Immunome Research

Sedda et al., Immunome Res 2017, 13:2
DOI: 10.4172/1745-7580.1000133

Review Article Open Access

Smad7 as a Target for Immunomodulation Strategy in Inflammatory Bowel Diseases

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Received date: March 17, 2017; **Accepted date:** May 17, 2017; **Published date:** May 22, 2017

Abstract

Inflammatory bowel diseases (IBD) are chronic inflammatory pathologies of the gut, characterized by a relapsing-remitting course. Although IBD pathogenesis is not fully understood, epidemiological and experimental data suggest that multiple environmental factors can, in genetically predisposed individuals, trigger an excessive immune response directed against the antigens of the normal intestinal microflora, which eventually leads to the tissue damage. Defects in the physiological mechanisms/factors of counter-regulation contribute to amplify and sustain such a detrimental response. For instance, in inflamed tissue of IBD patients there is diminished activity of the immunesuppressive cytokine transforming growth factor (TGF)-β1, due to elevated levels of Smad7, an intracellular inhibitor of TGF-β1 signaling. Consistently, knockdown of Smad7 with a specific antisense oligonucleotide suppresses inflammatory signals in cultured intestinal cells of IBD patients and in the gut of mice with IBD-like experimental colitis. Moreover, treatment of patients with active Crohn's disease, one of the two major IBD in human beings, with Mongersen, an oral compound containing Smad7 antisense oligonucleotide, is accompanied by induction of clinical remission. Altogether these data indicate that targeting Smad7 represents a promising approach to modulate the ongoing mucosal inflammation in IBD.

Keywords: Crohn's disease; Ulcerative colitis; Counter-regulatory mechanisms; Transforming growth factor-β1; Mucosal inflammation

Abbreviations IBD: Inflammatory Bowel Diseases; CD: Crohn's disease; UC: Ulcerative Colitis; TGF: Transforming Growth Factor; TNF: Tumor Necrosis factor; TGFβRII: Type II TGF-β receptor; TGFβRI: Type I TGF-β receptor; LPMC: Lamina Propria Mononuclear Cells; NF-kB: Nuclear Factor Kappa B; TNBS: Trinitrobenzene Sulfonic Acid

Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are the principal types of inflammatory bowel diseases (IBD) in human beings. CD is characterized by a transmural and segmental inflammation that can involve any part of the alimentary tract, even though lesions are more common in the terminal ileum and right colon. In contrast, in UC, the inflammatory process involves the mucosa of the rectum and can extend proximally to the colon [1]. The natural history of both CD and UC patients can be also marked by local complications and extra-intestinal manifestations. IBD arise as a result of the interaction between environmental and genetic factors, which leads to an excessive immune response directed against the components of the intestinal microflora [2,3]. Inflamed tissue of IBD patients is massively infiltrated with many immune cell types, which exhibit phenotypic features of activated cells and have the ability to produce huge amounts of inflammatory molecules [4,5]. Identification of the major inflammatory pathways leading to the IBD-associated tissue damage has contributed to the development of various immunomodulating drugs. For instance, different strategies have been explored to inhibit tumor necrosis factor (TNF), since this cytokine regulates positively multiple detrimental signals in the gut. Clinical trials and data emerging from the real-life indicate that monoclonal anti-human TNF antibodies (e.g. infliximab, adalimumab) are useful to induce and maintain clinical, endoscopic and histological remission in IBD thereby reducing the risk of complications, hospitalization and surgery [6-9]. More recently, monoclonal antibodies targeting integrins or other inflammatory cytokines have been used with success in IBD patients, reinforcing the notion that targeting therapy can help dampen the tissue-damaging immune response in these disorders [10,11]. However, not all the patients respond to or tolerate such therapies thereby indicating the need for additional effective and safe drugs.

In the last decade, evidence has been accumulated to suggest that IBD-related inflammation is also sustained by defects in counter-regulatory mechanisms. One such a mechanism involves transforming growth factor (TGF)-β1, a multifunctional cytokine that is produced by many intestinal cell types and controls negatively multiple inflammatory signals [2,12]. Indeed, mice deficient in TGF-β1 expression and/or activity develop intestinal inflammation while induction of TGF-β1 production in mice associates with diminished severity of colitis [13-15]. Along the same line is the demonstration that human IBD are marked by defective TGF-β1 activity due to elevated levels of Smad7, an intracellular inhibitor of TGF-β1 signaling [16]. We here review the available data supporting the pathogenic role of Smad7 in the gut.

