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Mini review

The role of transforming growth factor (TGF)-β in modulating the immune response and fibrogenesis in the gut

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ABSTRACT

Transforming growth factor (TGF)-β, a pleiotropic cytokine released by both immune and non-immune cells in the gut, exerts an important tolerogenic action by promoting regulatory T cell differentiation. TGF-β also enhances enterocyte migration and regulates extracellular matrix turnover, thereby playing a crucial role in tissue remodeling in the gut. In this review we describe the mechanisms by which abnormal TGF-β signaling impairs intestinal immune tolerance and tissue repair, thus predisposing to the onset of immune-mediated bowel disorders, such as inflammatory bowel disease and celiac disease. Additionally, we will discuss potential therapeutic strategies aiming at restoring physiologic TGF-β signaling in chronic intestinal diseases.

1. Introduction

Transforming growth factor (TGF)-β belongs to the TGF-β superfamily, which includes more than 40 members, comprising the three isoforms TGF-β1, TGF-β2 and TGF-β3, receptors and intracellular signaling molecules [1,2]. TGF-β is secreted as part of a large latent complex, which includes latent TGF-β binding protein and latency-associated peptide (LAP) [3], and in this form it cannot bind to its receptor and is therefore inactive (Fig. 1). TGF-β can be activated upon being released from the complex through the proteolytic action of a number of proteinases, such as plasmin, thrombospondin-1 [4], matrix metalloproteinase (MMP)-2 and MMP-9 [5], or upon the interaction between the tripeptide integrin-binding motif on LAP and the correspondent binding sequence on $\alpha_v\beta_3$, $\alpha_v\beta_5$, $\alpha_v\beta_6$ or $\alpha_v\beta_8$ integrins [6], expressed on the surface of myofibroblasts [7,8], epithelial cells [9] and dendritic cells [10]. Active TGF-β binds to TGF-β receptor (TβR)II, which consequently complexes with TβRI, and this in turn leads to the formation of the heterotetrameric transmembrane serine/threonine kinase TβR [11,12]. An accessory receptor without any intrinsic signaling function, TβRIII, is able to promote the binding of TGF-β to TβRII [13]. Once TβR is formed, TGF-β induces phosphorylation and activation of TβRI, and this latter subunit activates by binding and phosphorylation the two transcriptional proteins Smad2 and Smad3, which then translocate into the nucleus as a complex with Smad4 and here regulate the transcription of target genes [14]. The inhibitory protein Smad7 competes with Smad2 and Smad3 for the binding to TβRI, thereby blocking their phosphorylation [15]. Smad7 inhibits TGF-β signaling also by recruiting Smurf-containing E3 ubiquitin ligase, which in turn degrades TβRI [16], and by interacting with growth arrest and DNA damage protein, a regulatory subunit of protein phosphatase 1, resulting in TβRI dephosphorylation [17]. Interestingly, TGF-β exerts a negative feedback on itself by inducing the expression of Smad7 [18]. TGF-β also activates phosphoinositide 3-kinase, the small GTPase Ras, and several mitogen-activated protein kinases such as ERKs, p38, and c-Jun N-terminal kinases, which may interact with Smad proteins and ultimately modulate the effects of TGF-β [14,19,20].

TGF-β is a pleiotropic cytokine with potent immunoregulatory properties, which exerts a prominent role as a negative regulator of

Abbreviations: APRIL, a proliferation-inducing ligand; BAFF, B cell activating-factor of the TNF family; CD, Crohn's disease; ECM, extracellular matrix; IBD, inflammatory bowel disease; IFN, interferon; IL, interleukin; LAP, latency-associated peptide; LPMC, lamina propria mononuclear cell; MMP, matrix metalloproteinase; NF-κB, nuclear factor-κB; PPAR, peroxisome proliferator-activated receptor; TCR, T cell receptor; TGF, transforming growth factor; TβR, TGF-β receptor; Th, T helper; TIMP, tissue inhibitor of matrix metalloproteinases; TNBS, trinitrobenzene sulfonic acid; TNF, tumor necrosis factor; Treg, regulatory T cell; UC, ulcerative colitis.

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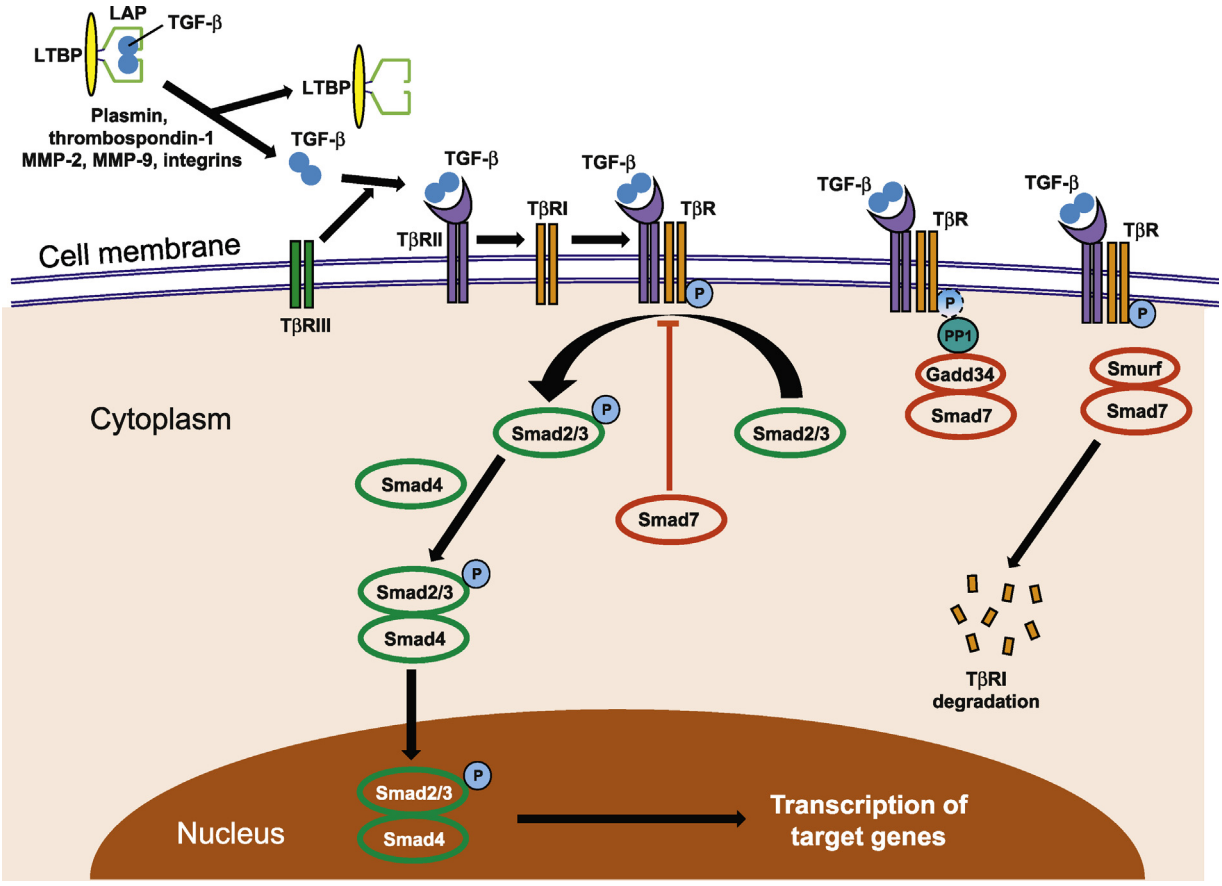

