Progressive pulmonary sarcoidosis--a fibroproliferative process potentially triggered by EGR-1 and IL-6

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BACKGROUND AND AIM OF THE WORK: Sarcoidosis is a chronic granulomatous disorder of unknown etiology. In most patients the disease is self-limited, although for reasons unclear, others progress or die from progressive organ fibrosis. Growth factors have been implicated in the pathogenesis of other fibrotic lung conditions. We have, therefore, examined the relationship between growth factor expression and disease phenotype in sarcoidosis. METHODS: Adopting a target gene approach utilizing gene expression arrays, growth factor gene expression profile was analyzed in the peripheral blood of 12 patients and 12 healthy controls. Expression, functional activity and the effect of oligonucleotide antisense treatment on selected proteins differentially expressed in progressive sarcoidosis were then tested in vitro on primary human lung fibroblasts. RESULTS: Genes regulating angiogenesis were preferentially upregulated in the self-limited form of disease, while early growth response-1 and interleukin-6 were predominantly activated in progressive sarcoidosis. Increased expression of early growth response-1 in sarcoid lung was confirmed by immunohistochemistry. Stimulated human fibroblasts also rapidly expressed interleukin-6 and early growth response-1 and these proteins were found to mediate serum-induced fibroblast proliferation as proliferation could be significantly abrogated with interleukin-6 and early growth response-1 antisense oligonucleotides. CONCLUSION: We conclude that progressive pulmonary sarcoidosis is characterized by a fibroproliferative dysregulation potentially triggered by early growth response-1 and interleukin-6. Our disease model underlines the inability of steroids to prevent ongoing fibroproliferation in the lung.