A74 EPITHELIAL CELLS UNDERGOING EPITHELIAL MESENCHYMAL TRANSITION (EMT) IN SYSTEMIC SCLEROSIS LACK CAVEOLIN-1 AND MODULATE WNT SIGNALING IN THE DERMIS BY SECRETING SFRP4

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10.1136/ard.2010.149104.18

Background Systemic sclerosis is a chronic fibrotic disease highly heterogeneous in clinical outcome, involving autoimmune activation, fibroproliferative vasculopathy and tissue

fibrosis of skin and multiple internal organs. The mechanisms linking immune activation and tissue fibrosis are still not fully characterised. A widely accepted model of immune-mediated skin fibrosis is chronic sclerodermoid graft versus host disease (Scl-GVHD), a form of chronic GVHD in patients receiving allogenic bone marrow transplant. Histopathologic studies of cGVHD skin biopsies confirmed the presence of both fibroproliferative vasculopathy and tissue fibrosis in Scl-GVHD.

Objective To identify which genes are differentially expressed in SSc skin biopsies are similarly expressed in the transcriptome of Scl-GVHD skin biopsies and therefore of potential importance in linking immune activation and skin fibrosis.

Methods Metanalysis of microarray data published in the literature identified a set of 80 genes whose differential expression is highly reproduced in our SSc skin biopsies signature. The mRNA expression level of these genes was then analysed in eight Scl-GVHD and three cGVHD skin biopsies, and compared to normal skin and their differential expression in SSc. Genes found to be significantly differentially expressed ($p<0.05$) in univariate analysis were tested in multivariate analysis. To validate our mRNA findings we preformed immunofluorescence studies on skin biopsies.

Results 46 genes were differentially expressed in cGVHD biopsies and 34 remained unique of SSc. 78.3% of the differentially expressed genes had a similar pattern of regulation in SSc. 25% were similarly expressed in both cGVHD variants, whereas 16.6% were specific of Scl-GVHD. Remarkably, this analysis identified several chemokines (CCL5, CXCL9-10-11) specifically involved in the fibrotic versus non-fibrotic response in GVHD and also increased expression of SFRP4, a potent angiogenesis inhibitor, in SSc and Scl-GVHD. Using confocal microscopy we identified as the source of increased SFRP4, cells in the basal layer of the epidermis which lost E-cadherin expression, co-expressed vimentin and specifically lacked Caveolin-1 expression.

Conclusion Approximately 50% of SSc signature genes presented an altered expression in cGVHD. The further characterisation of the cells that play a role both in the fibrotic process, by undergoing EMT, and in the vasculopathy, by inhibiting angiogenesis through SFRP4 inhibition of WNT signalling, may pave the way to understand the link between these two processes in SSc.