Fig. 1. Transforming growth factor (TGF)-β activation and signaling processes. The homodimeric cytokine TGF-β is secreted as part of a large latent complex, which includes latent TGF-β binding protein (LTBP) and latency-associated peptide (LAP). A number of proteinases, such as plasmin, thrombospondin-1, matrix metalloproteinase (MMP)-2 and MMP-9, and several integrins, such as $\alpha_v\beta_3$, $\alpha_v\beta_5$, $\alpha_v\beta_6$ or $\alpha_v\beta_8$, expressed on the surface of fibroblasts, epithelial cells, and dendritic cells, favor the release of TGF-β from the latent complex, resulting in the activation of this cytokine. TGF-β receptor (TβR)III promotes the interaction of active TGF-β with the homodimeric protein TβRII, which consequently complexes with the serine/threonine kinase homodimeric TβRI, leading to the formation of the heterotetrameric TβR and the phosphorylation and activation of TβRI. This latter, in turn, activates by binding and phosphorylation the two transcriptional proteins Smad2 and Smad3, which form a complex with Smad4 and translocate to the nucleus where they modulate the transcription of target genes. TGF-β signaling is inhibited by Smad7 through the following three mechanisms. First, Smad7 blocks the phosphorylation of Smad2 and Smad3 by competing with them for the binding to TβRI. Moreover, Smad7 induces TβRI dephosphorylation by interacting with growth arrest and DNA damage protein (Gadd34), a regulatory subunit of protein phosphatase 1 (PP1). Finally, Smad7 recruits Smurf-containing E3 ubiquitin ligase, which in turn degrades TβRI.

pro-inflammatory immune responses in various organs, including the gut [21]. Within the intestinal mucosa TGF-β plays a pivotal role in the maintenance of immune homeostasis by preventing abnormal and harmful pro-inflammatory responses against the normal constituents of the intestinal flora [22], and it is centrally implicated in the physiologic processes of intestinal remodelling and wound healing [23]. Abnormalities in TGF-β signaling play a central role in a number of immune-mediated intestinal disorders, including inflammatory bowel disease (IBD) and celiac disease [24–26]. After reviewing the role of TGF-β in the gut at the steady and diseased states, in the last section of this review we will discuss potential therapeutic strategies aiming at restoring physiologic TGF-β signaling in chronic intestinal diseases.

2. Physiologic role of TGF-β in the gut

2.1. *TGF-β as a modulator of the mucosal immune response*

Over the last 20 years, several studies have demonstrated that TGF-β plays a crucial role in maintaining immune homeostasis within the intestinal mucosa (Table 1). *Tgfb1* gene null mice develop inflammatory responses in several organs, including the intestine [27,28], and the lack of TGF-β signaling in transgenic mice expressing on T cells a functionally inactive form of TβRII promotes the differentiation of effector T cells and triggers gut inflammation [29]. The tolerogenic action of TGF-β in the bowel is further supported by its ability to induce T cell unresponsiveness to ovalbumin in mice [30]. Within the gut mucosa, which at the steady state is a TGF-β-rich environment, several cell types, including epithelial cells, macrophages, regulatory T cells (Treg) and myofibroblasts, can both produce and respond to TGF-β (Table 2, Fig. 2).

TGF-β and interleukin (IL)-8 act as chemokines on circulating blood monocytes and recruit them into the lamina propria [31], where during homeostasis they differentiate preferentially into inflammation-anergic intestinal macrophages [32]. This latter process is driven by TGF-β, which prevents the translocation of nuclear factor (NF)-κB into the nucleus and, therefore, down-regulates the subsequent production of pro-inflammatory cytokines [33]. Accordingly, pre-incubation of normal lamina propria mononuclear cells (LPMCs) with TGF-β1 prevents tumor necrosis factor (TNF)-α-induced nuclear factor-κB (NF-κB) activation [34]. TGF-β1 blocks NF-κB activation in macrophages in response to Toll-like receptor-2, -4 and -5 stimulation also by facilitating the

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Table 1
Main evidences for the role of transforming growth factor (TGF)-β in gut immune homeostasis.

Observation	Species	Type of experiment	Functional interpretation	References
Spontaneous colitis in the absence of TGF-β1	*Tgfb1*$^{-/-}$ mouse	*In vivo*	TGF-β has an anti-inflammatory action in the gut	[27,28]
Colitogenic T cell differentiation in the absence of TGF-β signaling	CD4-dn*TβRII* mouse	*In vivo*	TGF-β has an anti-inflammatory action in the gut	[29]
Suppression of pro-inflammatory cytokine production by TGF-β	Human	*In vitro* (monocytes, macrophages)	TGF-β has an anti-inflammatory action in the gut	[33]
Polarization of naïve T cells towards Foxp3^{+} Treg by TGF-β and retinoic acid	WT mouse	*In vivo*, *in vitro* (T cells, dendritic cells)	TGF-β induces Treg development in the gut	[44,45]
Preferential polarization of colonic Th1 cells in the absence of TGF-β1	*Tgfb1*$^{-/-}$ mouse	*In vivo*	TGF-β blockade promotes Th1 and Th17 differentiation	[55]
T-bet, IFN-γ and IL-17A overexpression by normal gut biopsies and LPMCs cultured with anti-TGF-β	Human	*Ex vivo*, *in vitro* (LPMCs)	TGF-β inhibits Th1 and Th17 differentiation	[58]
Reduction of IgA-expressing B cells from Peyer's patches upon impaired TGF-β signaling	*Smad2*$^{-/-}$, *TβRII*$^{-/-}$ and *iNOS*$^{-/-}$ mice	*In vivo* (biopsies), *in vitro* (B cells, dendritic cells)	TGF-β maintains the pool of IgA-producing B cells	[68,69,72]

dn, dominant negative; IFN, interferon; Ig, immunoglobulin; IL, interleukin; iNOS, inducible nitric oxide synthase; LPMC, lamina propria mononuclear cell; Th, T helper; Treg, regulatory T cells; TβR, TGF-β receptor; WT, wild-type.

proteasomal degradation of MyD88 [35], and lipopolysaccharide-induced TNF-α production by both human and murine macrophages is suppressed by TGF-β2 in the developing gut [36]. As a result, a breach in epithelial integrity normally triggers host defense activity but not an inflammatory response by macrophages in the gut [37]. TGF-β1 has also effects on human intestinal mast cells, as it down-regulates the release of the pro-inflammatory mediators hystamine, cysteinyl-leukotrienes and TNF-α, probably by modulating the expression of membrane IgE receptors, and it reduces the amounts of stem cell factor. In addition, TGF-β1 inhibits mast cell growth [38].

