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STAT3 in tissue fibrosis: Is there a role in the lung?

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ABSTRACT

Fibrosis is defined as an excessive deposition of connective tissue components that results in the destruction of normal tissue architecture and compromises organ function. When fibrosis occurs in the major organs such as the lung, for example in idiopathic pulmonary fibrosis, it inevitably leads to organ failure and premature death of the afflicted individual. Current evidence suggests that fibrosis initially develops along the same pathway as normal wound healing, although there is chronic progression of the disease without resolution, suggesting the control of intracellular processes that occur during wound healing is disturbed. It follows then that determining where this control is lost is key to preventing and treating this condition. The IL-6 cytokine family is a group of pleiotropic cytokines produced by a variety of cells in response to inflammatory stimuli. These cytokines are grouped together on the basis of overlapping functions, and common usage of gp130 as part of their multimeric receptor complexes. Activation of these receptor complexes results in the recruitment and phosphorylation of the latent transcription factor STAT-3 which induces a gene program involved in cell differentiation and proliferation. STAT3 also induces expression of a number of inhibitors including SOCS-3. In this manuscript we review the available literature on the IL-6/gp-130 family of cytokines and their role in regulating fibrosis. Despite a large number of studies in mouse models as well as human cells in vitro, the role of these cytokines or STAT3 activated by other cytokines in the development of fibrosis remains unclear.

Following injury, tissues undergo a series of overlapping events, requiring extensive communication between cells and the extracellular matrix (ECM), in order to heal. A breakdown in this communication leads to an imbalance in the stop and go signals necessary to regulate repair. This imbalance favours continued and exaggerated wound healing processes leading to excessive deposition of matrix components that result in destruction of normal tissue architecture and a compromise in tissue function. Which processes in particular are most important for the induction and progression of fibrosis are presently unclear but areas under intense investigation include: regulation, synthesis and processing of collagen and other ECM molecules, recruitment and activation of inflammatory cells, altered levels of cytokines, growth factors, chemokines and proteases, dysregulation of mediator receptors/signaling, fibroblast proliferation, recruitment and differentiation, epithelial to mesenchymal transition of epithelial cells and stem cell recruitment. The focus of this review is on the STAT3 signaling pathway in fibrosis.

1. STAT3

STAT3 is a latent cytoplasmic transcription factor that plays critical roles in several biological pathways crucial to cell function, including proliferation, migration, survival, and differentiation [1].

STAT3 exists in two isoforms generated by alternative splicing of a common gene; the full length STAT3α (86–92 kDa) and the truncated STAT3β (79–82 kDa) which lacks the C-terminal activation domain and is generally thought to act as a dominant negative factor [2–4]. STAT3β lacks the serine phosphorylation site within the carboxy-terminal transcriptional activation domain, but is phosphorylated at Tyr^{705} [2]. STAT3β is not required for viability, whereas STAT3α-deficient mice die at birth. For the most part, fibroblasts from STAT3$\alpha^{-/-}$ mice but not STAT3$\beta^{-/-}$ mice act like cells from mice lacking the whole gene [5]. Interestingly, in human inflammatory cells and leukemic blast cells, STAT3α can undergo

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limited proteolysis to generate STAT3β as well as a STAT3γ isoform (72 kDa). However, it appears that STAT3α, but not STAT3γ, regulates neutrophil functions such as survival [4].

2. Activation of STAT3

The predominant receptors coupled to STAT3 signaling are the gp130/interleukin-6 (IL-6) receptor family, although Receptor Tyrosine Kinase (RTK) and IL-10R signaling may also induce STAT3 activation.

2.1. IL-6 family of cytokines

The IL-6 family of cytokines is a group of closely related pleiotropic cytokines produced by a variety of cells in response to inflammatory stimuli. They are related in structure and function and include IL-6, IL-11, leukemia inhibitory factor (LIF), Oncostatin M (OSM), ciliary neurotrophic factor (CNTF), cardiotrophin 1 (CT-1), cardiotrophin like cytokine (CLC), IL-27, IL-31 and neuropoietin. The actions of these cytokines are mediated through specific cell surface receptors, which consist of a unique α chain and the shared signal transducing subunit, gp130 [6].

2.2. gp130

Identifying the signaling pathways of gp130 is essential in understanding the various effects of the IL-6 cytokine family on different cell types. gp130 has no intrinsic tyrosine kinase activities and so requires recruitment and activation of specific kinases and docking proteins. Following binding of the cytokine to its cognate receptor (α-subunit) and subsequent dimerization with gp130, cytoplasmic Janus kinases (JAKs) are recruited and phosphorylate gp130 [7,8]. The subsequent activation of intracellular signaling is dependent on specific phosphotyrosine residues on gp130. For example, the protein phosphatase SHP2 binds to membrane proximal tyrosine residues (Y^{759} in humans, Y^{757} in mice) and results in activation of the ERK–MAPK pathway. In contrast, members of the STAT transcription factors dock to several membrane distal phosphotyrosine residues (Fig. 1). Once phosphorylated, STAT proteins translocate to the nucleus and activate target genes [9].