Smad7 Limits TGF-β1 Activity in the Gut

Binding of TGF-β1 to the type II subunit of TGF-β receptor (TGFβRII) leads to phosphorylation and activation of TGFβR type I

subunit (TGFβRI) [17,18], which in turns promotes phosphorylation of Smad2 and Smad3, two intracellular proteins. Once activated, Smad2 and Smad3 associate with Smad4 and translocate to the nucleus, where Smad protein complexes suppress the transcription of many inflammatory genes [19,20]. Several pieces of evidence support the importance of TGF-β1-associated Smad2/3 signaling in the control of gut homeostasis. For instance, lamina propria mononuclear cells (LPMC) and biopsies taken from the small intestine and colon of healthy individuals and colonic specimens of normal mice express constitutively high levels of phosphorylated Smad3 [16,21]. Normal LPMC respond to exogenous TGF-β1 with enhanced Smad3 phosphorylation, inhibition of nuclear factor kappa B (NF-kB) activation and suppression of inflammatory molecule synthesis [22]. Mice lacking Smad3 have an infiltration of T cells and pyogenic abscess formation in the intestine [23].

In inflamed intestine of IBD patients there are high levels of TGF-β1 RNA transcripts [24] but diminished expression of phosphorylated Smad3 and Smad3/Smad4 complexes as compared with normal intestinal samples [16]. Moreover, in vitro treatment of IBD LPMC with TGF-β1 does not suppress NF-kB activation or production of pro-inflammatory cytokines, suggesting a defect of TGFβ1 signaling [22]. Indeed, IBD mucosal cells express elevated levels of Smad7, an intracellular protein that binds to TGFβRI and prevents Smad2/3 phosphorylation [16]. Knockdown of Smad7 in IBD LPMC and mucosal explants with a specific antisense oligonucleotide restores cell responsiveness to TGF-β1, as indicated by increased level of phosphorylated Smad3 and diminished expression of inflammatory cytokines [16]. The factors/mechanisms that sustain Smad7 expression in IBD remain to be determined. Smad7 is regulated at the post-transcriptional level by enhanced acetylation of the protein on lysine residues. This modification, which is partly mediated by the acetylase p300, prevents Smad7 ubiquitination-mediated proteasomal degradation with the downstream effect of enhancing Smad7 protein stability [25]. We have recently shown that the levels of Sirt1, an enzyme that deacetylates Smad7 lysine residues [26,27], are reduced in inflamed tissue of IBD patients, suggesting a further mechanism by which Smad7 overexpression is sustained in these disorders [28].

Studies in cancer cells have also shown that Smad7 levels are controlled by USP26, a deubiquitinating enzyme, which preventes Smad7 degradation [29]. On the other hand, there are intracellular mechanisms that counteract Smad7 activity. Among these, RNF11, an E3 ligase, has been reported to antagonize Smurf2/Smad7 complex, thus restoring cellular TGFβ signaling [30]. It remains unclear if these mechanisms are also acting in the gut of IBD patients. Mir-195 acts as a negative regulator of Smad7 expression [31] and decreased levels of mir-195 have been described in steroid-resistant UC patients, thus suggesting a link between such a defect and the enhanced expression of Smad7 in UC.

Preclinical Evidence Supporting the Immunoregulatory Effect of Smad7 Antisense Oligonucleotide in the Gut

A considerable amount of experimental data has been accumulated to support the pathogenic role of Smad7 in the gut. Studies in mice with trinitrobenzene sulfonic acid (TNBS)-induced colitis, which shows immunological similarities with CD, or oxazolone-induced colitis, which resembles UC, show that colonic inflammation in such animals is characterized by overproduction of TGF-β1, which associates with decreased expression of phosphorylated Smad3 and elevated content of Smad7 [32,33]. Inhibition of Smad7 with an oral antisense oligonucleotide enhances Smad3 phosphorylation, suppresses expression of STAT1 and T-bet, two T helper (Th)1-related transcription factors, and Th1 cytokines in mice with TNBS-induced colitis and interleukin (IL)-4 production in mice with oxazolone induced colitis, thus leading to attenuation of colitis [33,34].