TGF-β maintains mucosal tolerance by inducing the differentiation of spleen and peripheral blood naïve T cells into Foxp3^{+} Treg [30,39], a cell subset which has the ability to suppress autoimmune responses and to block experimental colitis [40]. Peripheral naïve T cells of transgenic mice with selective overexpression of Smad7 in the T cell compartment show a decreased capacity to differentiate into Treg upon TGF-β stimulation [41]. Accordingly, mice with a dominant-negative TβRII and, thus, impaired TGF-β signaling specifically in T cells show a reduced number of peripheral Treg and are more susceptible to dextran sodium sulphate-induced colitis [42]. Moreover, mice lacking the binding site for Smad3 on Foxp3 *locus* have a decreased number of Treg selectively in the gut [43].

Treg differentiation in the gut is promoted by the release of TGF-β and retinoic acid by lamina propria CD103^{+} tolerogenic dendritic cells [44–48]. These latter, in turn, develop upon the action of epithelium-derived TGF-β, retinoic acid and thymic stromal lymphopoietin [49], and have the ability to release TGF-β, in particular TGF-β1 and TGF-β2, upon *in vitro* stimulation with probiotics [50,51]. TGF-β production by dendritic cells is associated with high expression of $\alpha_v\beta_8$ integrin [10], which activates TGF-β by inducing its release from LAP [48]. Indeed, the absence of $\alpha_v\beta_8$ integrin on murine dendritic cells makes them unable to induce Treg differentiation *in vitro* and is associated with the development of severe colitis [52]. The ability of Treg to suppress colitis in RAG$^{-/-}$ mice depends on their release of IL-10 and TGF-β [53]. TGF-β also induces the expression of Foxp3 in invariant natural killer T cells, thus leading them to acquire an immunoregulatory phenotype [54].

In parallel, during homeostasis, TGF-β1 inhibits the development of Th1 cells in the gut. This is demonstrated by the increased frequency of colonic Th1 cells in mice with a T cell-specific deletion of *Tgfb1* gene [55]. TGF-β is essential for the prevention of Th1-mediated colitis following adoptive naïve T cell transfer in immunodeficient mice [56]. Indeed, intranasal TGF-β1 administration reduces the secretion of Th1-inducing IL-12 and of Th1-specific interferon (IFN)-γ by LPMCs of mice with experimental colitis [57]. Intestinal lamina propria T cells from normal subjects express high levels of phosphorylated Smad3 [58], whereas in the healthy human gut the inhibitory Smad7 is ubiquitinated and rapidly degraded [59]. Culture of biopsies and LPMCs from human normal gut with an anti-TGF-β neutralizing antibody up-regulates the production of IFN-γ and the expression of the Th1 transcription

Table 2
Main source and target cell types of transforming growth factor (TGF)-β in the gut.

Cell type	Source	Target	Main effects of TGF-β	References
Epithelial cells	Yes	Yes	Up-regulates MMP-1 and MMP-10 expression	[75]
			Induces cell migration across the wound margin	[76]
Dendritic cells	Yes	Yes	Promotes the development of CD103^{+} tolerogenic dendritic cells	[49]
Monocytes/macrophages	Yes	Yes	Recruits blood monocytes into the lamina propria	[31,37]
			Promotes monocyte differentiation into inflammation-anergic gut macrophages	[37]
Naïve T cells	Yes	Yes	Induces Treg development	[30]
			Inhibits Th1 cell polarization	[55,58]
			Suppresses Th17 cell differentiation	[58]
Treg	Yes	Unknown		[39,66]
iNKT cells	No	Yes	Induces Foxp3 expression	[54]
B cells	No	Yes	Promotes isotype switching to IgA	[65–69]
Mast cells	No	Yes	Down-regulates the release of hystamine and TNF-α	[38]
Stromal cells	Yes	Unknown		[31,37]
Fibroblasts/myofibroblasts	Yes	Yes	Promotes differentiation of fibroblasts into myofibroblasts	[83]

Ig, immunoglobulin; iNKT, invariant natural killer T; MMP, matrix metalloproteinase; Th, T helper cell type; TNF, tumor necrosis factor; Treg, regulatory T cells.

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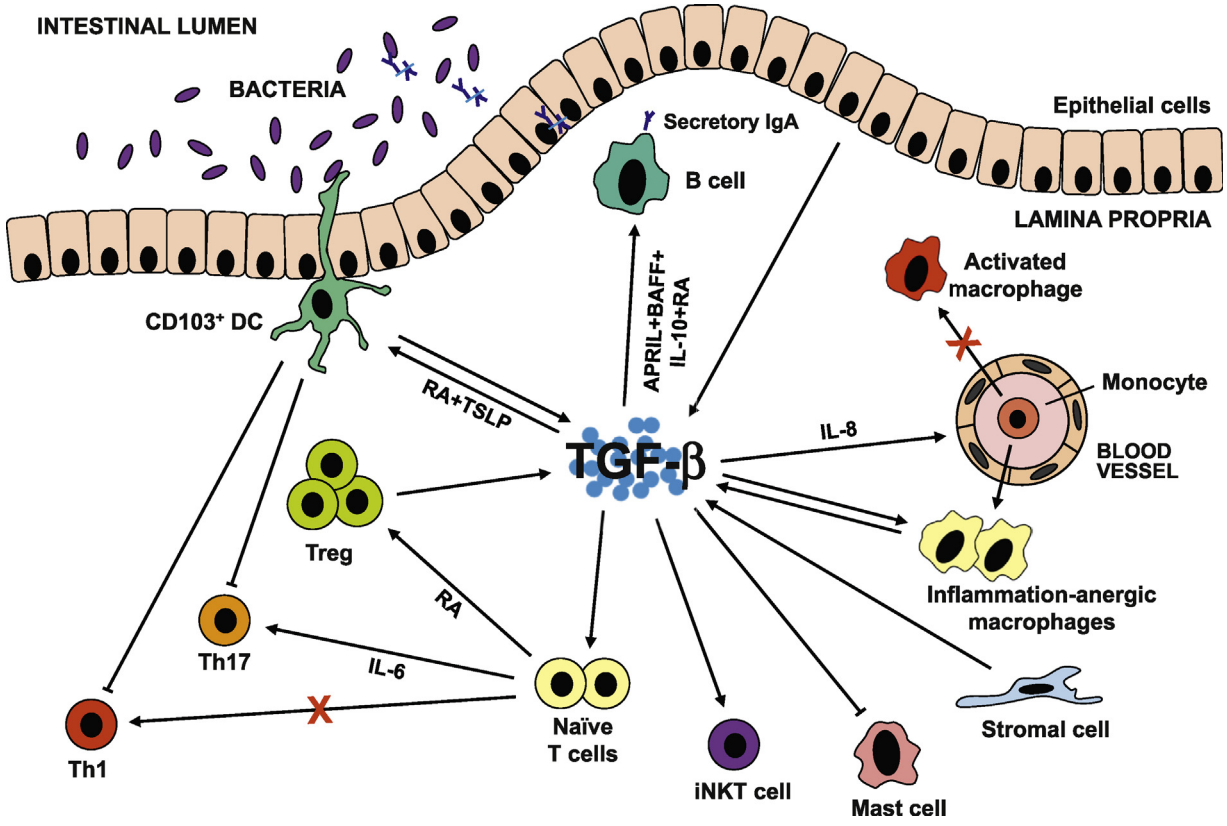

