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Review Article

A Review of the Mechanism of Intestinal Fibrosis: The Implication for Potential Therapeutic Strategies of Inflammatory Bowel Disease

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Abstract

Intestinal fibrosis is the intestinal tissue's response to the injury caused by recurrent chronic inflammation. It is a common and serious complication of inflammatory bowel disease, characterized by excessive proliferation and accumulation of extracellular matrix in the intestine. The mechanism of its formation may be related to the excessive proliferation of intestinal stromal cells, extracellular stroma, epithelial-mesenchymal transformation and the interaction of various cytokines. Here we review the mechanism of intestinal fibrosis and try to find the implication for potential therapeutic strategies.

Keywords: Intestinal fibrosis; Inflammatory bowel disease; Mechanism; Therapy

Introduction

Intestinal fibrosis is an irreversible pathological response caused by chronic inflammation in the intestinal tract, with complicated and unclear process. Intestinal injury is almost always accompanied by acute inflammation. In most cases, the inflammatory response is followed by the regeneration and repair of the damaged tissue [1]. On the other hand, if chronic inflammation occurs repeatedly, and then continues to damage the intestinal tract, it may lead to the formation of fibrosis. The healing response after injury caused by inflammation is a physiological process. Inflammation may lead to tissue repair, reconstruction of normal intestinal morphology and function, but also lead to the production of extracellular matrix (ECM). If ECM is amplifying beyond its degradation, fibrosis occurs [2,3]. Inflammation destroyed the normal anatomical structure of intestinal tissue. In general, the body can restore the tissue to its original state through self-regeneration and repair. When the inflammatory damage exceeds the ability of the body to repair, interstitial cells are stimulated and proliferated excessively, resulting in ECM accumulation, which leads to dysfunction of wound healing. The mucosal collagen assembling induces thickening of intestinal wall, stricture of intestinal canal, weakening of elasticity, finally resulting in intestinal fibrosis, stricture and even obstruction, a serious complication of many intestinal diseases [4]. More seriously, fibrosis may lead to tumors, organ failure and even death.

Inflammatory bowel disease (IBD) is caused by heredity, living environment, immunity and other unknown factors, with a high recurrence rate and heterogeneity. As a chronic inflammatory disease IBD includes two sub-types, ulcerative colitis (UC) and Crohn's disease (CD). Fibrosis frequently occurs in IBD. Compared with UC, CD violates entire digestive tract and is more likely to develop fibrosis. Because the ileocecal valve is a physiological stricture of the intestinal tract, CD significantly increases probability of intestinal obstruction [5]. The inflammation induced fibrosis even leads to perforation and organ failure. Up to now, no specific drug is reported to effectively treat fibrosis associated symptomatic. Surgical resection is considered. Many patients with CD are likely to relapse within one year after operation, and more than 50% of the patients will form new intestinal strictures and obstructions. These patients need surgical intervention and repeated treatment, resulting in a serious decline in their life quality [6]. So far, we are still in-depth understanding the pathogenesis of intestinal fibrosis. Due to various reasons, the production of extracellular matrix

is greater than degradation, resulting in excessive accumulation of extracellular matrix, which is the main mechanism of fibrosis. Up to now, there is no medicine that can effectively prevent the development of intestinal fibrosis in patients with CD. Thus, it is of great significance to study the pathogenesis of intestinal fibrosis in CD.

Fibrosis mechanism based on interstitial cells

The first step in intestinal fibrosis is tissue damage caused by chronic inflammation. Subsequently, inflammation activates fibroblasts and gathers them in the place where they occur, which in turn promotes wound repair. Excessive accumulation of extracellular matrix in the intestine is the final step leading to fibrosis [7]. Interstitial cells can promote the repair of damaged parts in the process of intestinal injury and are considered to be the key cells to initiate and regulate fibrosis, including fibroblasts, myofibroblasts and smooth muscle cells [8]. The production and degradation of extracellular matrix is completed by interstitial cells [9]. In the complex process of intestinal fibrosis, the production of extracellular matrix is an indispensable step, in which fibroblasts play a major role. The components of ECM are collagen and fibronectin (fibronectin, FN), and the most abundant structural protein is collagen. The interactions between intestinal epithelial and mesenchymal cells may play a key role in ECM remodeling and inflammation-related fibrosis. When acute inflammation occurs in the intestine, interstitial cells are regulated by the normal intestinal repair mechanism, promoting apoptosis and preventing the synthesis and accumulation of ECM. When inflammation begins, a large number of fibroblasts appear in the intestine, which is a sign that the wound begins to heal. If inflammation continues to progress or occurs repeatedly, fibroblasts transform into myofibroblasts and synthesize a large amount of collagen, so they ability to synthesize ECM is significantly enhanced [10], becoming the key factor in the formation and development of intestinal fibrosis. Myofibroblasts are the main mucosal cells that synthesize ECM components [11,12]. Myofibroblasts can produce matrix metalloproteinases (MMPs), regulating the metabolism of extracellular matrix [13-16]. The activity of MMPs is regulated by matrix metalloproteinase inhibitor (TIMPs)and TIMP1 seems to be the most important [17]. Under physiological conditions, there is a balance between MMPs and TIMPs, and normal ECM turnover is maintained. The imbalance caused by increased expression of TIMPs may lead to increased deposition of ECM protein, resulting in intestinal fibrosis. The activation of fibroblasts and excessive collagen deposition and synthesis of a large amount of ECM is the key step of fibrosis. The increasingly proliferating myofibroblast promote the occurrence and development of intestinal fibrosis, while growth factors, pro-inflammatory factors and chemokines promote further fibroblasts proliferation.

