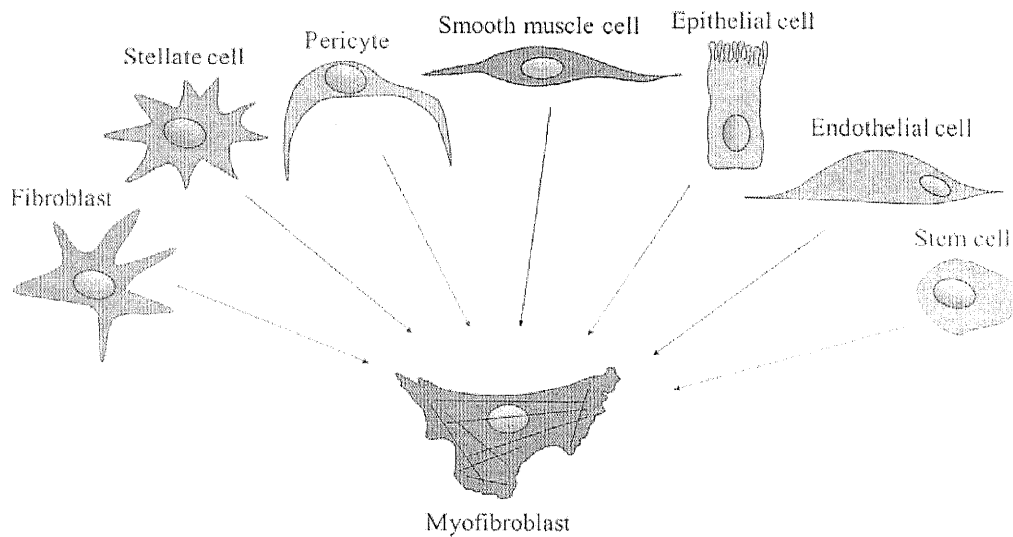
The other group of myofibroblasts in the gut, the SEMFs are mainly localized directly under the epithelial cell layer of the villi and crypts and form a fenestrated innervated sheath next to the vasculature (Figure 1).

During ontogenesis myofibroblasts appear at the 18.5th embryonic day in mice and at the 21st week in humans [18,28]. Regarding their origin they can differentiate from mesenchymal cells including fibroblasts, stellate cells, pericytes and smooth muscle cells. Other hypothesis suggest that myofibroblasts can originate from epithelial and endothelial cells through the processes of epithelial-mesenchymal and endothelial-mesenchymal transition

[14,22]. Moreover, myofibroblasts can derive from bone marrow stem cells as well [3] (Figure 2).



**Figure 1. Localization of fibroblasts, intestinal subepithelial myofibroblasts and interstitial Cajal cells in the duodenum.** Fibroblasts are localized in the apical region of the villi. Intestinal epithelial myofibroblasts are shown in the longitudinal (A) and cross section of the villus (B) and the crypt (C). Interstitial Cajal cells are found in the intramuscular space. Based on the work of Powell et al [24]

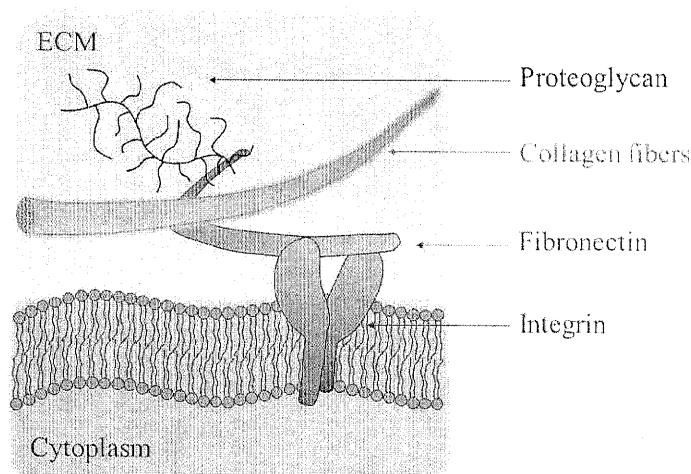


**Figure 2. Origin of myofibroblasts.** Myofibroblasts can differentiate from several cell types including other mesenchymal cells, epithelial, endothelial and stem cells

Intestinal SEMFs are involved in a broad range of biological processes including growth, mucosal protection, repair, inflammation and fibrosis [30]. The major function of SEMFs is the secretion of the components of the basement membrane and the extracellular matrix (ECM). The intestinal cells are connected to the ECM components via their adhesion receptors (e.g. integrins) localized in their cell surface membrane [1]. Alterations in the chemical composition or mechanical status of the ECM trigger signal transduction through these transmembrane receptors, which result in changes of the cell cycle, shape

and/or motility. Indeed ECM coordinates the cellular functions and provides support and nutrition to the epithelium. In this way myofibroblasts contribute to the maintenance of tissue homeostasis [17].