Fig. 2. The role of transforming growth factor (TGF)-β in the modulation of mucosal immune homeostasis in the gut. TGF-β is produced mainly by epithelial cells, stromal cells, regulatory T cells (Treg), dendritic cells (DCs) and macrophages within the intestinal mucosa. Epithelium-derived TGF-β, together with retinoic acid (RA) and thymic stromal lymphopoietin (TSLP), promotes the development of $CD103^+$ tolerogenic DCs. Moreover, TGF-β, together with RA, induces Treg differentiation from naïve T cells. Additionally, in the presence of IL-6, TGF-β directly promotes the differentiation of Th17 cells, whereas it inhibits the development of pro-inflammatory Th1 cells. Both Th17 and Th1 polarization are suppressed by $CD103^+$ tolerogenic DCs. TGF-β induces $Foxp3^+$ expression in invariant natural killer T (iNKT) cells, which have regulatory functions similarly to Treg, and down-regulates the release of the pro-inflammatory hystamine, cysteinyl-leukotrienes and tumor necrosis factor-α by mast cells. Stromal cell-derived TGF-β and IL-8 recruit circulating blood monocytes into uninflamed lamina propria, where they preferentially differentiate into inflammation-anergic macrophages, which in turn produce TGF-β. Finally, TGF-β is required together with B cell activating-factor of the TNF family (BAFF), a proliferation-inducing ligand (APRIL), interleukin (IL)-10 and RA for inducing secretory IgA class switching in B cells.

factor T-bet [58]. It has been recently observed that TGF-β down-regulates IL-2 and IFN-γ expression in human lamina propria T cells by enhancing miR-155 [60].

On the other hand, the role of TGF-β on Th17 cell differentiation is controversial. In the presence of IL-6, TGF-β promotes the development of Th17 cells from murine naïve splenic T cells [47,61] by inducing the expression of transcription factors ROR-γt and ROR-α [61]. The importance of TGF-β for the maintenance of the Th17 cell pool is supported by the observation that, in its absence, murine Th17 cells from the spleen and lymph nodes cultured with IL-12 and IL-23 start producing IFN-γ and stop releasing IL-17A and IL-17F [62]. Conversely, another study has shown that TGF-β promotes Th17 differentiation only indirectly through the suppression of Th1 and Th2 cell development, and that this cytokine is not strictly necessary for the generation of Th17 cells [63]. However, it has been observed that TGF-β blockade increases the production of IL-17A by both biopsies and LPMCs from human normal gut, which indirectly suggests an inhibitory effect of TGF-β on Th17 differentiation [58]. It has also been hypothesized that the gene expression profile of Th17 cells may be influenced by the presence or absence of TGF-β. Indeed, stimulation of murine myelin-reactive Th17 cells with TGF-β and IL-6 abrogates their pathogenic function by inducing the production of the anti-inflammatory IL-10 despite up-regulation of IL-17A [64]. However, it is worth noting that most of the aforementioned studies were conducted on cells from other organs than the gut, hence the exact role of TGF-β in intestinal Th17 cell development and function is still unclear.

Finally, TGF-β is the major cytokine involved in inducing the production of secretory IgA [65,66], a crucial immunoglobulin subclass for the development and maintenance of mucosal tolerance. The role of TGF-β in the generation of IgA has been demonstrated in different experimental models: mice deficient for the inhibitory protein Smad7 show raised isotype switching to IgA [67], and this process, conversely, is impaired in $Smad2^{-/-}$ mice [68]. Accordingly, $T\beta RII^{-/-}$ mice exhibit impaired IgA responses both at the steady state and upon antigen stimulation, both systemically and in the gut [69]. TGF-β1 induces IgA class switching in cooperation with B cell activating-factor of the TNF family (BAFF), a proliferation-inducing ligand (APRIL), and IL-10 [65]. Moreover, TGF-β1 has a synergistic effect with retinoic acid, leading to an increase in IgA switching [70,71]. Dendritic cells enhance TGF-β-mediated induction of IgA class switch by up-regulating TβRII expression on B cells through the production of inducible nitric oxide synthase [72].

2.2. TGF-β as a modulator of tissue remodelling

Tissue remodelling in the gut wall is characterized by physiological extracellular matrix (ECM) deposition and regeneration processes which are driven by the balanced action of MMPs and tissue inhibitors of matrix metalloproteinases (TIMPs) [73].

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Under homeostatic conditions, MMPs are constitutively expressed at low and tightly regulated levels and play a protective role in the normal turnover of gut barrier components, in the physiological migration of immune and non-immune cells within the mucosa, and in the re-epithelialization process [74,75]. TGF-β enhances the migration of intestinal epithelial cells across the wound margin by up-regulating their expression of MMP-1 and MMP-10 [75]. This healing mechanism can be blocked by both a neutralizing anti-TGF-β antibody and protease inhibitors able to prevent the activation of latent TGF-β [76,77]. It has also been shown that other cytokines, including TGF-α, IL-1β and IFN-γ, enhance TGF-β1 production by wounded intestinal epithelial layers [78]. Yamada et al. [79] have reported that *in vitro* stimulation of intestinal epithelial cells with TGF-β1 promotes their differentiation and suppresses their proliferation through Smad2- and Smad3-dependent pathways, and that enterocytes display up-regulated expression of the inhibitory Smad7 as a form of negative feedback.

