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ANGIOGENESIS

TGFβ makes a new friend

Our understanding of angiogenesis and vasculogenesis has mushroomed in the last two decades, yielding molecular data that have allowed the development of clinically useful therapeutic agents. Despite these successes, a complete appreciation of how individual angiogenic pathways interact and cooperate remains an important goal. Redondo and colleagues have made some headway towards realizing this goal by identifying a novel link between two important effectors of tumour angiogenesis: transforming growth factor β (TGFβ) and prostaglandin E2 (PGE_2).

The authors noticed that treatment of human vascular endothelial cells (ECs) with PGE_2 led to enhanced phosphorylation, nuclear localization and DNA binding of SMAD3 complexes, reminiscent of the cellular response observed when TGFβ binds to its type I receptor ALK5. To investigate this further, the authors incubated ECs with antibodies against TGFβ1, and found that this completely abolished the SMAD3 response following PGE_2 treatment. Moreover, *in vitro* Matrigel angiogenesis assays showed that treatment with PGE_2 resulted in an increase in the number of endothelial cords and that this could be blocked by ALK5 inhibition. Similarly, ALK5 was necessary for PGE_2-mediated, but not VEGF-mediated angiogenesis in a murine *in vivo* corneal model. Taken together, these data show that ALK5 is a crucial mediator of PGE_2-induced neovascularisation.

How does PGE_2 signal to TGFβ? Previous studies have implicated some metalloproteinases (MMPs) in the mobilization and activation of TGFβ and the authors found that treatment with the metalloproteinase inhibitor GM6001 attenuated SMAD3 nuclear translocation. They hypothesized that this was through inhibition of MT1-MMP, which is known to have a role in TGFβ activation. Accordingly, anti-MT1-MMP antibodies blocked PGE_2-mediated SMAD3 activation and immunofluorescence analysis showed that PGE_2 increases the accumulation of MT1-MMP at specific membrane sites rather than increasing its absolute levels. MT1-MMP clustering has been associated with an increase in its enzymatic activity and the formation of multi-protein complexes, and the authors suggest that interaction with proteins such as integrins may contribute to TGFβ activation at the EC membrane.

This study identifies novel cross-talk between PGE_2 and TGFβ, two mediators of tumour growth and angiogenesis. More importantly, this new pathway might, in the future, prove to be a useful target for anti-angiogenic therapeutics.

Safia Ali Danovi

ORIGINAL RESEARCH PAPER Alfranca, A. *et al.* PGE_2 induces angiogenesis via MT1-MMP-mediated activation of the TGFβ/ALK5 signalling pathway. *Blood* 9 Jun 2008 (doi 10.1182/blood-2007-09-112268)