A98 MODULATING TLR RESPONSES IN SYSTEMIC SCLEROSIS VIA HEME OXYGENASE-1

L van Bon, A Scharstuhl, B Pennings, R J F Huijbens, M H Wenink, K C M Santegoets, M Vonk, W van den Berg, F Wagener, T R D J Radstake *Radboud University Medical Centre, Nijmegen, The Netherlands*

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Background Systemic sclerosis (SSc) is an autoimmune disease characterised by fibrosis of the skin and the internal organs. The aetiology is still unknown, but prominent features are vascular injury and chronic inflammation resulting in fibrosis. Accumulating evidence suggests a role for Toll-like receptor (TLR)-mediated activation of dendritic cells (DC). Heme oxygenase-1 (HO-1) is a known cytoprotective enzyme induced in response to stress factors like oxygen radicals or inflammation, both of which are abundantly present in SSc. The authors therefore investigated HO-1 protein and HO activity and found that the altered TLR response in SSc can be normalised via HO-1.

Methods 20 patients with SSc were included. Patients were stratified as having diffuse SSc (dSSc) or limited SSc (lSSc) according to the extent of skin involvement. To asses HO-1 activity, bilirubin, a product of HO-1 activity, was measured in serum using the HPLC technique. After isolation from 50 ml of venous blood, monocytes were cultured to generate monocyte derived DCs (moDC). HO-1 levels were assessed with western blot and qPCR before and after induction with the HO-1 inducer cobalt protoporphyrin (CoPP). MoDCs were stimulated with several TLR ligands on day 6 with or without prestimulation with CoPP for 24 h. Levels of interleukin (IL)10, tumour necrosis factor α (TNF α, IL12p70 and IL6 were measured in the supernatants using the Luminex Bead Array.

Results Serum bilirubin levels and HO-1 western blot analysis suggested decreased HO-1 activity in SSc patients compared with healthy controls. Using the known HO-1 inducer CoPP, the levels of the enzyme could be increased. Interestingly, via the induction of HO-1, the TLR responses could be adjusted, especially the IL12 production in response to TLR4 and TLR8 ligands. These effects were more pronounced in dSSc but significantly different in both lSSc and dSSc.

Conclusion The decreased HO-1 activity in SSc patients is intriguing due to all the natural inducers which are present.

The authors show that induction of this enzyme could benefit SSc patients by ameliorating inflammation and therefore reducing the progression of the disease. Induction of HO-1 activity with a pharmacological inducer could therefore offer a new therapeutic target in SSc.