Tissue repair is facilitated by the scavenger activity of macrophages, which enter the wounded site to remove pathogens, damaged tissue and apoptotic cells. As a consequence, macrophages acquire an immunoregulatory phenotype [80], characterized by reduced production of pro-inflammatory cytokines and chemokines due to increased release and autocrine/paracrine action of TGF-β1, prostaglandin E2 and platelet-activating factor [81,82]. Accordingly, the addition of an anti-TGF-β neutralizing antibody reverses the inhibitory effect of apoptotic cell uptake on chemokine and TNF-α secretion by macrophages [82]. However, the above studies were conducted on mouse and human peripheral blood-derived macrophages, therefore it is uncertain whether similar mechanisms occur in the human gut mucosa.

TGF-β1 induces mesenchymal cell activation and differentiation into myofibroblasts [84]. These are characterized by the expression of α-smooth muscle actin, which enables them to contract thereby facilitating the closure of wound margins, and by the release of MMP-1 and ECM proteins, such as collagen and fibronectin [75,83]. The interaction between TGF-β latent complex, which is covalently bound to the ECM, and integrins such as the $\alpha_v\beta_5$ integrin on the surface of myofibroblasts [8], followed by the contraction of these latter, leads to the release and activation of TGF-β1 [84]. This mechanism is directly correlated to the stiffness of the ECM, which represents a reservoir of latent TGF-β in the tissue [85]. Indeed, *ITGB2*$^{-/-}$ mice, which lack β2 integrin, display wound healing alterations in the skin due to reduced active TGF-β1 and remarkable scarcity of myofibroblasts [86]. Moreover, intestinal myofibroblasts enhance epithelial migration in wounded epithelial monolayers by secreting bioactive TGF-β3 [87]. Myofibroblasts, which play a central role in the physiologic process of wound healing, disappear by apoptosis once the re-epithelialization process is complete [88].

While controlled amounts of TGF-β play an essential role in the physiological processes of wound healing, increased levels of TGF-β may suppress the production and activity of tissue-degrading MMPs, which are critical contributors in the processes of ECM turnover in the gut [89]. This causes intestinal fibrosis, a condition characterized by excessive production, deposition and contraction of ECM.

3. Abnormal TGF-β signaling in intestinal diseases

3.1. Experimental colitis

Both trinitrobenzene sulfonic acid (TNBS)- and oxazolone-induced colitis are characterized by unexpectedly increased expression of TGF-β1 in inflamed tissue associated with impaired TGF-β signaling due to elevated levels of Smad7, which in turn leads to reduced phosphorylated Smad3 [90]. Other studies showed that the intranasal administration of TGF-β1 or the oral treatment with haptenized colonic proteins, which induce TGF-β-dependent oral tolerance, are effective in preventing [57,91] and ameliorating [57] TNBS colitis. TGF-β1 and haptenized colonic proteins exert their immunoregulatory effects in experimental colitis by promoting the differentiation of T cells and macrophages which produce increased amounts of TGF-β1 and reduced quantities of IL-12 and IFN-γ [57,91]. Conversely, the treatment of mice with an anti-TGF-β neutralizing antibody abrogates the suppressive effects of haptenized colonic proteins on colonic inflammation and lamina propria Th1 cytokine profile following TNBS administration [91]. $CD103^+$ dendritic cells from colitis models express reduced levels of TGF-β2 and ALDH1A2, a critical enzyme for the synthesis of retinoic acid from retinal [92]. Smad7 overexpression in transgenic mice increases the severity of disease in dextran sodium sulphate-mediated colitis and unexpectedly prevents colitis-associated cancer by inducing a marked Th1 response [93]. Oral administration of a Smad7 antisense oligonucleotide ameliorates both TNBS- and oxazolone-induced colitis by enhancing phosphorylated Smad3, whereas it is not effective in the adoptive naïve T cell-transplanted SCID mouse model of colitis, in which TGF-β signaling pathway is not impaired [90]. Indeed, in this latter model TGF-β, together with IL-2, induces the differentiation of Treg which are effective in suppressing colonic inflammation [94,95]. Chronic experimental colitis is characterized by the development of TGF-β-dependent gut fibrosis, as shown by the observation that chronic intrarectal TNBS-induced colonic fibrosis, marked by increased mucosal transcripts of TGF-β1 [96], is effectively prevented by a TGF-β1 peptide-based vaccine, able to suppress excessive TGF-β1 activity [97]. Moreover, adenoviral vector-induced overexpression of TGF-β1 in murine colon leads to obstructive intestinal fibrosis [98].

3.2. Inflammatory bowel diseases

IBD, including Crohn's disease (CD) and ulcerative colitis (UC), are chronic and relapsing inflammatory disorders of the gastrointestinal tract [99,100]. Intestinal inflammation in IBD is thought to derive from an excessive immune response against the normal constituents of the commensal flora [101,102], and is characterized by up-regulated mucosal levels of pro-inflammatory cytokines, such as TNF-α, IFN-γ and IL-17A, and by defective immunoregulatory mechanisms [103]. The chronic inflammatory process ultimately determines an imbalanced production of MMPs and TIMPs, finally causing tissue damage and the formation of erosions and ulcerations [73].

Surprisingly, TGF-β1 expression is increased in the inflamed gut of IBD patients with active disease compared to control mucosa [104]. However, pre-incubation of IBD LPMCs with TGF-β1 is unable to prevent TNF-α-induced NF-κB activation, implying their resistance to the TGF-β1-mediated immunosuppression [34]. Indeed, TGF-β signaling pathway is defective in IBD, as demonstrated by the reduced levels of phosphorylated Smad3 and Smad3-bound Smad4 in inflamed IBD intestinal mucosa [105]. This is due to the marked up-regulation of Smad7 in CD and UC mucosa, where it is overexpressed by both T cells and non-T cells and critically impairs TGF-β signaling [105]. Smad7 increase in IBD inflamed gut does not derive from a negative feedback by TGF-β itself, as suggested by the low levels of phosphorylated Smad3 [105], but it is due to post-transcriptional acetylation and stabilization by the p300 acetyltransferase, which prevents Smad7 ubiquitination and degradation in the proteasome [59]. The blockade of Smad7 using a specific antisense oligonucleotide increases the amount of phosphorylated Smad3 in CD inflamed intestinal biopsies and LPMCs, and ultimately reduces the

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production of the pro-inflammatory cytokines TNF-α and IFN-γ [105]. This is likely to derive from the restoration of endogenous TGF-β activity, as the *ex vivo* effects of the Smad7 antisense oligonucleotide are decreased by the addition of a TGF-β neutralizing antibody [105]. Elevated levels of Smad7 and impaired TGF-β1 signaling are not specific features of IBD, since the same alterations have been also observed in the gastric mucosa of patients with *Helicobacter pylori* infection [106].

