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SHORT COMMENTARY

A Commentary on "TGF-β1-Induced Expression of the Anti-Apoptotic PAI-1 Protein Requires EGFR Signaling"

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Abstract: Plasminogen activator inhibitor-1 (PAI-1) has been found to affect a number of important cell processes and therefore abnormal expression of PAI-1 has been associated with a number of diseases and disorders. Understanding the transactivation of PAI-1 may result in identifying novel therapeutic targets.

Keywords: PAI-1, EGFR, TGF-β1, apoptosis, angiogenesis, tubulogenesis

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Plasminogen activator inhibitor-1 (PAI-1) is a 46-kDa single chain glycoprotein containing 402 amino acids. PAI-1 belongs to the serine protease inhibitor (SERPIN) family and is the primary physiologic inhibitor of the plasminogen activators (uPA and tPA). Through its inhibition of the plasminogen activators, PAI-1 can affect a number of cellular processes for example migration, adhesion, intracellular signalling, proliferation and apoptosis.[1] Abnormal expression of PAI-1 therefore is a significant causative factor in the progression of a number of diseases and disorders (for example arteriosclerosis, thrombosis, and fibrosis) as well as being a biomarker for poor prognosis for a number of conditions.[2,3] Therefore understanding the controls of PAI-1 transcription may result in a number of therapeutic options.

TGF-β1 signalling in endothelial cells utilizes the heteromeric receptor complex, which comprises of TGFβRII and the activin receptor like kinases (ALK1/ALK5). In endothelial cells TGF-β1 binding can bind to the ALK1 receptor resulting in the phosphorylation of the receptor Smads 1/5 which causes endothelial cell proliferation and migration. Whereas TGF-β1 binding to the ALK5 receptor complex results in the phosphorylation of the receptor Smads 2/3 which results in the inhibition of endothelial cell proliferation and migration. PAI-1 has been identified as an early TGF-β1 response gene and, has been shown to be an ALK-5 specific target.[4] TGF-β1 phosphorylates both Smad and non-Smad pathways in vascular, epithelial and endothelial cells and recent studies have shown that TGF-β1 causes the transactivation of EGFR in non-human cells.[5]

Higgins et al[6] in their recent study confirmed that in human cells TGF-β1 plays an important role in tubular differentiation as the use of a pan-neutralizing antibody prevented this differentiation. They further showed that pharmacological inhibitors targeted against EGFR and the MEK/ERK signalling pathway prevented the TGF-β initiated tubular differentiation. The use of pharmacological inhibitors however has been identified as being potentially non-specific as they can alter other signalling pathways.[7] Higgins et al[6] demonstrated that PAI-1 expression is elevated when T2 cells are cultured on Matrigel and they further showed that the blocking of PAI-1 (using a genetic approach) prevented the formation of a stable highly branched tubular network. This was also identified in human endothelial cells using blocking antibodies against PAI-1.

PAI-1 has been shown to affect cell survival being anti-apoptotic in several cell systems,[8–10] protecting endothelial cells from FasL mediated programmed cells death.[11] Higgins et al[6] demonstrated that T2 cells could be protected from serum deprivation by the addition of the stable 14-1b recombinant PAI-1 protein but not bovine serum albumin. This PAI-1 dependent pro-survival was associated with the phosphorylation of ERK as the pro-survival effect was prevented with the use of MEK inhibitors (PD98059 or U0126).

Pharmacological inhibitors (AG1478 and GM6001) reduced ERK phosphorylation and PAI-1 expression. However phosphorylation of Smad2 was retained, with these inhibitors, indicating that PAI-1 expression is through the MEK/ERK signalling pathway and not the canonical Smad pathway. Higgins et al showed through molecular methods that TGF-β mediated PAI-1 expression required EGFR. As with other studies[12,13] they showed that EGFR is phosphorylated in response to TGF-β at Y845 though interestingly they demonstrated that TGF-β phosphorylated reduced numbers of EGFR compared to EGF in HMEC-1 cultures. The reduced number of phosphorylated EGFR indicates that only a subset of EGF receptors may be phosophorylated by TGF-β and indicate an existence of some form of control on EGFR in response to TGF-β1. This potential control is further highlighted by the transient nature of EGFR phosphorylation compared to the phosphorylation of Smad2. Other studies have demonstrated that the Y845 is the src kinase target residue in human endothelial cells and therefore implicates a src member in EGFR transactivation. Recently this Src has been identified as $pp60^{c\text{-}src}$[12,14] as TGF-β failed to stimulate expression of PAI-1 in mouse embryonic fibroblasts deficient in src family kinases but PAI-1 could be restored when the cells where engineered to re-express $pp60^{c\text{-}src12}$ (Fig. 1).

Abnormal expression of PAI-1 has been associated with a number of conditions and the understanding of the specific controls of PAI-1 transcription is therefore important. The paper therefore by Higgins et al[6] confirms that human epithelial and endothelial cells require TGF-β to transactivate EGFR and the MEK-ERK signalling pathways for PAI-1 expression and these pathways may allow new novel therapeutic targets to be considered.

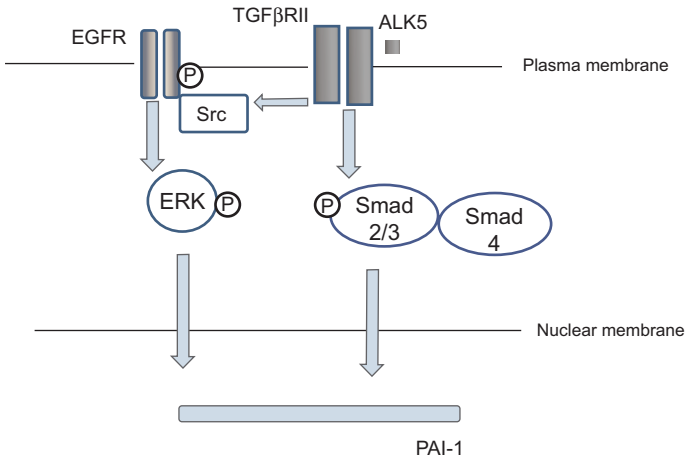

Figure 1. Diagrammatic representation of TGF-β1 induced PAI-1 expression.

Disclosures

The authors report no conflicts of interest.

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