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BIObrief

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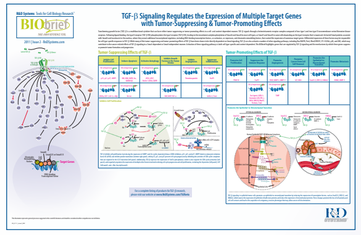

TGF-β Signaling Regulates the Expression of Multiple Target Genes with Tumor-Suppressing & Tumor-Promoting Effects

TGF-β signaling can have either tumor-suppressing or tumor-promoting effects in a cell- and context-dependent manner. The tumor suppressive effects of TGF-β signaling arise from its ability to induce the expression of genes that inhibit cell proliferation, induce apoptosis, activate autophagy, inhibit growth factor signaling by stromal fibroblasts, suppress inflammation, and inhibit angiogenesis. These effects maintain homeostasis in normal tissues and prevent the early stages of tumor formation. As a result of mutations or epigenetic modifications that are introduced during cancer progression, cancer cells can become resistant to the suppressive effects of TGF-β signaling. Loss of the tumor suppressive arm of the TGF-β signaling pathway allows cancer cells to utilize this pathway to specifically promote processes that support tumor progression, including the stimulation of cell proliferation, immunosuppression, angiogenesis, cancer stem cell self-renewal, the epithelial-to-mesenchymal transition, and metastasis. Understanding the mechanisms by which the tumor-suppressing or tumor-promoting effects of TGF-β signaling can be regulated may have therapeutic potential for inhibiting the progression of several different types of human cancer.

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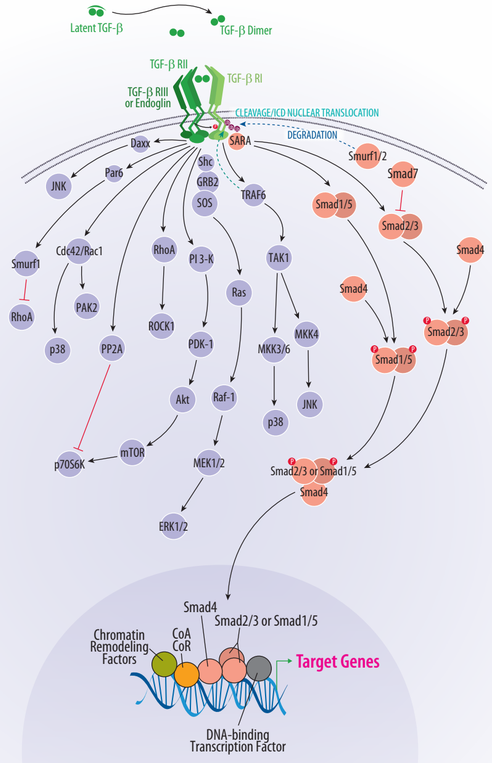


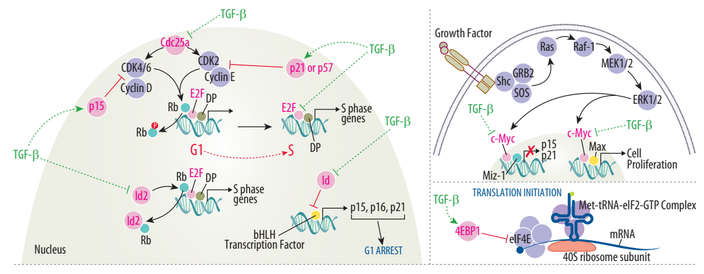
TGF-β Signaling Regulates the Expression of Multiple Target Genes with Tumor-Suppressing & Tumor-Promoting Effects

Transforming growth factor (TGF)-β is a multifunctional cytokine that can have either tumor-suppressing or tumor-promoting effects in a cell- and context-dependent manner. TGF-β signals through a heterotetrameric receptor complex composed of two type I and two type II transmembrane serine/threonine kinase receptors. Following ligand binding, the type II receptor (TGF-β RII) phosphorylates the type I receptor (TGF-β RI), leading to the recruitment and phosphorylation of Smad2 and Smad3 in most cell types, or Smad1 and Smad5 in some cells depending on the type I receptor that is expressed. Activated Smad proteins associate with Smad4 and translocate to the nucleus, where they recruit additional transcriptional regulators, including DNA-binding transcription factors, co-activators, co-repressors, and chromatin remodeling factors, that control the expression of numerous target genes. Differential expression of these factors may be responsible for cell type-specific responses to TGF-β. While many of the tumor-suppressing and tumor-promoting effects of TGF-β have been shown to be directly dependent on Smad signaling, TGF-β can also activate a number of other signaling pathways, including Ras/MAPK, Par6, RhoA/ROCK1, PI 3-K/Akt, p38, and JNK, which may contribute to the cancer-related effects of TGF-β signaling in a Smad-dependent or Smad-independent manner. Activation of these signaling pathways is both cell type-specific and context-dependent. This BIObrief highlights genes that are regulated by TGF-β signaling and the mechanisms by which these genes suppress or promote tumor formation and progression.