Treg, while being reduced in peripheral blood of patients with active IBD, are increased in the inflamed intestinal mucosa of IBD patients [107,108]. However, T cells from IBD gut mucosa are hyporesponsive to Treg-mediated suppressive action [109]. This depends on defective TGF-β signaling due to high Smad7 expression, as T cell responsiveness to Treg is restored by the culture with Smad7 antisense oligonucleotide [109–111]. Interestingly, TGF-β is able to induce the development of IL-17A-producing Foxp3$^+$ T cells, which exert suppressive activity similar to Treg *in vitro* and are increased in the inflamed mucosa of CD patients but not in UC patients [112].

In CD, where inflammation is transmural, subsequent damage and repair processes may ultimately cause architectural distortion and thickening of all layers of the bowel wall, thus leading to intestinal fibrosis and stricture development [113]. This represents a major clinical problem in CD patients and may often require the surgical removal of the affected tract [114]. TGF-β signaling is centrally involved in intestinal fibrogenesis in CD (Fig. 3). Indeed, in the uninflamed mucosa overlying intestinal strictures of CD patients TGF-β1 is higher compared to uninflamed mucosa overlying non-strictured areas [115]. Myofibroblasts isolated from the mucosa overlying CD strictures express increased TGF-β1 transcripts and release higher TGF-β1 protein levels compared to myofibroblasts from uninflamed non-strictured CD and control areas [115]. Collagen levels are increased in CD intestinal strictures compared to non-strictured CD and control gut [116], and the production of both collagen and other ECM components, such as fibronectin, by intestinal myofibroblasts is up-regulated in CD strictures [115,117]. Stimulation with TGF-β1 increases collagen III production by gut myofibroblasts, and its effect is enhanced in cells isolated from CD intestinal strictures [117]. The reduction of tissue-degrading proteases, such as MMP-3 and MMP-12, and the increase in MMP inhibitors, including TIMP-1, observed in CD strictures, may also contribute to the abnormal ECM accumulation characterizing CD intestinal fibrosis [115]. TGF-β1 increases TIMP-1 production by myofibroblasts isolated from strictured, uninflamed non-strictured CD and control mucosa, and reduces MMP-12 release by myofibroblasts isolated from uninflamed mucosa overlying non-strictured CD and control areas [115,118]. On the other hand, TGF-β blockade with an anti-TGF-β neutralizing antibody increases myofibroblast migration and MMP-12 production [115]. Moreover, TGF-β2, but not TGF-β3, enhances TIMP-1 production by normal intestinal myofibroblasts [118].

3.3. Celiac disease

Celiac disease is an immune-mediated enteropathy, characterized by villous atrophy and consequent malabsorption, induced in genetically susceptible individuals by the ingestion of proline- and glutamine-rich proteins contained in wheat (gliadins), rye (hordeins), and barley (secalins) [119]. Several aspects of the molecular mechanisms driving the immune response in celiac

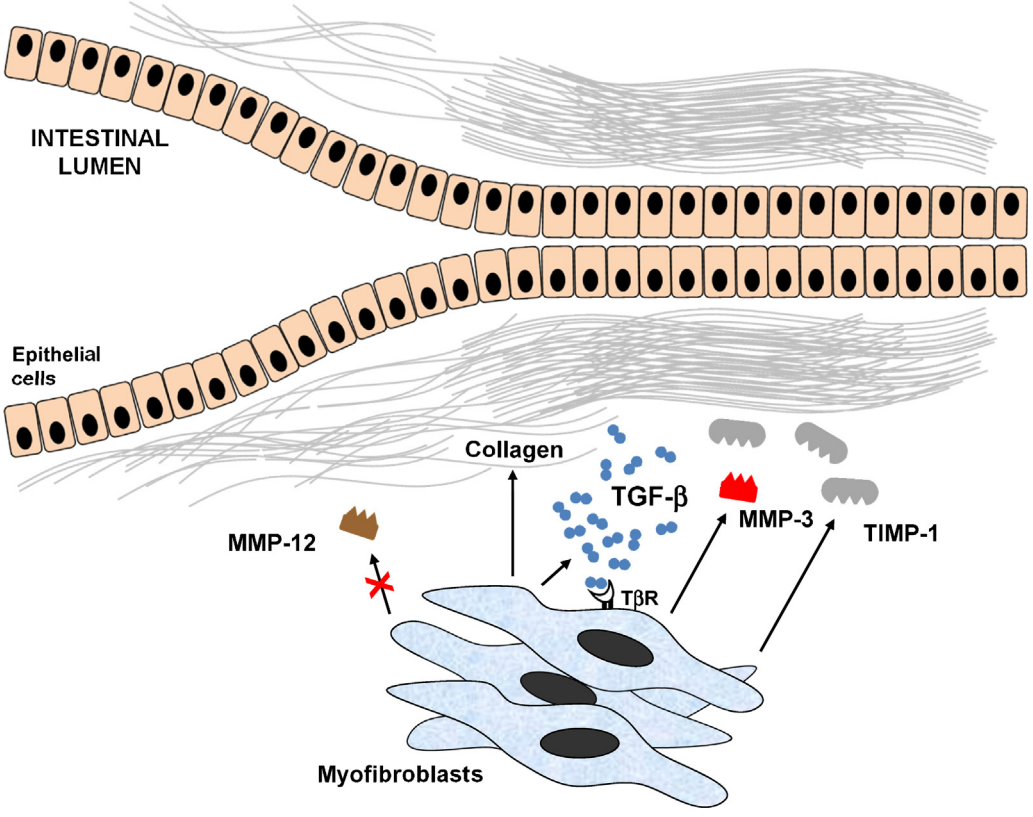

Fig. 3. The role of transforming growth factor (TGF)-β in Crohn's disease (CD) intestinal fibrosis. The right part of the diagram represents an intestinal CD stricture, preceded by a pre-stenotic dilatation of an uninflamed non-strictured tract (left part of the diagram). In CD intestinal strictures myofibroblasts, a cell population playing a key role in gut fibrogenesis, produce excessive amounts of TGF-β. Stricture development in CD is characterized by excessive synthesis and accumulation of collagen and other extracellular matrix components by intestinal myofibroblasts, by the reduction of tissue-degrading proteolytic enzymes, such as matrix metalloproteinase (MMP)-3 and MMP-12, and by the increase in tissue inhibitors of matrix metalloproteinases (TIMPs), including TIMP-1. TGF-β stimulates the release of collagen III by gut myofibroblasts, and its effect is particularly pronounced on cells from CD intestinal strictures. Moreover, TGF-β enhances TIMP-1 secretion and reduces MMP-12 production by intestinal myofibroblasts.