Following gp130 activation, ERK and STAT3 are rapidly phosphorylated, and under normal circumstances, gradually switched off. A number of in vitro studies have suggested that gp130-mediated activation of the SHP2–ERK pathway results in the generation of proliferative signals. In contrast, STAT3 activation appears to be critical for regulation of cellular differentiation, apoptosis and gene

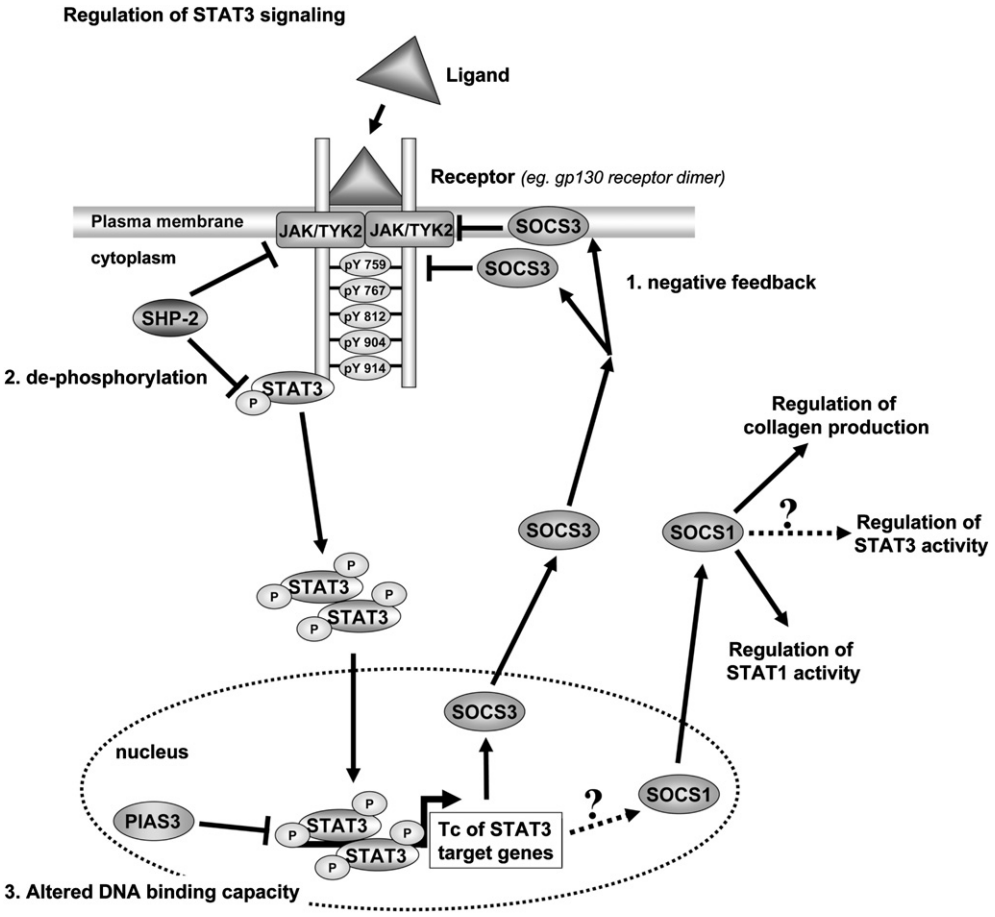

Fig. 1. Regulation of STAT3 signaling. STAT3 signaling is initiated following receptor activation. In the case of the gp130 receptor, activation of downstream signaling requires the docking of STAT molecules to distal phosphotyrosine residues. Once phosphorylated, STAT proteins translocate to the nucleus where they regulate transcription of target gene. STAT signaling is regulated as follows; 1. Negative Feedback: SOCS molecules are induced in an STAT-dependent manner and regulate downstream signaling via two mechanisms, through blocking JAK protein activity preventing STAT phosphorylation or by targeting these proteins for ubiquitnation and proteosomal degradation. While SOCS3 is the known regulator of STAT3 activity, SOCS1, which is known to target STAT1, has also recently been implicated in STAT3 regulation. 2. De-Phosphorylation: The protein-tyrosine phosphatase, SHP2, regulates STAT signaling by de-phosphorylating both JAKs and STATs. 3. Altered DNA-binding capacity: Association of PIAS proteins with activated STATs within the nucleus leads to a loss of STAT DNA-binding activity.