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Experimental animal models in Inflammatory Bowel Disease

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Inflammatory Bowel Diseases (IBD) including Ulcerative Colitis (UC) and Crohn's Disease (CD) are chronic and progressive inflammatory disorders characterized by transmural tissue damage that promotes an excessive wound-healing response. The intestinal alterations elicit to a distorsion of the tissue architecture that may lead to fibrosis, strictures, stenosis and obstructions [1,2]. The medical treatment currently used in IBD (salicylates, antibiotics, steroids, immunosuppressive drugs, biological therapies) may relieve the inflammatory symptoms but are no effective to improve fibrosis and associate complications that still remain the major causes of surgical interventation [3,4].

It is well established that physiological fibrogenesis may result in tissue repair or fibrosis depending on the balance between Extracellular Matrix (ECM) synthesis and degradation. During IBD, intestinal fibrosis results from an abnormal response to a chronic local injury and is characterized by abnormal production and deposition of ECM proteins produced by intestinal mesenchymal cells [smooth muscle cells, fibroblasts and myofibroblasts including Subepithelial Myofibroblasts (SEMs) and Intestitial Cells of Cajals (ICCs)] [5-7]. The activation of ECM-producing cells is due to involvement of cytokines, chemokines, growth factors, Peroxisome Proliferator-Activated Receptors (PPARs), mammalian Target of Rapamycin (mTOR) [8,9],matrix-degrading enzymes [Matrix Metalloproteinases (MMPs)] and their specific inhibitors tissue (TIMPs) and ECM remodeling is orchestrated by the TGFβ/Smad pathway, the major driving force of fibrosis [10]. This pathway has been also identified as one of the stronger stimuli of Epithelial-Mesenchymal-Transition (EMT) a complex process in which epithelial cells can differentiate in mesenchymal cells such as myofibroblasts that leave the epithelial layer (mainly due to the E-caderin loss) and accumulate in the interstitium where they begin the ECM synthesis [10].

Upon ligation and activation of TGFβ with its receptors, the phosphorylated Smad2 and Smad3 form a complex with the common mediator Smad4 that can translocate into the nucleus where it regulates specific TGFβ target genes that are directly or indirectly involved in fibrogenesis [11].

Experimental animal models are useful to study *in vivo* both morphological alterations of colonic wall and the intracellular transduction pathways involved in intestinal inflammation and fibrosis that can occur during IBD [12].

These models are also crucial to test several antifibrotic drugs (chemical and biological) able to inhibit, mitigate or even reverse the fibrotic process [13]. Among the several experimental models that mimic IBD, TGFβ knockout mouse is characterized by the loss a critical regulator of immune function which leads to an excessive inflammatory response with massive infiltration of leukocytes in several organs that rapidly results in severe injuries and death by the fouth week of animal life. The targeted disruptions of Smad2 and Smad4 are also lethal while Smad3 knockout mice can survive to adulthood and since these mice are resistant to intestinal fibrosis, this model appeared to be useful to unravel the molecular mechanisms that occur during IBD [14].

We have demonstrated that 2,4,5 Trinitrobenzene Sulphonic Acid (TNBS) induced in Smad3 Wild Type (WT) a chronic colitis characterized by shorter, dilated and oedematous colonic wall while Smad3 knockout mice showed a normal aspect of the colon. In Smad3 WT mice, histology and immunohistochemistry also showed an abnormal accumulation of collagen in the submucosal and serosal layers altering the architecture of colonic wall. On the contrary, in Smad3 Null mice the colonic structure was preserved demonstrating that TGFβ/Smad signaling plays an important role in intestinal fibrosis [15]. We also used Dextran Sulfate Sodium (DSS) that is able to induce both acute and chronic colitis with morphological aspects and clinical symptoms similar to that of human IBD [16,17].

Although TGFβ/Smad signaling represents the "core pathway" of fibrosis process, we demonstrated that there is an extensive crosstalk between TGFβ/Smad and αvβ6 integrin, PPARγ and mTOR that is related to fibrosis development and appear to interact directly with TGFβ/Smad.

Integrins regulate cell-cell and cell and ECM interactions influencing growth, differentiation and development wound healing and fibrosis. In normal conditions αvβ6 integrin is not expressed while it is upregulated and colocalized together with TGFβ in many fibrosis diseases of various organs including intestine during IBD [18]. Interaction between αvβ6 integrin with several legands especially Latency Associated Peptide (LAP) activates TGFβ and promotes fibrosis; on the contrary, inhibitors of αvβ6 integrin significantly reduced tissue levels of profibrogenic transcripts including α-SMA, TGFβ, and Connective Tissue Growth Factor (CTGF).

mTOR is also involved in cell proliferation and survival, metabolic regulation and actin cytosckeleton organization and mTOR is activated by hormons, growth factors, amino acid levels and alteration in cellular energy status [19]. mTOR inhibitors exert direct antifibrotic activities by reducing fibroblast and myofibroblast number and also by down regulating the production of TGFβ and the synthesis of type I and III collagen [20-22].There are evidences that αvβ6 integrin may act by stimulating TGFβ canonical (mediated by Smads) and non canonical (mediated by mTOR) intracellular pathways.

Increased expression of αvβ6 integrin, TGFβ, Smad3 and mTOR is associated to the development of intestinal fibrosis. Nevertheless, blockade of the TGFβ signaling either at extracellular (ligand receptors) or intracellular level (signal transduction pathways), that may represent a potential molecular strategy to prevent and/or treat fibrosis but it can be problematic for survival and vital cellular homeostasis since TGFβ is also implicated in several crucial cellular functions.

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PPARs are nuclear receptors which regulate gene transcription by binding to retinoid X-receptors (RXR) and PPARγ isoform is present in colorectal mucosa and is involved in intestinal fibrosis. In particular, PPARγ is strongly related to the TGFβ/Smad pathway as PPARγ with its specific legand interferes with the Smad3 signaling by directly antagonizing Smad3 or downregulating (CTGF) expression that promotes the TGFβ synthesis of collagen [23]. Upregulation of PPARγ appears to be protective towards fibrosis since PPARγ agonists inhibit the fibroblast migration and proliferation as well as the trans differentation of epithelial and mesenchimal cells in activated myofibroblasts another one of the key points in fibrosis development [24]. It has recently reported that a new PPARγ modulator, GED-0507-34 levo (GED) ameliorated intestinal fibrosis in DSS induced chronic colitis in mice and inhibited *in vitro* and *in vivo* the TGFβ induced differentiation both of intestinal fibroblasts and epithelial cells into activated ECM-producing myofibroblasts [10,24].

All these important observations demonstrate that the medical treatment of IBD has to act none only in controlling intestinal inflammation but also in preventing or eliminating the fibrotic process that is the main responsible for associated local and extraintestinal manifestations (skin, joins, biliary tract and eye).

Further researches are needed to understand if these colitis models can be useful to study extra intestinal IBD impairment that involve almost any organs and request a multidisciplinary approach in the management of the affected patients.

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