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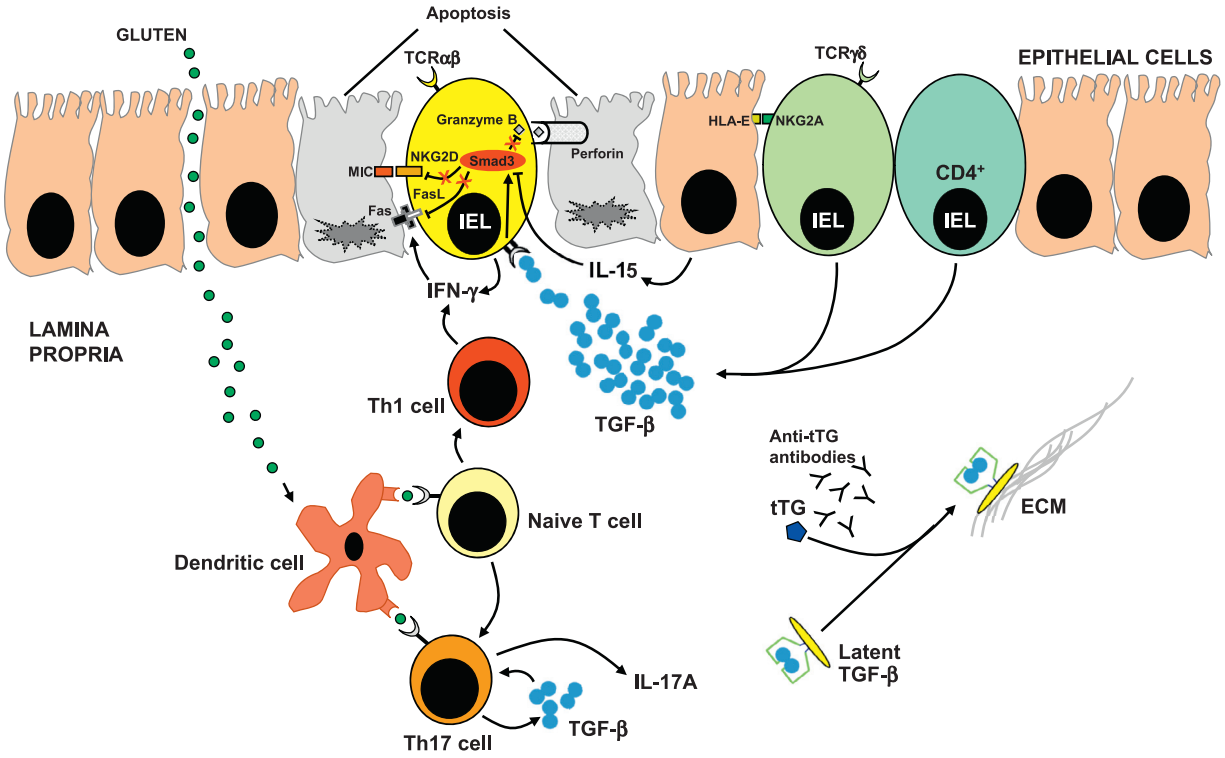

Fig. 4. Transforming growth factor (TGF)-β in the intestinal epithelium and the lamina propria of celiac disease patients. In active celiac disease, increased levels of interleukin (IL)-15 impair TGF-β signaling in intraepithelial lymphocytes (IELs) by blocking Smad3. As a result, TGF-β is unable to suppress the expression of granzyme B and NKG2D and the production of interferon (IFN)-γ by T cell receptor (TCR)$\alpha\beta^+$ IELs. The consequent IFN-γ-induced activation of the Fas/Fas ligand (FasL) system and the interaction between the activating receptor NKG2D and granzyme B on IELs and, respectively, the major histocompatibility complex-class I-related ligands (MIC) and perforin on epithelial cells are major factors triggering enterocyte apoptosis in active celiac disease. Conversely, gluten-free diet restores the regulatory effects of TGF-β, mainly produced by $CD4^+$ IELs and TCR$\gamma\delta^+$ $NKG2A^+$ IELs upon the interaction between the inhibitor receptor NKG2A and HLA-E, on TCR$\alpha\beta^+$ IELs. Within the lamina propria of active celiac disease patients, high levels of anti-tissue transglutaminase (tTG) antibodies prevent latent TGF-β accumulation by inhibiting the ability of tTG to induce its cross-linking to the components of the extracellular matrix (ECM). However, TGF-β is up-regulated in active celiac disease mucosa, where the presentation of gluten peptides by dendritic cells to naïve T cells drives the differentiation of naïve T cells into IFN-γ-producing T helper (Th)1 cells and IL-17A-expressing Th17 cells. These latter produce increased TGF-β amounts, which in turn act in an autocrine fashion by enhancing IL-17A release.

disease are still unclear, however it is known that both Th1 and Th17 cells can induce and sustain small bowel lesions [120,121].

Tissue transglutaminase, which is increased in active celiac disease duodenal mucosa [122], normally plays an important role in local TGF-β accumulation by promoting the cross-linking of its latent form to the ECM [123]. However, in active celiac disease this mechanism is inhibited by the presence of anti-tissue transglutaminase antibodies (Fig. 4) [124]. Nevertheless, TGF-β has been reported to be increased in the duodenal mucosa of active celiac patients [122,125], and its expression is particularly prominent in the lamina propria, thus suggesting an association with the local immune and inflammatory response [126]. TGF-β1 mRNA levels are increased in $CD4^+$ intraepithelial lymphocytes isolated from active celiac mucosa [127]. Moreover, it has been shown that after gliadin stimulation celiac Th17 cells produce increased amounts of TGF-β, which in turn acts in an autocrine fashion by enhancing IL-17A release [128]. TGF-β signaling pathway has not been extensively investigated in the resident and infiltrating cells within the lamina propria of active celiac disease patients, therefore the functional consequences of the increase in TGF-β at this level are unclear.

On the other hand, within the intestinal epithelium of active celiac disease patients TGF-β signaling has been studied and appears to be impaired. Indeed IL-15, which is up-regulated in active celiac disease mucosa and plays a central role in promoting the cytotoxic activity of T cell receptor (TCR)$\alpha\beta^+$ intraepithelial T cells [129–131], inhibits TGF-β signaling in T lymphocytes via Smad3 blockade, without affecting Smad7 activity [26,132]. Gluten-free diet restores the normal regulatory activity of TGF-β within the intestinal epithelium in uncomplicated celiac disease. In fact, TGF-β1 released by TCR$\gamma\delta^+$ $NKG2A^+$ intraepithelial lymphocytes in treated celiac patients down-regulates the expression of IFN-γ, granzyme B and NKG2D by TCR$\alpha\beta^+$ intraepithelial lymphocytes, thus reducing their pro-inflammatory and pro-apoptotic potential [131].

