TGF-β SIGNALING BY THE SMAD PATHWAY

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Zawel, L., Dai, J.L., Buckhaults, P., Zhou, S., Kinzler, K.W., Vogelstein, B. and Kern, S.E. Human Smad3 and Smad4 are sequence-specific transcription activators. ***Mol. Cell*** 1998, 4:611-617

Screening random oligonucleotides, the authors have defined a palindromic sequence (GTCTAGAC) recognized by both Smad3 and Smad4. Tandem repeats of this sequence conferred TGF-β responsiveness to a minimal promoter, which was abbrogated by targeted deletion of the cellular Smad4 gene. These data establish a role for Smad3 and Smad4 as potential sequence-specific transcription factors.

Kawabata, M., Inoue, H, Hanyu, A., Imamura, T, and Miyazono, K. Smad proteins exist as monomers *in vivo* and undergo homo- and hetero-oligomerization upon activation by serine/threonine kinase receptors. ***EMBO J.*** 1998, 17:4056-4065

The authors report that both Smad2 and Smad3 exist as monomers in the absence of TGF-β stimulation. Upon phosphorylation, they undergo a Smad4-independent homo-oligomerization. Smad3 homooligomers are capable of binding DNA. Both Smad2 and Smad3 can form hetero-oligomers with Smad4, the later binding DNA. These results indicate that the transitionof Smad proteins from monomers to oligomers is a critical event in TGF-β signal transduction.

Vindevoghel, L., Lechleider, R.J., Kon, A., de Caestecker, M.P., Uitto, J., Roberts, A.B., and Mauviel, A. Smad3/4 Dependent Transcriptional Activation of the Human Type VII Collagen Gene (COL7A1) Promoter by TGF-β. ***Proc. Natl. Acad. Sci. USA*** 1998, 95:14769-14774

In this study, detailed characterization of the first human Smad binding sequence (SBS), identified in the COL7A1 promoter (Vindevoghel et al., Smad-dependent transcriptional activation of human type VII collagen gene (COL7A1) promoter by transforming growth factor-beta. J. Biol. Chem. 1998, 273:13053-13057), is provided. Results indicate that Smad3 is present in the transcription complex induced rapidly by TGF-β. The COL7A1 SBS is bipartite and comprises a CAGA repeat, as well as an oligonucleotide strech matching the consensus Medea (Drosophila Smad4 homolog) binding site.

In addition, this study raises the possibility that Smad4, although essential for transactivation, may not be part of the transcription factor complex binding the COL7A1 SBS in response to TGF-β.

Dennler, S., Itoh, S., Vivien, D., ten Dijke, P., Huet, S., Gauthier, J.M. Direct binding of Smad3 and Smad4 to critical TGF beta-inducible elements in the promoter of human plasminogen activator inhibitor-type 1 gene. ***EMBO J*** 1998, 17:3091-3100

This report describes the identification of CAGA boxes within the PAI-1 promoter, binding both Smad3 and Smad4 in response to TGF-β. These CAGA boxes confer both TGF-β and activin, but not BMP, responsiveness to a heterologous promoter. Mutations within these CAGA boxes within the PAI-1 promoter abolished TGF-β responsiveness. The presence of these boxes in a variety of

genes suggests that it may be a widely used motif in TGF-β-regulated transcription.

Rodeck, U., Nishiyama, T., and Mauviel, A.: Independent Regulation of Growth and SMAD-Mediated Transcription by TGF-β in human melanoma cells: ***Cancer Res***. 1999, 59:547-550

In this report, it is demonstrated that The TGF-β/Smad signaling pathway is intact, and even activated in an autocrine way, in human melanoma cells. Further, it is established that no correlation exists in this cell type between Smad-mediated transcriptional activity and the inhibition of cell proliferation by TGF-β.

Mauviel, A. Récentes avancées dans la compréhension de la voie de signalisation du TGF-β par les Smad. ***Médecine/Science***, 1999, 15:535-537

Recent review in french language, summarizes the article above by Vindevoghel et al. and positions it in the context of the current literature on Smad-mediated regulation of gene expression.

Ulloa, L., Doody, J. and Massagué, J. Inhibition of transforming growth factor-beta/SMAD signalling by the interferon-gamma/STAT pathway. ***Nature*** 1999, 397:710-713

The authors uncover the molecular basis for some of the antagonism that TGF-β and IFN-γ exert on various cellular functions. Specifically, it is demonstrated that IFN-γ inhibits TGF-β-induced phosphorylation of Smad3 and its attendant events, such as nuclear translocation in association with Smad4, nuclear accumulation, and transactivation of TGF-β responsive genes. Furthermore, IFN-γ, through Jak1 and Stat1, induces Smad7 expression, an inhibitory Smad that antagonizes Smad3 action. Together, these results indicate transmodulation mechanisms between the Stat and Smad signaling pathways.

Yanagisawa, J., Yanagi, Y., Masuhiro, Y., Suzawa, M., Watanabe, M., Kashiwagi, K., Toriyabe, T., Kawabata, M., Miyazono, K. and Kato, S. Convergence of transforming growth factor-beta and vitamin D signaling pathways on SMAD transcriptional coactivators. ***Science*** 1999, 283:1317-1321

In this report, evidence is provided for a cross-talk between the vitamin D and TGF-β signaling pathways. Specifically, is is shown that Smad3 acts as a co-activator specific for the vitamin D receptor-mediated transactivation of vitamin D-responsive genes, by forming a complex with a member of the steroid receptor coactivator-1 protein family in the nucleus. Together with the article above, these data indicate the complexity of transcriptional regulation with cross-talks between highly specific signaling pathways such as that of the Smads, Stats, and vitamin D/vitamin D receptor.

Nakao, A., Fujii, M., Matsumura, R., Kumano, K., Saito, Y., Miyazono, K. and Iwamoto, I. Transient gene transfer and expression of Smad7 prevents bleomycin-induced lung fibrosis in mice. ***J. Clin. Invest***. 1999, 104:5-11

The authors demonstrate that adenovirus-mediated intratracheal delivery of Smad7, an antagonist of TGF-β signaling, reduces both type I procollagen mRNA levels and hydroxyproline contents, as well as fibrotic features induced by bleomycin in an experimental model of lung fibrosis. This is the first demonstration for the applicability of Smad targeting in the treatment of fibrosis.