

the hypothesis of a possible interaction between the above-mentioned molecules in the development of colorectal fibrosis in mice. Development of molecules to regulate the synthesis of S1P and to selectively block or stimulate different S1P receptor subtypes could be an attractive target for the development of new pharmacological treatments of intestinal fibrosis.²⁹

References

1. Fiocchi C, Lund PK. Themes in fibrosis and gastrointestinal inflammation. *Am J Physiol Gastrointest Liver Physiol* 2011;300:G677-83.
2. Rieder F, Fiocchi C. Mechanisms of tissue remodeling in inflammatory bowel disease. *Dig Dis* 2013 31:186-93.
3. Lawrance IC, Rogler G, Bamias G, Breynaert C, Florholmen J, Pellino G, et al. Cellular and molecular mediators of intestinal fibrosis. *J Crohns Colitis* 2017;11:1491-503.
4. Di Gregorio J, Sferra R, Specia S, Vetusch A, Dubuquoy C, Desreumaux P, et al. Role of glycogen synthase kinase-3 β and PPAR- γ on epithelial-to-mesenchymal transition in DSS-induced colorectal fibrosis. *PLoS One* 2017;12:e0171093.
5. Latella G, Vetusch A, Sferra R, Specia S, Gaudio E. Localization of α v β 6 integrin-TGF- β 1/Smad3, mTOR and PPAR γ in experimental colorectal fibrosis. *Eur J Histochem* 2013;57:e40.
6. Sferra R, Vetusch A, Pompili S, Gaudio E, Specia S, Latella G. Expression of pro-fibrotic and anti-fibrotic molecules in dimethylnitrosamine-induced hepatic fibrosis. *Pathol Res* 2016;213:58-65.
7. Bhowmick NA, Ghiassi M, Bakin AV, Aakre M, Lundquist CA, Engleman AV, et al. Transforming growth factor-beta1 mediates epithelial to mesenchymal transdifferentiation through a RhoA-dependent mechanism. *Mol Biol Cell* 2001;12:27-36.
8. Patel S, Takagi KI, Suzuki J, Imaizumi A, Kimura T, Mason RM, et al. RhoGTPase activation is a key step in renal epithelial mesenchymal transdifferentiation. *J Am Soc Nephrol* 2005; 16:1997-84.
9. Lawrence J, Nho R. The role of the mammalian target of rapamycin (mTOR) in pulmonary fibrosis. *Int J Mol Sci* 2018;19:778.
10. Ammit AJ, Hastie AT, Edsall LC, Hoffman RK, Amrani Y, Krymskaya VP, et al. Sphingosine 1-phosphate modulates human airway smooth muscle cell functions that promote inflammation and airway remodeling in asthma. *FASEB J* 2001;15:1212-4.
11. Hla T. Signaling and biological actions of sphingosine 1-phosphate. *Pharmacol Res* 2003;47:401-7.
12. Alemany R, van Koppen CY, Dannenberg K, Ter Braak M, Meyer Zu, Heringdorf D. Regulation and functional roles of sphingosine kinases. *Naunyn Schmiedebergs Arch Pharmacol* 2007;374:413-28.
13. Liu W, Lan T, Xie X, Huang K, Peng J, Huang J, et al. S1P2 receptor mediates sphingosine-1-phosphate-induced fibronectin expression via MAPK signaling pathway in mesangial cells under high glucose condition. *Exp Cell Res* 2012;318:936-43.
14. Yang AH, Ishii I, Chun J. In vivo roles of lysophospholipid receptors revealed by gene targeting studies in mice. *Biochim Biophys Acta* 2002;1582:177-203.
15. Schwalm S, Timcheva TM, Filipecki I, Ebadi M, Hofmann LP, Zambmeister-Wittke U, et al. Sphingosine Kinase 2 deficiency increases proliferation and migration of renal mouse mesangial cells and fibroblasts. *Biol Chem* 2017;396:813-24.
16. Giacomini MN, Travis MA, Kudo M, Sheppard D. Epithelial cells utilize cortical actin/myosin to activate latent TGF- β through integrin α (v) β (6)-dependent physical force. *Exp Cell Res* 2012;318:716-22.
17. Kono Y, Nishiuma T, Nishimura Y, Kotani Y, Okada T, Nakamura S, et al. Sphingosine kinase 1 regulates differentiation of human and mouse lung fibroblasts mediated by TGF-beta1. *Am J Respir Cell Mol Biol* 2007;37:395-404.
18. Milara J, Navarro R, Juan G, Peiró T, Serrano A, Ramón M, et al. Sphingosine-1-phosphate is increased in patients with idiopathic pulmonary fibrosis and mediates epithelial to mesenchymal transition. *Thorax* 2016;67: 147-56.
19. Gellings LN, Swaney JS, Moreno KM, Sabbadini RA. Sphingosine-1-phosphate and sphingosine kinase are critical for transforming growth factor-beta-stimulated collagen production by cardiac fibroblasts. *Cardiovasc Res* 2009;82:303-12.
20. Pchejetski D, Foussal C, Alfarano C, Lairez O, Calise D, Guilbeau-Frugier C, et al. Apelin prevents cardiac fibroblast activation and collagen production through inhibition of sphingosine kinase 1. *Eur Heart J* 2011;33:2360-9.
21. Lan T, Shen X, Liu P, Liu W, Xu S, Xie X, et al. Berberine ameliorates renal injury in diabetic C57BL/6 mice: Involvement of suppression of SphK-S1P signaling pathway. *Arch Biochem Biophys* 2010;502:112-20.
22. Ikeda H, Yatomi Y, Yanase M, Satoh H, Maekawa H, Ogata I, et al. Biological activities of novel lipid mediator sphingosine 1-phosphate in rat hepatic stellate cells. *Am J Physiol Gastrointest Liver Physiol* 2000;279:G304-10.
23. Latella G, Vetusch A, Sferra R, Zambmeister-Wittke G, D'Angelo A, Catitti V. Smad3 loss confers resistance to the development of trinitrobenzene sulfonic acid-induced colorectal fibrosis. *Eur J Clin Invest* 2009;39:145-56.
24. Dusaban SS, Chun J, Rosen H, Purcell NH, Brown JH. Sphingosine 1-phosphate receptor 3 and RhoA signaling mediate inflammatory gene expression in astrocytes. *J Neuroinflammation* 2017;14:111.
25. Tauseef M, Kini V, Knezevic N, Brannan M, Ramchandaran R, Fyrst H, et al. Activation of sphingosine kinase-1 reverses the increase in lung vascular permeability through sphingosine-1-phosphate receptor signaling in endothelial cells. *Circ Res* 2008;103: 1164-72.
26. Liu RH, Ning B, Ma Xiao-EN, Gong Wei-Ming, Jia TH. Regulatory roles of microRNA-21 in fibrosis through interaction with diverse pathways. *Mol Med Rep* 2016;13:2359-66.
27. Kattla JJ, Carew RM, Heljic M, Godson C, Brazil DP. Protein kinase B/Akt activity is involved in renal TGF- β 1-driven. *Physiol Renal Physiol* 2008; 295:F215-2.
28. Wynn TA. Cellular and molecular mechanisms of fibrosis. *J Pathol* 2008; 214:199-210.
29. Rieder F, Latella G, Magro F, Yuksel ES, Higgins PD, Di Sabatino A, et al. European Crohn's and Colitis Organisation Topical review on prediction, diagnosis and management of fibrotic Crohn's Disease. *J Crohns Colitis* 2016;10:873-85.