In recent years, intestinal fibrosis was proved to be affected by a complex network of cytokines [18]. Fibrotic cytokines can be divided into two types: pro- fibrosis and anti-fibrosis. TGF-β, IL-17A and TNF-α are pro-fibrosis factors, and the main anti-fibrosis factors include IFN-γ, IL-10 and HGF. TGF-β is the most important cytokine in the pro-fibrosis cytokines network [19]. TGF-β can regulate the expression of both TIMP-1 and MMP-1. TGF-β level increased in myofibroblasts from patients with intestinal fibrosis. Considered to be the main driving force of fibrosis, TGF-β1 can stimulate the proliferation of fibroblasts stimulated by other cytokines, such as insulin-like growth factor (IGF1). In fibrotic tissues from patients with CD, these cytokines can be detected. The high level of TGF-β can also be detected in many other fibrotic organs. IL-17 increases the expression of heat shock protein 47 (Hsp47) by promoting the production of matrix metalloproteinases and promotes the production of human intestinal collagen, which is of great significance to intestinal fibrosis [20]. IL-10 and IFN-γ have anti-inflammatory properties and are attributed to anti-fibrosis factors. In a study, under the condition of routine feeding, the mice with IL-10 deficiency showed mucosal inflammation in the upper digestive tract and more mucosal inflammation in the lower digestive tract, which could form complications in the whole body. The lack of IL-10 leads to the absence of intestinal immunomodulatory activity, subsequently resulting in intestinal inflammation. In a mouse colitis model, CD4+ T cells transfer to RAG- receptors (lack of mature T and B cells) and can induce colitis. IFN-γ may mediate this process. IFN-γ is an immunomodulatory factor that can be produced after T cell activation. Anti-IFN-γ antibodies can treat colitis and prevent its further development [21]. Under normal circumstances, these two cytokines maintain dynamic balance to preserve the stability of the intestinal environment. Once the balance is destroyed by inflammation, injury or other factors, intestinal fibrosis occurs.

Transforming Growth Factor Beta

The Role of TGF-β

A number of experiments and studies have shown that TGF-β is involved in the formation of a variety of organ fibrosis, such as liver, kidney, lung and other organs. As a signal peptide in human body, hydrolyzed by protein leucine aminopeptidase (LAP), TGF-β is activated and secreted in various tissues, playing a key role in cell proliferation, tissue and organ regeneration, repair, fibrosis, especially in immune regulation [22]. TGF-β is located all through the intestine and maintains the balance of intestinal immunity through binding its own receptors and ligands. Excessively expressed TGF-β accelerates the progress of intestinal fibrosis.

TGF-β promotes the synthesis of ECM

TGF-β can be divided into three types: TGF-β1, TGF-β2 and TGF-β3. They are distributed in different regions of the human body and play different. As the major driving force of tissue fibrosis, β1 subtype is produced by a large number of immune and non-immune cells, promoting the production of extracellular matrix-related proteins [23]. β2 subtype also participates in intestinal fibrosis, and β3 subtype exerts inhibitory activity in intestinal fibrosis. TGF-β1 also mediates the regeneration and proliferation of mesenchymal cells. In the gastrointestinal tract, the resident immune and stromal cells or recruited inflammatory cells are likely

to be the source of this cytokine. TGF-β1 stimulates macrophages and other cells to produce a variety of mediators related to fibrosis [24]. Local administration of TGF-β1 induces fibrosis in multiple organs related to chronic inflammation, while the decreased TGF-β1 prevents inflammation and excessive matrix accumulation [25,26]. In addition, Tol E A found that TGF-β1 may increase its expression in intestinal myofibroblasts by self-regulating stimulation of different TGF-β1 promoter sites [27].