Analysis of Smad7-expressing cells in the gut revealed that such a protein is overexpressed in both T cells and non-T cells [16]. To examine the role of Smad7 in T cells, we developed a transgenic mouse overexpressing Smad7 in this cell type. The transgenic mice do not spontaneously develop intestinal inflammation but show increased mucosal production of inflammatory cytokines and more severe colitis than wild-type mice following oral ingestion of dextran sulfate sodium [35]. Interestingly, Smad7-overexpressing T cells transferred into immunodeficient mice cause a severe colitis that is resistant to regulatory T-cell (Tregs)-mediated immunosuppression [36]. This finding is consistent with the demonstration that CD mucosal T cells are not responsive to Tregs-mediated immunosuppression, a phenomenon that is reverted by Smad7 knockdown. T cells of Smad7-transgenic mice also exhibit a defective expression of aryl hydrocarbon receptor (AhR), a transcription factor that promotes IL-22 production thus delivering protective signals in the gut [37]. In immunodeficient mice, 6-formylindolo[3,2-b]carbazole, an activator of AhR, ameliorates colitis induced by wild-type T cells but does not affect colitis induced by transfer of Smad7-overexpressing T cells [37]. CD mucosal cells have reduced levels of AhR but expression of such a protein is increased by TGF-β1 stimulation following Smad7 knockdown [38].

Treatment of IBD mucosal cells with Smad7 antisense oligonucleotide also increases production of both interleukin 25 [39], a cytokine that negatively regulates Th1 and Th17 inflammatory responses in the gut, and tissue inhibitor of matrix metalloproteinase-3, an enzyme that inhibits multiple tissue degrading enzymes [40].

Mongersen: the Clinical Relevance of Smad7 Inhibition

The demonstration that inhibition of Smad7 restores a TGF-β-dependent counter-regulatory mechanism leads to the development of a pharmaceutical compound, named Mongersen, containing the Smad7 antisense oligonucleotide. This drug is given orally to patients and is protected by an external coating that determines gastro-resistance and allows the compound to be released in the terminal ileum and right colon [41]. A phase 1, clinical, open-label dose-escalating study was conducted in 15 patients with active steroid-dependent or resistant CD. Patients were divided into 3 cohorts and received Mongersen once a day for 7 days at doses of 40, 80, and 160 mg [41]. Treatment with Mongersen was well tolerated and no drug-related adverse event was observed. Measurement of the circulating levels of the drug revealed a very low systemic bioavailability as the compound was detectable at low levels in the plasma of only one patient at a single time point. All CD patients showed a clinical improvement following treatment and more than two thirds of them experienced a clinical remission. Treatment associated with a reduction of the fraction of circulating CCR9-positive T cells producing interferon-γ or IL-17A, a subset of inflammatory T cells with gut-homing properties, which are increased in active CD [41,42]. Since TGF-β1 has pro-fibrogenic effects and CD natural history can be marked by the development of fibrostrictures [43], all the patients receiving Mongersen were monitored for the development of such a complication. No patient developed strictures or obstructive symptoms during the study nor had a significant increase in the serum levels of

fibrogenic markers [44]. A subsequent phase II, multicenter, double-blind placebo-controlled study was conducted to assess the efficacy of Mongersen. One hundred sixty-six, steroid-dependent or resistant, CD patients were enrolled to receive placebo or Mongersen at 10, 40, or 160 mg/d for 2 weeks. Patients receiving the highest doses of the drug had significantly higher rates of remission than those treated with placebo. All patients receiving the drug showed a greater rate of clinical response in comparison with those receiving placebo. No drug-related adverse event was seen [45]. Responders to Mongersen had reduced serum levels of CCL20, a chemokine over-produced in epithelium of CD patients that contributes to recruit immune cells to inflamed gut [46]. This finding is in line with the demonstration that CCL20 production is induced in intestinal epithelial cells by TNF-α through a mechanism which is negatively regulated by TGF-β1 [46].