4. Targeting TGF-β signaling as a therapeutic strategy

TGF-β supplementation has been thought to be potentially beneficial for the treatment of intestinal inflammation in IBD. However, in the inflamed gut of CD and UC patients TGF-β levels are actually increased [104], and immune cells are hyporesponsive to the action of TGF-β due to the excess of inhibitory Smad7 [24,105]. Therefore, a single-stranded oligonucleotide matching the region 107-128 of the human Smad7 complementary DNA sequence in the antisense orientation has been synthesized and has been used in several *in vitro* and *ex vivo* models in order to evaluate the potential effectiveness of a therapeutic strategy aimed at restoring TGF-β signaling in intestinal inflammation [105,133–135]. In parallel, a Smad7 sense oligonucleotide, matching the same DNA sequence, has also been synthesized and used as a negative control [105]. Indeed, Smad7 blockade by the specific antisense – but not the control sense – oligonucleotide reduces the production of pro-inflammatory cytokines by IBD biopsies and LPMCs [105] and restores the responsiveness of T cells from IBD patients to the suppressive action of Treg [109], most likely by

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Table 3
Possible strategies to modulate transforming growth factor (TGF)-β in gut fibrosis.

Strategy	Rationale	References
Neutralizing antibodies	Anti-TGF-β increases intestinal myofibroblast migration and MMP-12 production	[115]
PPARγ agonists	GED-0507-34 Levo, a PPARγ modulator, ameliorates DSS-induced intestinal fibrosis by counteracting the effects of TGF-β	[145]
ACE inhibitors	Captopril and enalaprilat prevent TNBS- and DSS-induced intestinal fibrosis by down-regulating TGF-β expression	[146,147]
ANGIIR inhibitors	Losartan reduces TNBS-induced colonic fibrosis via TGF-β inhibition	[148]

ACE, angiotensin-converting enzyme; ANGIIR, angiotensin II receptor; DSS, dextran sodium sulphate; MMP, matrix metalloproteinase; PPAR, peroxisome proliferator-activated receptor; TNBS, trinitrobenzene sulfonic acid.

re-enabling endogenous TGF-β signaling [105]. Moreover, *ex vivo* culture of IBD biopsies with the Smad7 antisense oligonucleotide leads to increased production of IL-25 [136], a cytokine with immunoregulatory properties which dampens Th1 and Th17 inflammatory responses in the gut and is down-regulated in inflamed CD and UC mucosa [137]. Smad7 antisense treatment of CD biopsies and LPMCs also increases the release of TIMP-3, which is up-regulated by TGF-β, exerts a potent anti-inflammatory action by inhibiting TNF-α converting enzyme and is down-regulated in CD mucosa as a consequence of defective TGF-β1 signaling [138].

On this basis, the pharmaceutical compound GED0301, which is based on the same Smad7 antisense oligonucleotide matching the region 107-128 of the human Smad7 DNA sequence, has been developed [139]. GED0301 is administered orally, is gastroresistent and is released in the terminal ileum and the right colon, which are the most frequent localizations of CD [139]. GED0301 abrogates TNBS- and oxazolone-induced colitis, which are both characterized by mucosal overexpression of TGF-β and Smad7 [90]. In a phase I, open label study GED0301 has been administered once daily for a total of 7 days to 15 patients with moderate-to-severe, steroid-dependent or steroid-resistant active CD [139]. GED0301 treatment resulted in a substantial clinical benefit, with 86% of the enrolled patients entering remission, and was well-tolerated, with no serious adverse events being observed [139]. Moreover, treatment with GED0301 was associated with a significant reduction of IFN-γ^+ or IL-17A$^+$ circulating T cells expressing the gut-homing molecule CCR9 [139]. Due to the pro-fibrogenic properties of TGF-β, six months after the administration of GED0301 the formation of strictures was investigated using small intestine contrast ultrasonography, which did not detect any small bowel stricture in any of the patients [140]. Furthermore, no change was detected in the serum levels of fibrogenic markers, such as basic fibroblast growth factor and TIMP-1 [140]. A phase II clinical trial in patients with active CD is currently underway in order to investigate GED0301 efficacy and long-term safety [141].

As the development of CD intestinal strictures is driven by local excessive levels of TGF-β [115], strategies aimed at counteracting the effects of this cytokine are currently being explored or could be promising in the context of gut fibrosis (Table 3). Indeed, *Smad3* null mice are resistant to TNBS-induced intestinal fibrosis [142]. Moreover, the administration of *Boswellia* and *Scutellaria* extracts prevents colonic fibrosis in TNBS-induced colitis by inhibiting TGF-β expression [143]. Peroxisome proliferator-activated receptor (PPAR)γ overexpression prevents tissue fibrosis in several organs, and PPARγ agonists reduce lung, kidney and liver fibrosis through TGF-β inhibition [144]. It has been recently reported that GED-0507 34 Levo, a novel PPARγ modulator, ameliorates dextran sodium sulphate-induced intestinal fibrosis by counteracting the effects of TGF-β [145]. Angiotensin II plays an important role in kidney and liver fibrosis by enhancing TGF-β expression. Indeed, angiotensin-converting enzyme inhibitors prevent fibrosis in TNBS- and dextran sodium sulphate-induced colitis [146,147], and the angiotensin II receptor antagonist losartan reduces TNBS-induced colonic fibrosis [148]. Losartan has shown promising results also in human liver fibrosis [149], however its use in human intestinal fibrosis has not been investigated so far. Finally, it needs to be underlined that all the data on the inhibition of TGF-β for the treatment of intestinal fibrosis derive from animal models or primary cell cultures, and have to be filtered through the notions that experimental fibrosis does not necessarily resemble human fibrosis, that cells may have a different behavior *in vitro* and *in vivo*, and that cell-cytokine networks are more important than single cell and cytokine functions.

5. Concluding remarks

While the overall regulatory actions of TGF-β on gut immune homeostasis and wound healing and on immune cell types such as Treg and B cells are well established, a number of effects of TGF-β on immune and non-immune cells are still the subject of extensive investigation. Several studies have shown the importance of controlled TGF-β activity, resulting not only from the overall cytokine levels but also from the functional integrity of TGF-β signaling pathway, within the gut. Abnormal TGF-β signaling plays a central role in driving chronic intestinal disorders, including IBD and celiac disease. In CD, restoration of TGF-β signaling through Smad7 inhibition appears to be promising, and soon the clinical studies on the Smad7 antisense oligonucleotide GED0301 are going to define the therapeutic potential of this strategy.

Conflict of interest statement

None.

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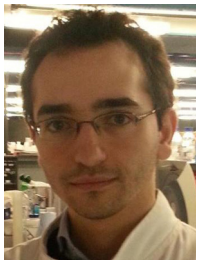

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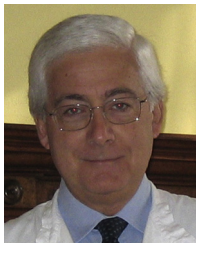

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