TGF-β/smads pathway

Smads protein is most closely related to TGF-β. Phosphorylated TGF-β/smads pathway can be divided into three types: inhibitory type, receptor regulated type and coregulatory type. TGF-β/smads pathway can not only correct the disorder of intestinal environment [28], but also participate in the proliferation and differentiation of interstitial cells and enteritis [29]. The biological function of transforming growth factor β1 is mediated by the interaction between cytokines and type II receptors, which promotes the phosphorylation of two intracellular proteins Smad2/3. After phosphorylation, the complex produced by the interaction between Smad2/3 and Smad4 migrates into the nucleus, thus controlling the expression of target genes. Smad6 and Smad7 belong to inhibitory Smad proteins, which block TGF-β1/smads signal pathway. Smad6 and Smad7 bind to TGF β receptor I to prevent Smad2/3 phosphorylation. On the contrary, the deletion of Smad3 makes people resistant to colon fibrosis induced by trinitrobenzenesulfonic acid. It can be seen that Smad3 can promote fibrosis, while Smad7 can promote fibrosis. On the other hand, whether it causes the loss of Smad3 or the increase of Smad7, it can lead to the breaking of TGF-β/Smad signal pathway, which in turn reduces the fibrosis of several organs, including the intestinal tract. The loss of Smad7 and the increase of pSmad2/3 further support the fibrogenesis of TGF-β/ Smad pathway in congenital CD stenosis [30].

Epithelial-mesenchymal transition (EMT)

Epithelial-mesenchymal transition (EMT) is a biological process characterized by changes in cell phenotype [31], that is, the transformation from epithelium into mesenchyma in some specific cases [32]. EMT is closely related to embryo formation and development, tissue injury and recovery, organ development and other physiological conditions. Under pathological conditions, EMT can lead to fibrosis, tumor formation and metastasis. In the process of EMT, catenin shifts from the cell membrane to the cytoplasm due to the unconformity of the epithelial cell adhesion zone. The cytoplasmic cistern of catenin is transferred to the nucleus and regulates gene expression, thus initiating the process of EMT, resulting in decreased epithelial surface markers and increased stromal surface markers [33]. The repeatedly occurring chronic inflammation triggers EMT and eventually induces fibrosis. EMT breaks the balance between the degradation and production of extracellular matrix (ECM), resulting in abundant synthesis and accumulation of ECM in intestine and leading to intestinal fibrosis. Up to now, various animal models of intestinal fibrosis were established. In the model induced by TNBS, EMT originated from fibroblasts. A large number of interstitial cells and epithelial cells are distributed in the intestinal fibrotic areas, symbolizing the occurrence of EMT.

The key pro-inflammatory cytokines of intestinal EMT are TNF-α and TGF-β. The mechanism of EMT induced by TNF-α is to promote the high expression of FSP1 and α-SMA in the intestinal tract. TGF-β induces fibrosis by increasing the expression of insulin-like growth factor-1 (IGF-1) mRNA. The production and secretion of IGF by intestinal interstitial cells play a dual role in the healing of intestinal injury. When normally expressed, IGF can facilitate the proliferation of epithelial cells in the form of paracrine, nourish the intestine and promote the healing of intestinal injury. However, overexpressed IGF stimulates intestinal smooth muscle cells and myofibroblasts to proliferate, leading to the increase of collagen synthesis and the formation of intestinal fibrosis. IGF and TGF-β help each other to promote the migration of myofibroblasts. In addition, the interaction between them can further induce the regeneration of intestinal myofibroblasts, and then produce a large amount of collagen and accumulate in the intestine.

Conclusion

In view of the clinical study of effective anti-fibrotic treatments for organ fibrosis, including lung and skin, anti-fibrotic medicine is expected to also improve intestinal fibrosis. However, for intestinal fibrosis, in terms of pathogenesis, early diagnosis and treatment, fibrosis is still one of the less known complications of Crohn's disease, and no specific anti-fibrosis therapy is available. Therefore, more work is needed in the near future to analyze the main mechanisms leading to such complications and to identify effective preventive or therapeutic targets. We need to better understand the pathogenesis of intestinal fibrosis, improve the ability of these target molecules to predict the comparable response of new compounds in clinical practice, and find more solutions to prevent and treat intestinal fibrosis, especially in IBD.

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