11 T CELL DERIVED IL-6 AND IL-13 DRIVE FIBROBLAST FIBROSIS: IMPLICATIONS FOR SYSTEMIC SCLEROSIS

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Systemic Sclerosis (SS) is an autoimmune disease of unknown aetiology that is characterised by inflammation, vasculopathy and excessive extracellular matrix deposition. The extracellular matrix deposition is primarily in the skin and organs. The immune abnormalities in the disease include T and B cell activation and a host of proinflammatory cytokines that may mediate the fibrotic response characteristic of the disease. Tumour necrosis factor α (TNF α) is a pro-inflammatory cytokine that may be involved in disease pathogenesis and has been demonstrated to be upregulated in SS. TNF α signals through two receptors causing a variety of downstream effects that depends on cell type and context. The aim was to investigate the role of TNF α in T cells and the role of cytokines in scleroderma

and matrix deposition. The authors used T cells from scleroderma and controls and analysed these for the TNF α receptor using flow Cytometry to examine expression, both in skin and PBMCs. Specific mutant ligands that are recombinant for TNF α receptor subtypes or soluble TNF was used to examine downstream effects. T cell conditioned medium was added to normal dermal fibroblasts and markers of fibrosis were examined including collagen type I by real time PCR (RT-PCR). T cell-derived cytokines were measured using ELISA and subsequent cytokines neutralised with antibodies or isotype controls and collagen I measured.

Results T cells were present in high numbers in the skin of patients. Also TNF α R II was elevated in T cells from both the skin of affected patients and also T cells from peripheral blood compared to healthy controls. Mutant ligands to receptor subtypes leads to elevated interleukin-6 and also IL-13 expression from healthy and scleroderma donors. However scleroderma donors have a much higher constitutive level of both cytokines without the addition of TNF α ligands suggesting activation of T cells. Conditioned medium leads to upregulated α -smooth muscle actin content in dermal fibroblast and also upregulated collagen I expression by 20-fold after incubation with TNFR subtypes both R1 and R2. A differential response was seen between 'activated' and non 'activated' T cells in collagen expression. Suppression of T cell derived cytokines IL-6 and IL-13 in combination by neutralising antibodies leads to an attenuated increase in collagen I mRNA expression as compared to the relevant matched isotype controls, indicating a pivotal role of these cytokines in fibrogenesis. There is also a differential response between patients and controls.

Conclusion Scleroderma T cells expressed elevated TNFR 2 expression, this maybe an activation marker in scleroderma. T cells are activated 'in vivo' and secrete the cytokines IL-6 and IL-13. IL-6 and IL-13 work in a synergistic fashion leading to enhanced extracellular matrix deposition.