Conclusion

The data described in this article highlight the inflammatory role of Smad7 in the gut and support the notion that knockdown of Smad7 with Mongersen can be a promising therapeutic approach for CD patients. However, further studies on larger populations are needed to confirm the clinical benefit seen in phase 1 and phase 2 studies, to examine whether Mongersen promotes also endoscopic/histological remission/improvement and prolongs the remission phases and to identify which subsets of patients could benefit from such treatments. Since phase 1 and phase 2 studies were performed in patients with lesions confined to terminal ileum and/or right colon, it would be relevant to assess whether Mongersen is also useful to control the active phases of the disease in patients with distal colitis. Similarly, further work is needed to evaluate whether Mongersen is effective in UC as this disease is also characterized by elevated mucosal production of Smad7. So far, short-term treatment with Mongersen has been associated with no adverse event perhaps due to the fact that the drug is poorly absorbed following oral administration. However, the safety profile of this compound must be confirmed by long-term studies. In this context, it would be relevant to confirm the preliminary evidence suggesting that inhibition of Smad7 expression by Mongersen is not followed by formation of fibro-strictures.

Studies in other systems have recently shown that expression of Smad7 in antigen presenting cells, such as dendritic cells and macrophages, can facilitate the progression of destructive inflammatory responses and induction of Smad7 seems to rely on bacterial-derived stimuli [47,48]. Therefore, experimental work is still needed to better characterize which cell types over-express Smad7 in the different phases of the natural history of CD and UC and which factors account for such an induction.

Acknowledgments and Declaration of Personal Interests:

The authors have received research funding for the work on Smad7 from Fondazione U. Di Mario (Rome, Italy) and Broad Medical Research Foundation (IBD-0301R). GM has filed a patent related to the treatment of inflammatory bowel diseases with Smad7 antisense oligonucleotides, while the remaining authors have no conflict of interest.

References

1. Xavier RJ, Podolsky DK (2007) Unravelling the pathogenesis of inflammatory bowel disease. Nature 448: 427-434.
2. Bouma G, Strober W (2003) The immunological and genetic basis of inflammatory bowel disease. Nat Rev Immunol 3: 521-533.
3. MacDonald TT, Vossenkaemper A, Fantini M, Monteleone G (2012) Reprogramming the immune system in IBD. Dig Dis 30: 392-395.
4. Strober W, Fuss IJ (2011) Proinflammatory cytokines in the pathogenesis of inflammatory bowel diseases. Gastroenterology 140: 1756-1767.
5. Neurath MF (2014) Cytokines in inflammatory bowel disease. Nat Rev Immunol 14: 329-342.
6. Hanauer SB, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, et al. (2002) Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. Lancet 359: 1541-1549.
