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Commentary

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Transforming growth factor-β (TGF-β): master regulator of inflammation and fibrosis

Key words: TGF-β; Asthma; Fibrosis; COPD; IPF; CLOCK

Transforming growth factor-β (TGF-β) is one of three related gene products TGF-β 1-3 that activate the activin-like kinase receptor, ALK5, to elicit a bewildering array of (patho)physiological effects. The label, "master regulator" is well justified, as TGF-β is a morphogen, inflammogen, immune- and inflammatory- modulator, mediator of tissue remodelling and wound healing, a fibrogen, and yet more functions are anticipated as the intense investigation of this intriguing and tightly-regulated protein continues. Previous commentaries on TGF-β have highlighted contextualisation as a means to make sense of its myriad actions, some of which are even mutually antagonistic. This contextualisation includes, the target tissue and cell types, soluble and mechanical microenvironments, concurrent exposure to other growth factors, inflammogens and modulators, and bi-directional circadian influences [1], the latter likely having a relationship relevant to the effectiveness of the CLOCK-modulating casein kinase 1δ/ε inhibitor PF670462, in fibrogenesis [2].

The contribution of TGF-β to chronic respiratory disease is extensively evidenced [3]. In cystic fibrosis, TGF-β gene polymorphism, which results in increased production, is recognized as a modifier of variable disease phenotypes. Increased TGF-β levels are associated with an accelerated decline in lung function in cystic fibrosis [4]. In addition, TGF-β suppresses expression and function of the chloride transporter, CFTR, which may be a mechanism for the lung pathology associated with TGF-β polymorphisms. More recently, microRNA-145 was shown to mediate TGF-β-induced suppression of CFTR[5]. Similarly, in chronic obstructive lung disease (COPD) and asthma, polymorphisms associated with TGF-β signalling are linked to disease severity, suggesting a role in the pathogenesis of obstructive lung diseases. This data is being complemented by compelling evidence of roles in acute exacerbations driven by allergen, viral infection or poor air quality.

We have highlighted the importance of cellular mechanics in the actions of endogenous mediators and in the evaluation of drug candidates. TGF-β induced cellular stiffening is accompanied by elaboration of extracellular matrix (ECM) components that are remodelled into a dense stiff ECM. Application of tension to this ECM promotes mobilisation of TGF-β from the latent peptide that is sandwiched between cellular integrins and extra-cellular collagen /other ECM components. This setting provides the potential for a positive feedback loop that would render all tissue fibrotic, except for some handbrakes opposing the process. One important modulator is prostaglandin E_2 (PGE_2), the product of cyclo-oxygenase (COX) and PGE_2 synthase (Figure 1). PGE_2 activates the signal transducer cyclic AMP which activates protein kinase A that has well-established anti-fibrotic effects, including the capacity to relax (soften) mesenchymal cells. PGE_2 levels and activity are greatly diminished in lungs of patients with idiopathic pulmonary fibrosis [6] suggesting this handbrake is released. As biomechanical stiffening greatly diminishes PGE_2 production, early fibrotic tissue stiffening may release a negative feedback, concurrently with activation of the positive feedback loop involving TGF-β activation, to create a level of mutual re-inforcement of the original fibrogenic signal.

The signal transduction entrained by TGF-β is dependent on ALK5 kinase activity which phosphorylates Smad2/3 promoting association with Smad4, and nuclear translocation where specific response element sequences in the promoter regions of target genes are activated by this heteromeric protein complex, resulting in extensive changes in gene expression. This so-called canonical signalling pathway is complemented by an extensive series of signals commencing with ALK5 activation that are responsible for many of the effects of TGF-β, manifesting through chains of signals transmitted by the mitogen-activated protein kinase family (MAPK) and many other intracellular cellular kinases. Some of the TGF-β activities, including epithelial-mesenchymal transition, also depend on interactions between these distinct signalling cascades. These pathways have been the subject of many reviews, but their diagrammatic representation almost always overstates the simplicity and perhaps the

broader importance of the highlighted signals. The heterogeneity of tissue and cell specific actions of TGF-β are likely dictated by the abundance and importance of proteins subserving a particular signalling chain within the target cell phenotype.

Our focus on TGF-β signalling has been sharpened by observations of interactions with glucocorticoid signalling pathways. TGF-β causes a profound inhibition of the anti-inflammatory effects of glucocorticoids in the epithelium. The underlying signalling pathways proved elusive, with canonical Smad signalling and well-known mitogen-activated protein kinase cascades being excluded. This challenge to elucidate the responsible pathways provided encouragement that success would reveal a set of signals that have a high level of specificity, and when blocked, could leave intact important physiological impacts of TGF-β. Global inhibition of TGF-β could be expected to have many beneficial effects on chronic respiratory diseases by reducing remodelling, restoring glucocorticoid sensitivity, and opposing the suppressant effects of TGF-β on antiviral interferon production by epithelium. However, the detrimental effects of systemic TGF-β inhibition include impaired induction of Treg lymphocytes, diminished immune surveillance and cardiac valve dysfunction [3]. In contrast, blockade of downstream signalling that is specific to pathways influencing glucocorticoid activity may yield a more acceptable safety/efficacy profile for chronic inhibition in respiratory disease. As the casein kinase 1δ/ε inhibitor, PF670462, also shows glucocorticoid-enhancing activity and overcomes TGF-β signalling of resistance, targetting this pathway offers a potentially safe TGF-β modulator with activities that include suppression of fibrogenesis [2, 3] and allergic inflammation [7].

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FIGURE LEGEND

Figure 1 Stiffening in response to repeated cycles of injury and repair is able to mobilise latent TGF-β from the extracellular matrix, causing further stiffening in a positive feedback loop that is further amplified by stiffening repressing the enzymes for prostaglandin E_2 (PGE_2) synthesis and its receptors. As PGE_2 is normally able to soften/relax myofibroblasts, this repression results in yet further stiffening.