CELL SIGNALLING

# TMEPAI keeps TGFβ under control

"TMEPAI…has an essential role in the negative regulation of TGFβ signalling."

Signalling by transforming growth factor-β (TGFβ) controls various cellular responses, including cell growth and differentiation, so it must be strictly regulated to maintain tissue homeostasis and prevent diseases. Watanabe *et al.* show that transmembrane prostate androgen-induced protein (TMEPAI; also known as PMEPA1), the physiological functions of which were not understood, has an essential role in the negative regulation of TGFβ signalling.

TGFβ binds to a receptor complex comprising a type I and a type II TGFβ Ser/Thr receptor kinase (TβRI and TβRII, respectively), which triggers TβRII to phosphorylate and activate TβRI. TβRI then phosphorylates the carboxyl terminus of the transcription factors SMAD2 and SMAD3, enabling them to form a complex with SMAD4. This Smad complex translocates to the nucleus to regulate the transcription of TGFβ-induced genes. The authors found that TMEPAI, the transcript of which is upregulated by TGFβ signalling, inhibits transcription from a TGFβ-driven reporter gene in mammalian cells. A decrease in the level of proteins (including plasminogen activator inhibitor 1 (PAI-I; also known as SERPINE1) and cyclin-dependent kinase inhibitor 1 (p21; also known as CDKN1A)) encoded by TGFβ-induced genes was also seen in TMEPAI overexpressing cells compared with control cells following TGFβ treatment. The ability of TMEPAI to inhibit TGFβ signalling is physiological, as TMEPAI overexpression inhibits mesoderm formation induced by the TGFβ ligand (activin) in *Xenopus laevis* embryos. Thus, TGFβ signalling induces transcription of the gene encoding TMEPAI, such that the protein can feedback and inhibit further TGFβ signalling.

How does TMEPAI inhibit TGFβ signalling? TβRI-mediated SMAD2 and SMAD3 C-terminal phosphorylation in response to TGFβ, which is crucial for TGFβ-induced transcription, is decreased in the presence of TMEPAI. Smad anchor for receptor activation (SARA) is an adaptor protein that presents inactive Smads to the TβRI–TβRII complex to facilitate Smad phosphorylation and transduce the TGFβ signal. Overexpression of SARA prevents TMEPAI-mediated repression of TGFβ-induced transcription in a dose dependent manner and restores TGFβ-mediated SMAD2 phosphorylation in the presence of TMEPAI. As the authors found that SMAD2 Trp368 is required for efficient SMAD2–TMEPAI binding, and this residue is also essential for SMAD2–SARA binding, TMEPAI might compete with SARA for SMAD2, preventing SARA from recruiting SMAD2 to TβRI for phosphorylation when the receptors are activated by TGFβ.

This study identifies a physiological role for the TGFβ target TMEPAI in the inhibition of TGFβ signalling, provides further mechanistic insight into how TβRI-mediated Smad phosphorylation is fine-tuned and adds to our understanding of how TGFβ can negatively regulate its own signalling.

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**ORIGINAL RESEARCH PAPER** Watanabe, Y. *et al.* TMEPAI, a transmembrane TGF-β-inducible protein, sequesters Smad proteins from active participation in TGF-β signaling. *Mol. Cell* **37**, 123–134 (2010)

**FURTHER READING** Schmierer, B. & Hill, C. S. TGFβ–SMAD signal transduction: molecular specificity and functional flexibility. *Nature Rev. Mol. Cell Biol.* **8**, 970–982 (2007)