CCL24 -A novel target playing a significant role in Systemic Sclerosis (SSc)

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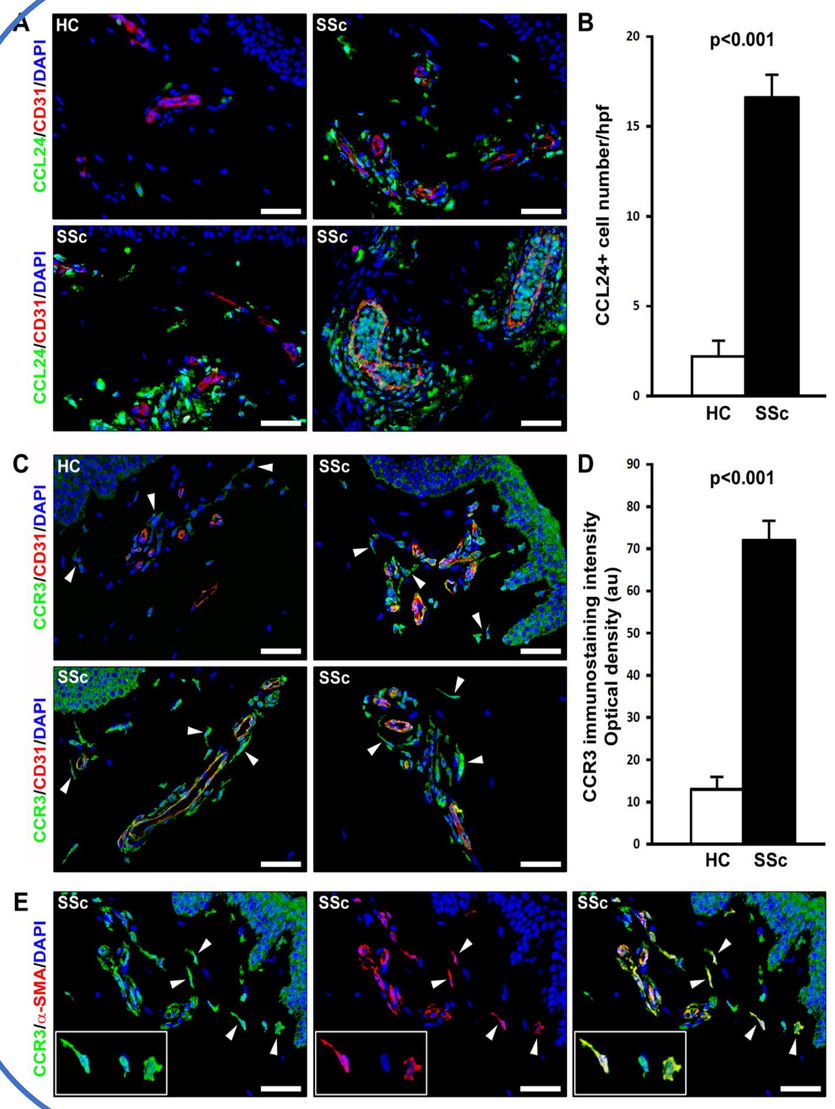
Background: CCL24 (C-C chemokine ligand 24) is a chemokine that promotes pro-inflammatory and pro-fibrotic activities through its receptor, CCR3. Previous studies showed that both CCL24 and CCR3 are involved in lung and skin inflammation and fibrosis.

Aim: to assess the expression of CCL24 in SSc and to evaluate the pathogenic implications of the CCL24/CCR3 axis in these patients.

Materials and methods: Serum samples from healthy volunteers, diffuse and limited SSc were tested for CCL24 levels using a commercial Elisa kit. Skin forearm biopsies from early diffuse cutaneous SSc patients were co-stained for CCL24/CD31 and CCR3/αSMA. Comparison between WT and CCL24 knockout mice was done using the Bleomycin (BLM)-induced dermal fibrosis murine model. Dermal thickness, immune cells infiltration to BAL as well as αSMA expression levels were quantified.