The ECM is composed mainly by fibrillar collagens, containing primarily type I and III collagens or type IV collagen, which latter is one of the major components of a basement membrane forming the intestinal barrier. Besides collagens ECM consists of glycoproteins (fibronectin) and proteoglycans building up a complex molecular network [30] (Figure 3).



**Figure 3. Major components of the extracellular matrix (ECM).** Transmembrane receptors such as integrins, which are localized in the cell surface membrane, connect the cells to the ECM components

### 3. Mucosal Rearrangement in CD

Under normal circumstances the intestinal mucosal architecture is maintained and continuously controlled by the interactions among epithelial, mesenchymal and immune cells [16]. This sensitive balance is disturbed in patients with CD [2]. CD is characterized by a remarkable rearrangement of the mucosal architecture, in which process myofibroblasts were shown to play a crucial role.

Characteristic architectural changes in patients with CD include the flat duodenal mucosa surface with seriously damaged epithelium and elevated number of intraepithelial immune cells, thickened basement membrane and elongated crypts [33]. The lamina propria is increased two to threefold with excessive deposition of ECM compared to that of healthy individuals [9]. Myofibroblasts, the major sources of the ECM in CD, secrete large amounts of ECM molecules, which process is modulated by several proinflammatory cytokines and growth factors. Interleukin (IL)-1 $\beta$  and tumor necrosis factor (TNF)- $\alpha$  were demonstrated to induce the production of collagen I and IV in intestinal SEMFs [21]. Another known profibrotic protein, tumor growth factor (TGF)- $\beta$ , is able to activate myofibroblasts inducing the synthesis of type I collagen and stimulating the expression of  $\alpha$ -smooth muscle actin and the formation of stress fibers [29]. For the development of the typical three-dimensional structure of ECM, specific enzymes are needed which are also secreted by myofibroblasts. The most important of such enzymes is type 2 transglutaminase (TG2), which has the ability to catalyze the formation of isopeptide bonds resulting in covalent cross-linking of the protein chain via a glutamine residue to the lysine residue of another protein chain [10]. TG2 is anchored at the external surface of cell membranes or it is associated with fibronectin thus modulating cell adhesion and stabilizing the integrin-ECM interaction [36]. In patients with CD immunoglobulin (Ig)A autoantibodies against TG2 as an endomysial autoantigen are present leading to biological dysfunctions [8]. These antibodies disturb the TGF- $\beta$  mediated crosstalk between myofibroblasts and enterocytes resulting in the inhibition

of enterocyte differentiation and increased epithelial cell proliferation. This finding indicates that certain components of the ECM may function as autoantigens and the CD-specific autoantibodies contribute to the formation of gluten-triggered architectural alterations of the mucosa in CD [13].

The degradation of ECM components are controlled by a fine balance between matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) produced by fibroblasts, myofibroblasts, epithelial cells and immune cells including macrophages, neutrophils, eosinophils and lymphocytes [5,19]. MMPs are endopeptidases that play a key role in tissue remodeling through their ability to degrade ECM and basement membrane components in both physiological and pathological conditions [20]. Increased expression of MMP-1, MMP-3, MMP-12 and TIMP-1 was demonstrated in the duodenal mucosa of patients with active CD [6]. Myofibroblasts isolated from active CD patients constitutively expressed MMPs, while those from treated patients (maintained on gluten-free diet) were in a resting condition [5]. Moreover, IL-1 $\beta$  and TNF- $\alpha$  have been shown to induce the expression of MMP-1, MMP-3 and TIMP-1 in SEMFs [35]. These data suggest the key role of MMPs in intestinal tissue injury in CD.

Recently, it was demonstrated that the shape of myofibroblasts isolated from patients with CD differs from that of controls. Furthermore, CD-derived myofibroblasts showed a signet pattern of collagen I and IV, while the control myofibroblasts had a spindle-like geometry. Also the motility and velocity of CD myofibroblasts were decreased compared to that of control individuals [25]. Presumably all these differences in shape and motility of CD-derived myofibroblasts may contribute to the typical architectural changes of the duodenal mucosa observed in CD patients, however further studies are needed to clarify their relevance in the future.

### 4. Conclusions

Architectural rearrangement of the duodenal mucosa is a key feature of CD. Intestinal SEMFs play a critical role in this process through their ability to produce large