7. Colombel JF, Sandborn WJ, Rutgeerts P, Enns R, Hanauer SB, et al. (2007) Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. Gastroenterology 132: 52-65.
8. Sandborn WJ, Feagan BG, Marano C, Zhang H, Strauss R, et al. (2014) Subcutaneous golimumab induces clinical response and remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology 146: 85-95.
9. Van Dullemen HM, van Deventer SJ, Hommes DW, Bijl HA, Jansen J, et al. (1995) Treatment of Crohn's disease with anti-tumor necrosis factor chimeric monoclonal antibody (cA2). Gastroenterology 109: 129-135.
10. Feagan BG, Rutgeerts P, Sands BE, Hanauer S, Colombel JF, et al. (2013) Vedolizumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med 369: 699-710.
11. Sandborn WJ, Feagan BG, Rutgeerts P, Hanauer S, Colombel JF, et al. (2013) Vedolizumab as induction and maintenance therapy for Crohn's disease. N Engl J Med 369: 711-721.
12. Letterio JJ, Roberts AB (1998) Regulation of immune responses by TGF-beta. Annu Rev Immunol 16: 137-161.
13. Shull MM, Ormsby I, Kier AB, Pawlowski S, Diebold RJ, et al. (1992) Targeted disruption of the mouse transforming growth factor-beta 1 gene results in multifocal inflammatory disease. Nature 359: 693-699.
14. Neurath MF, Fuss I, Kelsall BL, Presky DH, Waegell W, et al. (1996) Experimental granulomatous colitis in mice is abrogated by induction of TGF-beta-mediated oral tolerance. J Exp Med 183: 2605-2616.
15. Gorelik L, Flavell RA (2000) Abrogation of TGFbeta signaling in T cells leads to spontaneous T cell differentiation and autoimmune disease. Immunity 12: 171-181.
16. Monteleone G, Kumberova A, Croft NM, McKenzie C, Steer HW, et al. (2001) Blocking Smad7 restores TGF-beta1 signaling in chronic inflammatory bowel disease. J Clin Invest 108: 601-609.
17. Shi Y, Massagué J (2003) Mechanisms of TGF-beta signaling from cell membrane to the nucleus. Cell 113: 685-700.
18. Heldin CH, Miyazono K, ten Dijke P (1997) TGF-beta signalling from cell membrane to nucleus through SMAD proteins. Nature 390: 465-471.
19. Abdollah S, Macías-Silva M, Tsukazaki T, Hayashi H, Attisano L, et al. (1997) TbetaRI phosphorylation of Smad2 on Ser465 and Ser467 is required for Smad2-Smad4 complex formation and signaling. J Biol Chem 272: 27678-27685.
20. Derynck R, Zhang Y, Feng XH (1998) Smads: transcriptional activators of TGF-beta responses. Cell 95: 737-740.
21. Di Sabatino A, Pickard KM, Rampton D, Kruidenier L, Rovedatti L, et al. (2008) Blockade of transforming growth factor beta upregulates T-box transcription factor T-bet, and increases T helper cell type 1 cytokine and matrix metalloproteinase-3 production in the human gut mucosa. Gut 57: 605-612.
22. Monteleone G, Mann J, Monteleone I, Vavassori P, Bremner R, et al. (2004) A failure of transforming growth factor-beta1 negative regulation maintains sustained NF-kappaB activation in gut inflammation. J Biol Chem 279: 3925-3932.
23. Yang X, Letterio JJ, Lechleider RJ, Chen L, Hayman R, et al. (1999) Targeted disruption of SMAD3 results in impaired mucosal immunity and diminished T cell responsiveness to TGF-beta. EMBO J 18: 1280-1291.

