TGF-β signaling in tumor suppression and cancer progression

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The label "p160ROCK" was incorrectly placed, owing to an error in the production of the electronic image. The label should have been placed underneath "RhoA", as in the figure below.

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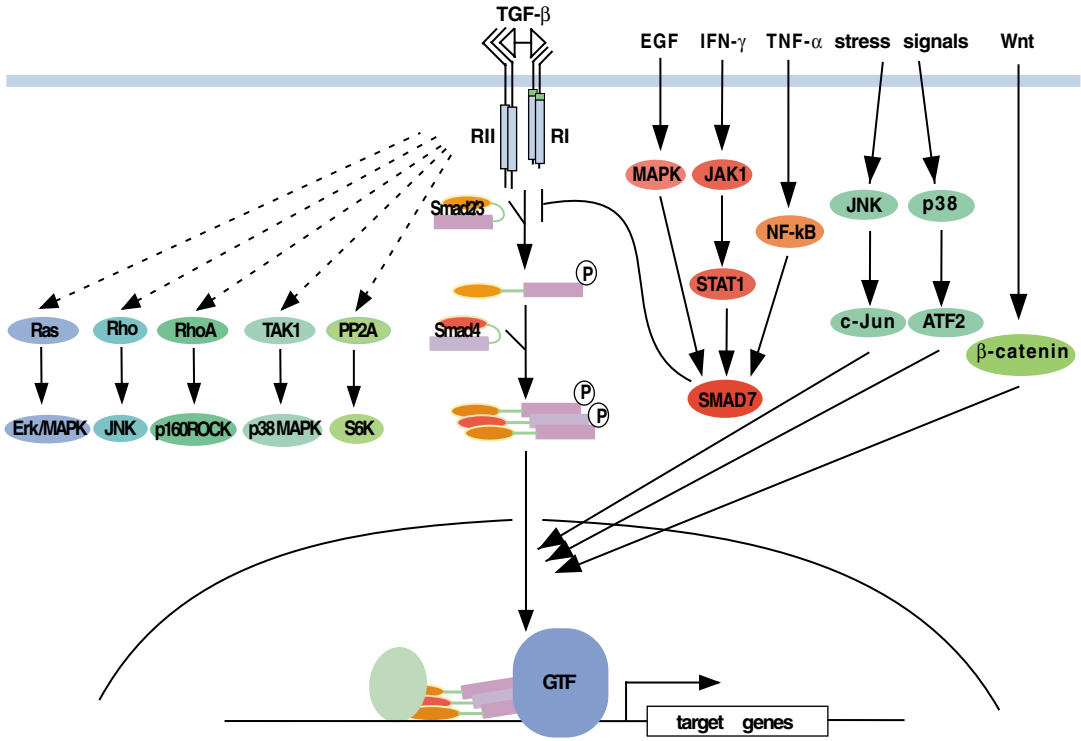

Fig. 1 TGF-β-induced signaling through Smads, and several non-Smad signaling mechanisms. After ligand-induced activation of the receptor, Smad2 and/or Smad3 interact transiently with the TβRI receptor (RI), and this interaction is stabilized by the FYVE protein SARA. Smad2 and Smad3 are phosphorylated on their C terminals by TβRI, and then dissociate from the receptor to form a heterotrimeric complex comprising two receptor-activated Smads and Smad4. This complex then translocates into the nucleus, where it interacts at the promoter with transcription factors with sequence-specific DNA binding to regulate gene expression. The heteromeric Smad complex also interacts with the CBP/p300 transcriptional coactivator, which connects the Smad complex with the general transcription factors (GTF). Smad7 inhibits activation of Smad2 and/or Smad3 by the receptors, and Smad7 expression is induced on stimulation of one of several signaling pathways—for example, in response to EGF, interferon-γ (IFN-γ) or tumor necrosis factor-α (TNF-α). Several other signaling pathways also regulate both signaling by Smads and Smad-mediated gene expression, as exemplified here by the activation of JNK and p38 MAP kinase signaling in response to various stress signals, and β-catenin signaling in response to Wnt proteins. TGF-β also induces activation of Ras, RhoB and RhoA, as well as of TAK1 and protein phosphatase 2A, which leads to the activation of several MAP kinase pathways and the downregulation of S6 kinase activity. The mechanisms of activation of these non-Smad signaling events and how they connect to the heteromeric TGF-β receptor complex remain to be characterized.