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A morphological and immunohistochemical study of human intestinal fibrogenesis during Crohn's disease

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Background. Several enteropathies are characterized by an intestinal fibrosis that may lead to stenosis and obstruction (1). The most frequent and severe intestinal fibrosis occurs in Crohn's disease (CD) that is related to the abnormal accumulation of extracellular matrix (ECM) proteins. In experimental model TGF-β1/Smad3 signalling plays a major role in tissue fibrogenesis as a potent stimulus of ECM accumulation (2).

Aim. To evaluate the potential role of the TGF-β1/Smads pathway in the pathogenesis of intestinal fibrosis in patients affected by CD.

Methods.Human samples from terminal ileum were processed for histological (H&E, Masson, Pas) morphometric and immunohistochemical (IHC) analyses. For IHC studies TGF-β1, CTGF, collagen types I-III, Smad3, Smad7, PDGF, C-kit, α-SMA, GFAP and a neuronal cocktail (S100, antineurofilament, NSE) antibodies were used. Smooth muscle cells (SMC) were cultured (3) for morphofunctional and cell cycle analysis.

Results. Histological and morphometrical evaluation of stenotic fragments revealed a significantly high degree of intestinal fibrosis with an increase in mucosa, submucosa and muscle layer thickness. Transmural inflammation was also present in stenotic lesions compared to normal tracts. SMC isolated from inflamed fragments presented a 18.7% ±5.9% lenght shortening and a 44.5%±2.9% inhibition in contractile response to acetylcholine. Furthermore, under inflammatory burst a shift from the G0/G1 to the S cell cycle phase was observed. IHC analysis showed an increase in TGF-β1,CTGF, collagen I-III, Smad3, PDGF, C-kit and α-SMA staining in stenotic lesions compared to pre-post stenotic intestinal tracts, whereas Smad7 was positive only in pre-post stenotic samples. IHC evaluation of GFAP and neuronal cocktail showed a reduction of immunoreactivity in stenotic lesions.

Conclusions. The data demonstrate that the TGF-β1/Smads pathway may play a central role in the development and differentiation of mesenchymal cells and in sustaining fibrosis of intestinal tissues in CD. The results confirm those obtained previously in our experimental mice model.

1) Burke JP et al. Am J Gastro, 2007
2) Latella G. et al. Eur J Clin Invest, 2008
3) Tattoli I et al. Dig Liv Dis, 2004.

Keywords: Crohn's disease, intestinal fibrosis, TGFbeta1, Smads