Role of connective tissue growth factor in scleroderma

Objective of the project:

We have shown through previous RSA funding that a key growth factor protein called connective tissue growth factor (CTGF) is over expressed in Scleroderma. The aim of this study is to investigate:

- What controls CTGF expression in fibroblasts?
- How CTGF causes scarring and fibrosis?
- Does CTGF cause other cells to become fibroblasts and contribute to scarring?
- Can we use small molecule pharmacological inhibitors to block CTGF action?

Our long term aim is to identify new targets for the design of a new generation of drugs that are effective at preventing further scarring and fibrosis in patients with scleroderma.

Lay Project: Second Year Report:

Scleroderma is a complex disorder of uncertain aetiology characterised by progressive vascular and interstitial fibrosis. Our previous work has shown that the soluble growth factor connective tissue growth factor (CTGF/CCN2) is an important component of the fibrotic process being over-produced especially in the skin and lung. We have recently shown that we can inhibit CTGF expression by fibroblasts by blocking the angiotensin pathway (ANGII; angiotensin receptor II), or by activating the PPAR-g and PTEN signalling pathway using receptor antagonists and agonists. We have also carried out experiments using small molecule pharmacological inhibitors specific for CTGF. These inhibitors not only suppressed CTGF production, but they also modulated the expression of other scarring proteins including fibronectin, alpha smooth muscle actin and a group of novel proteins including Snail, Sox9, and E-cadherin. These proteins are thought to play an important role in the transition of epithelial cells into fibroblasts.

These studies suggest that CTGF, in addition to a role on fibroblasts, may also control the function of epithelial cells, although the mechanism of regulation is unclear. Fibroblast-epithelial cell interactions are believed to be important, not only during normal tissue repair but during fibrosis, as aberrant cellular cues may signal the switching from an epithelial to fibroblast cell type. We have found that the epidermis of scleroderma skin exhibits abnormalities, taking on an activated phenotype reminiscent of that observed during the normal wound healing response. Common features of the activated scleroderma phenotype include elevation in the level of tissue reactive oxygen species. These chemicals are known to activate cell signalling pathways such as the ERK map kinase pathway. Interestingly, this pathway is also activated by CTGF. Recently, we have also demonstrated the potential mechanism by which we can bring about a reduction in CTGF and ERK signalling as well as other fibrotic markers, in scleroderma skin fibroblasts, by specific inhibitor drugs which reduce reactive oxygen species (1).

Our data show that CTGF may be an important regulator of novel proteins which mediate the transition of an epithelial to fibroblast cell type. Increasing the number of pro-fibrotic, collagen producing cells may be an important aspect of the scarring and fibrotic process, while targeting parts of this mechanism with pharmacological inhibitors may be a potential therapeutic treatment.

Publications:

1) Dooley A, Shi-wen X, Aden N, Tranah T, Desai N, Denton CP, Abraham DJ, Bruckdorfer R. Rheumatology (Oxford). 2010 Nov;49(11):2024-36.

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