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Interaction between Sphingosine Kinase/Sphingosine 1 Phosphate and Transforming Growth Factor-β/Smads pathways in experimental intestinal fibrosis: an in vivo immunohistochemical study

Roberta Sferra[1], Simona Pompili[1], Giovanni Latella[2], Giulia Sabetta[1], Amarildo Smakaj[1], Gloria Stati[1] and Antonella Vetuschi[1]

[1] Università degli Studi, Dipartimento di Scienze Cliniche Applicate e Biotecnologiche, L'Aquila, Italia
[2] Università degli Studi, Dipartimento Medicina Clinica, Sanità Pubblica, Scienze della Vita e dell'Ambiente, L'Aquila, Italia

Intestinal fibrosis is characterized by an abnormal deposition of Extracellular Matrix (ECM) produced by activated myofibroblats. Despite many biological mediators are implicated in ECM proteins accumulation, a pivotal role is certainly played by TGF-β that acts mainly through Smad proteins (1). Recently, it has been thought that different molecules could be involved in TGFβ-dependent fibrotic signaling (2) and for this reason, aim of this study was to evaluate the involvement of Sphingosine kinase/Sphingosine 1 phosphate in an experimental mice model of intestinal fibrosis induced by oral administration of DSS. 20 mice were divided into 2 groups: control (H2O) n=5 and DSS n=15. Histological and immunohistochemical evaluation using TGF-β, p-Smad3, Collagen I-III, α-SMA, SPHK1, RhoA, PI3K, Akt, p-Akt and p-mTOR were performed. In DSS mice histological analysis assessed in H&E and Masson's Trichrome showed marked signs of inflammation and fibrosis. Immunopositivity for canonical TGF-β/Smads pathway molecules TGF-β, p-Smad3, Collagen I-III and α-SMA resulted mild expressed in control mice, while there was a significant increase in DSS group. Immunohistochemical analysis for non-Smad TGF-β pathway proteins SPHK1, RhoA, PI3K, Akt, p-Akt and p-mTOR showed a high positivity in DSS mice compared to untreated group. These preliminary results demonstrated the hypothesis that the development of intestinal fibrosis could be influenced not only by TGFβ/Smad pathway but also by a crosstalk between TGFβ/SPHK1/S1P signaling that could represent a new crucial driver in colonic fibrosis. Development of molecules able to control the synthesis of S1P, through the regulation of its kinase SPHK1, could provide a novel attractive therapeutic target to control fibrogenic process.

References

[1] Vetuschi A, Latella G et al. (2014) Ital J Anat Embryol. 119(3):286-303.
[2] Lawrence J and Nho R. (2018) Int J Mol Sci.8;19(3). pii: E778.

Key words
Fibrosis, TGF-β, S1P.