24. Babyatsky MW, Rossiter G, Podolsky DK (1996) Expression of transforming growth factors alpha and beta in colonic mucosa in inflammatory bowel disease. Gastroenterology 110: 975-984.
25. Monteleone G, Del Vecchio Blanco G, Monteleone I, Fina D, Caruso R, et al. (2005) Post-transcriptional regulation of Smad7 in the gut of patients with inflammatory bowel disease. Gastroenterology 129: 1420-1429.
26. Kume S, Haneda M, Kanasaki K, Sugimoto T, Araki S, et al. (2007) SIRT1 inhibits transforming growth factor beta-induced apoptosis in glomerular mesangial cells via Smad7 deacetylation. J Biol Chem 282: 151-158.
27. Zhang J, Lee SM, Shannon S, Gao B, Chen W, et al. (2009) The type III histone deacetylase Sirt1 is essential for maintenance of T cell tolerance in mice. J Clin Invest 119: 3048-3058.
28. Caruso R, Marafini I, Franze E, Stolfi C, Zorzi F, et al. (2014) Defective expression of SIRT1 contributes to sustain inflammatory pathways in the gut. Mucosal Immunol 7: 1467-1479.
29. Kit Leng Lui S, Iyengar PV, Jaynes P, Isa Z, Pang B, et al. (2017) USP26 regulates TGF-beta signaling by deubiquitinating and stabilizing SMAD7. EMBO Rep 18: 797-808.
30. Malonis RJ, Fu W, Jelcic MJ, Thompson M, Canter BS, et al. (2017) RNF11 sequestration of the E3 ligase SMURF2 on membranes antagonizes SMAD7 down-regulation of transforming growth factor beta signaling. J Biol Chem 292: 7435-7451.
31. Chen G, Cao S, Liu F, Liu Y (2015) miR-195 plays a role in steroid resistance of ulcerative colitis by targeting Smad7. Biochem J 471: 357-367.
32. Boirivant M, Fuss IJ, Chu A, Strober W (1998) Oxazolone colitis: A murine model of T helper cell type 2 colitis treatable with antibodies to interleukin 4. J Exp Med 188: 1929-1939.
33. Neurath MF, Fuss I, Kelsall BL, Stüber E, Strober W (1995) Antibodies to interleukin 12 abrogate established experimental colitis in mice. J Exp Med 182: 1281-1290.
34. Boirivant M, Pallone F, Di Giacinto C, Fina D, Monteleone I, et al. (2006) Inhibition of Smad7 with a specific antisense oligonucleotide facilitates TGF-beta1-mediated suppression of colitis. Gastroenterology 131: 1786-1798.
35. Rizzo A, Waldner MJ, Stolfi C, Sarra M, Fina D, et al. (2011) Smad7 expression in T cells prevents colitis-associated cancer. Cancer Res 71: 7423-7432.
36. Fantini MC, Rizzo A, Fina D, Caruso R, Sarra M, et al. (2009) Smad7 controls resistance of colitogenic T cells to regulatory T cell-mediated suppression. Gastroenterology 136: 1308-1316.
37. Monteleone I, Rizzo A, Sarra M, Sica G, Sileri P, et al. (2011) Aryl hydrocarbon receptor-induced signals up-regulate IL-22 production and inhibit inflammation in the gastrointestinal tract. Gastroenterology 141: 237-248.
38. Monteleone I, Marafini I, Zorzi F, Di Fusco D, Dinallo V, et al. (2016) Smad7 Knockdown Restores Aryl Hydrocarbon Receptor-mediated Protective Signals in the Gut. J Crohns Colitis 10: 670-677.
39. Fina D, Franze E, Rovedatti L, Corazza GR, Biancone L, et al. (2011) Interleukin-25 production is differently regulated by TNF-alpha and TGF-beta1 in the human gut. Mucosal Immunol 4: 239-244.
40. Monteleone I, Federici M, Sarra M, Franze E, Casagrande V, et al. (2012) Tissue inhibitor of metalloproteinase-3 regulates inflammation in human and mouse intestine. Gastroenterology 143: 1277-1287.
41. Monteleone G, Fantini MC, Onali S, Zorzi F, Sancesario G, et al. (2012) Phase I clinical trial of Smad7 knockdown using antisense oligonucleotide in patients with active Crohn's disease. Mol Ther 20: 870-876.
42. Saruta M, Yu QT, Avanesyan A, Fleshner PR, Targan SR, et al. (2007) Phenotype and effector function of CC chemokine receptor 9-expressing lymphocytes in small intestinal Crohn's disease. J Immunol 178: 3293-3300.
43. Burke JP, Mulsow JJ, O'Keane C, Docherty NG, Watson RW, et al. (2007) Fibrogenesis in Crohn's disease. Am J Gastroenterol 102: 439-448.
44. Zorzi F, Calabrese E, Monteleone I, Fantini M, Onali S, et al. (2012) A phase 1 open-label trial shows that smad7 antisense oligonucleotide (GED0301) does not increase the risk of small bowel strictures in Crohn's disease. Aliment Pharmacol Ther 36: 850-857.
45. Monteleone G, Neurath MF, Ardizzone S, Di Sabatino A, Fantini MC, et al. (2015) Mongersen, an oral SMAD7 antisense oligonucleotide, and Crohn's disease. N Engl J Med 372: 1104-1113.
46. Marafini I, Monteleone I, Dinallo V, Di Fusco D, De Simone V, et al. (2016) CCL20 Is Negatively Regulated by TGF-beta1 in Intestinal Epithelial Cells and Reduced in Crohn's Disease Patients With a Successful Response to Mongersen, a Smad7 Antisense Oligonucleotide. J Crohns Colitis 11: 603-609.
47. Lukas D, Yogev N, Kel JM, Regen T, Mufazalov IA, et al. (2017) TGF-beta inhibitor Smad7 regulates dendritic cell-induced autoimmunity. Proc Natl Acad Sci U S A 114: E1480-E1489.
48. MohanKumar K, Namachivayam K, Chapalamadugu KC, Garzon SA, Premkumar MH, et al. (2016) Smad7 interrupts TGF-beta signaling in intestinal macrophages and promotes inflammatory activation of these cells during necrotizing enterocolitis. Pediatr Res 79: 951-961.