Tumor-Suppressing Effects of TGF-β

Inhibits Cell Proliferation	Induces Apoptosis	Activates Autophagy	Inhibits Growth Factors in the Tumor Stroma	Inhibits Angiogenesis	Suppresses Inflammation
TGF-β Target Genes p15, p21, p57, 4EBP1	TGF-β Target Genes BIK, BIM, DAPK, Fas, GADD45β	TGF-β Target Genes ATG5, ATG7, Beclin 1/ATG6, DAPK		TGF-β Target Genes Thrombospondin	TGF-β Target Genes FoxP3
TGF-β Target Genes CD25a, E2F-1, Id1-3, c-Myc	TGF-β Target Genes Bcl-xL		TGF-β Target Genes HGF, MSP, TGF-α		TGF-β Target Genes GATA-3, T-bet

Inhibits Cell Proliferation



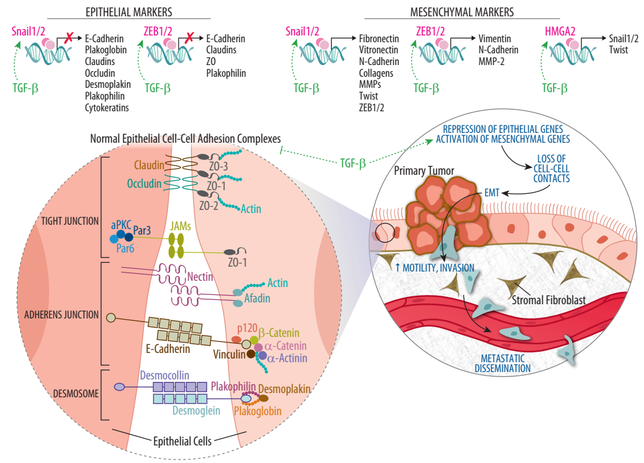
TGF-β inhibits cell proliferation by inducing the expression of 4EBP1 and the cyclin-dependent kinase (CDK) inhibitors, p15, p21, and p57. 4EBP1 binds to eukaryotic initiation factor 4E (eIF4E) and inhibits protein translation (bottom right panel), while p15, p21, and p57 prevent cell cycle progression by inhibiting the activities of CDK-cyclin complexes that are required for the G1/S transition (left panel). Additionally, TGF-β represses the expression of Cdc25a phosphatase, which is also required for CDK-cyclin activation (left panel), and negatively regulates the expression of multiple other factors involved in driving cell cycle progression and cell proliferation, including the Id proteins (left panel), E2F (left panel), and c-Myc (top right panel).

For a complete listing of products for TGF-β research, please visit our website at **www.RnDSystems.com/TGFbeta**

Tumor-Promoting Effects of TGF-β

Promotes Cell Proliferation	Suppresses the Immune Response	Promotes Angiogenesis	Promotes Cancer Stem Cell Self-Renewal	Promotes the Epithelial-to-Mesenchymal Transition	Promotes Metastasis
TGF-β Target Genes PDGF-B	TGF-β Target Genes FoxP3	TGF-β Target Genes VEGF, MMP-2, MMP-9	TGF-β Target Genes LIF, SOX4	TGF-β Target Genes Snail1/2, ZEB1/2, HMGA2	TGF-β Target Genes HDM2, MMP-9
	TGF-β Target Genes Fas Ligand, GATA-3, Granzyme A/B, IFN-γ, MICA, NKG2D, Nkp30, Perforin, T-bet	TGF-β Target Genes TIMP			

Promotes the Epithelial-to-Mesenchymal Transition



TGF-β signaling in epithelial tumor cells promotes an epithelial-to-mesenchymal transition by inducing the expression of transcription factors, such as Snail1/2, ZEB1/2, and HMGA2, which repress the expression of epithelial cell adhesion proteins and induce the expression of mesenchymal proteins. These changes promote the loss of cell polarity and cell-cell contacts and lead to the acquisition of a migratory, invasive phenotype that may allow cancer cell dissemination.

This illustration represents general processes suggested in the scientific literature and should be considered neither comprehensive nor definitive.

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