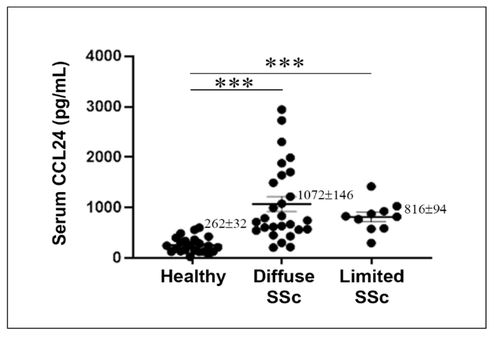
Expression of CCL24 and CCR3 in SSc forearm skin biopsies:

Immunostaining of diffuse SSc skin biopsies, showed a significant upregulation of CCL24 (8-fold increase in number of cells, p<0.001) and CCR3 (6-fold increase in immunostaining intensity, p<0.001) compared to control skin.

CCL24-positive mononuclear cells were captured during extravasation through the vessel wall, as well as in the dermis and the perivascular areas. Significant CCR3 expression was detected on dermal spindle-shaped fibroblasts, microvascular endothelial cells and epidermal keratinocytes in the SSc biopsies. Double immunostaining with α-smooth muscle actin (α-SMA) confirmed CCR3 expression on profibrotic myofibroblasts.

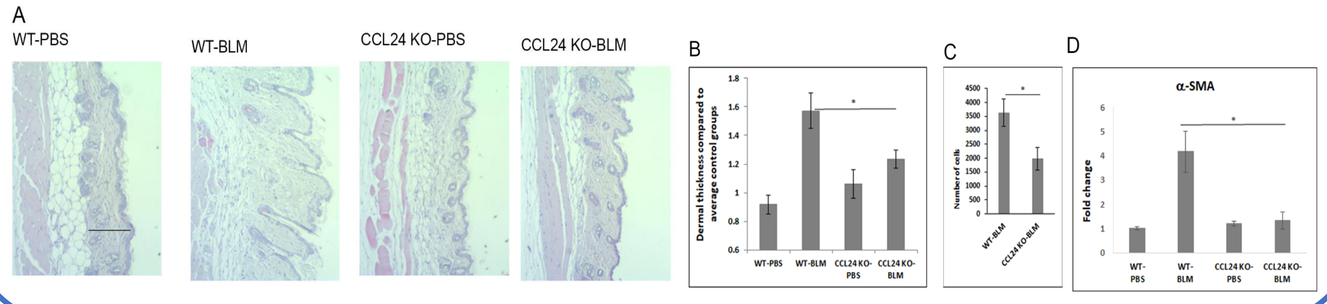
CCL24 circulating levels:

Serum samples of SSc patients (n=37) and healthy controls (n=23) were tested for CCL24 levels. We found four-fold elevation of CCL24 in diffuse SSc and slightly lower, three-fold elevation of CCL24 in limited SSc compared to healthy controls (1072±146, 816±94 and 262±32 in diffuse SSc, limited SSc and control, p<0.0001, U-test).



Dermal BLM fibrotic model in CCL24 knockout mice:

CCL24 knockout mice induced with bleomycin model showed reduced fibrotic and inflammatory response as compared to WT mice. The dermal thickness decreased significantly as well as the infiltration of immune cells into the BAL fluid. This was further supported by a substantial reduction of α-SMA expression in the skin lesions of CCL24 KO mice compared to WT mice.



Conclusion:

CCL24/CCR3 axis was found to be significantly involved in the pathogenesis of SSc which supports testing CCL24 as a potential therapeutic target for SSc.

ChemomAb LTD. Is developing a novel blocking monoclonal antibody that targets CCL24 and is planned to be tested in SSc patients in the near future.

Reference:

Mor A, Segal Salto M, Katav A, et al. Ann Rheum Dis [Epub ahead of print] doi:10.1136/annrheumdis-2019-215119

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