

Supplemental Table – Pathways of interest associated with previous evidences in systemic sclerosis (SSc)

Reactome ID	Pathway	Effect	Reference
R-HSA-114608	Platelet degranulation	↑	1
R-HSA-76005	Response to elevated platelet cytosolic Ca ²⁺	↑	2
R-HSA-1592389	Activation of metalloproteinases	↑	3, 4
R-HSA-3371453	Regulation of the heat shock factor 1 (HSF1)-mediated heat shock response	↑	5
R-HSA-171007 R-HSA-198753	p38-mitogen-activated protein kinase (p38MAPK) events extracellular signal-regulated kinases (ERK)/MAPK targets	↑	6, 7
R-HSA-140877 R-HSA-140875 R-HSA-140837	Formation of Fibrin Clot (Clotting Cascade) Common Pathway of Fibrin Clot Formation Intrinsic Pathway of Fibrin Clot Formation	↑	8
R-HSA-400685 R-HSA-373755 R-HSA-416700	Sema4D in semaphorin signaling Semaphorin interactions Other semaphorin interactions	↑	9
R-HSA-5654738 R-HSA-5655253 R-HSA-190236	Signaling by fibroblast growth factor (FGFR)-2 Signaling by FGFR2 in disease Signaling by FGFR	↓	10-12
R-HSA-389356 R-HSA-38935	CD28 co-stimulation CD28 dependent PI3K/Akt signaling	↓	13, 14

Validated reactome pathways whose deregulation may be linked with previously existing evidences or pathogenetic mechanisms observed in SSc. Effect, effect size indicating an increased (upward pointing arrow) or a decreased (downward pointing arrow) expression in SSc compared to controls.

Table references

1. Maugeri N, Franchini S, Campana L, *et al.* Circulating platelets as a source of the damage-associated molecular pattern HMGB1 in patients with systemic sclerosis. *Autoimmunity*

- 2012;**45**:584–7. doi:10.3109/08916934.2012.719946
2. Postlethwaite AE, Chiang TM. Platelet contributions to the pathogenesis of systemic sclerosis. *Curr Opin Rheumatol* 2007;**19**:574–9. doi:10.1097/BOR.0b013e3282eeb3a4
 3. Kim W-U, Min S-Y, Cho M-L, *et al.* Elevated matrix metalloproteinase-9 in patients with systemic sclerosis. *Arthritis Res Ther* 2005;**7**:R71-9. doi:10.1186/ar1454
 4. Asano Y, Ihn H, Jinnin M, *et al.* Serum levels of matrix metalloproteinase-13 in patients with eosinophilic fasciitis. *J Dermatol.* 2014;**41**:746–748. doi:10.1111/1346-8138.12563
 5. Chu H, Jiang S, Liu Q, *et al.* Sirtuin1 Protects against Systemic Sclerosis-related Pulmonary Fibrosis by Decreasing Proinflammatory and Profibrotic Processes. *Am J Respir Cell Mol Biol* 2018;**58**:28–39. doi:10.1165/rcmb.2016-0192OC
 6. Sato M, Shegogue D, Gore EA, *et al.* Role of p38 MAPK in transforming growth factor beta stimulation of collagen production by scleroderma and healthy dermal fibroblasts. *J Invest Dermatol* 2002;**118**:704–11. doi:10.1046/j.1523-1747.2002.01719.x
 7. Matsushita T, Date M, Kano M, *et al.* Blockade of p38 Mitogen-Activated Protein Kinase Inhibits Murine Sclerodermatous Chronic Graft-versus-Host Disease. *Am J Pathol.* 2017;**187**(4):841–850. doi:10.1016/j.ajpath.2016.12.016
 8. Ludwicka-Bradley A, Silver RM, Bogatkevich GS. Coagulation and autoimmunity in scleroderma interstitial lung disease. *Semin Arthritis Rheum* 2011;**41**:212–22. doi:10.1016/j.semarthrit.2010.10.002
 9. Romano E, Rosa I, Fioretto BS, *et al.* A new avenue in the pathogenesis of systemic sclerosis: the molecular interface between the endothelial and the nervous systems. *Clin Exp Rheumatol*; **37 Suppl 1**:133–40. <http://www.ncbi.nlm.nih.gov/pubmed/31025932>
 10. Seghezzi G, Patel S, Ren CJ, *et al.* Fibroblast growth factor-2 (FGF-2) induces vascular endothelial growth factor (VEGF) expression in the endothelial cells of forming capillaries: an autocrine mechanism contributing to angiogenesis. *J Cell Biol* 1998;**141**:1659–73. doi:10.1083/jcb.141.7.1659

11. Matucci-Cerinic M, Manetti M, Bruni C, *et al.* The ‘myth’ of loss of angiogenesis in systemic sclerosis: a pivotal early pathogenetic process or just a late unavoidable event? *Arthritis Res Ther* 2017;**19**:162. doi:10.1186/s13075-017-1370-5
12. Correia ACP, Moonen J-RAJ, Brinker MGL, *et al.* FGF2 inhibits endothelial-mesenchymal transition through microRNA-20a-mediated repression of canonical TGF- β signaling. *J Cell Sci* 2016;**129**:569–79. doi:10.1242/jcs.176248
13. Akieda Y, Wakamatsu E, Nakamura T, *et al.* Defects in regulatory T cells due to CD28 deficiency induce a qualitative change of allogeneic immune response in chronic graft-versus-host disease. *J Immunol* 2015;**194**:4162–74. doi:10.4049/jimmunol.1402591
14. Li G, Larregina AT, Domsic RT, *et al.* Skin-Resident Effector Memory CD8+CD28- T Cells Exhibit a Profibrotic Phenotype in Patients with Systemic Sclerosis. *J Invest Dermatol* 2017;**137**:1042–50. doi:10.1016/j.jid.2016.11.037