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Different role of Gadd45b in TGF-β and Fas-induced apoptosis

Jiyun Yoo

Department of Microbiology/Research Institute of Life Science, Gyeongsang National University, Jinju 660-701, Korea

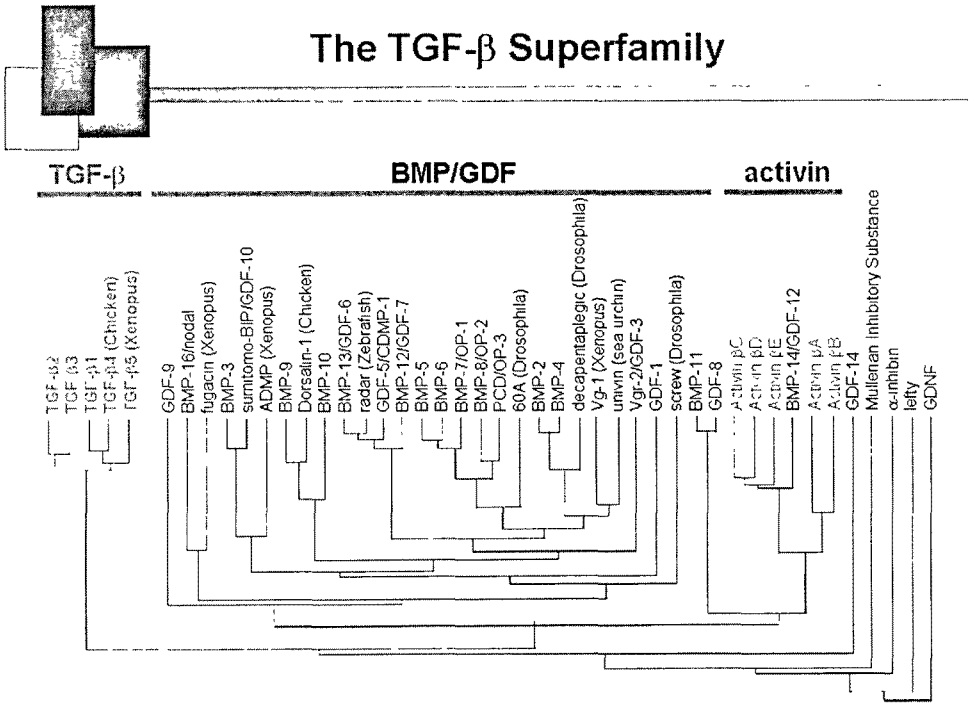
TGF-β and Fas-induced apoptosis are important in hepatic injury and contribute to the development of liver fibrosis in chronic hepatitis. We previously identified the immediate early response gene Gadd45b as an effector of TGF-β-induced apoptosis and delineated the pathway TGF-β → Smad3→Gadd45b → p38 → apoptosis. We are now extending these studies to investigate the role of Gadd45b in Fas-induced apoptosis. AML12 cells undergo apoptosis when treated with a Fas agonist, Jo2 antibody, and this is blocked strongly by a p38 inhibitor and partially in cells stably expressing antisense Gadd45b. Whereas Jo2 strongly induces phosphorylation of p38, effects of loss of Gadd45b are downstream of p38, in contrast to TGF-β-induced apoptosis. From these results we suggest that Fas-induced apoptosis, like TGF-β-induced apoptosis, ultimately converges on p38, but that the upstream activator of Fas-induced p38 activation is ASK1 or another unknown kinase rather than MEKK4 (which is Gadd45b/Smad3-dependent). Gadd45b likely also binds to p38 directly regulating phosphorylation of its downstream targets such as Rb, such that some of the targets may be modulated in cells in which levels of Gadd45b are reduced.

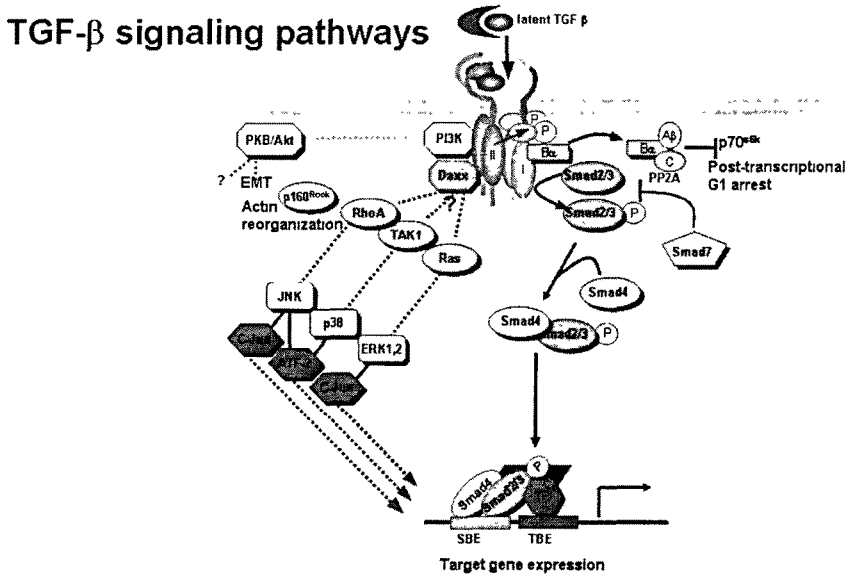
Major biological responses and diseases regulated by TGF-β

- Wound healing
- Autoimmune disease
- Fibrosis
- Carcinogenesis

- Inhibits proliferation
- Regulates apoptosis
- Regulates differentiation
- Regulates immune cell function
- Stimulates accumulation of ECM
- Promotes chemotaxis

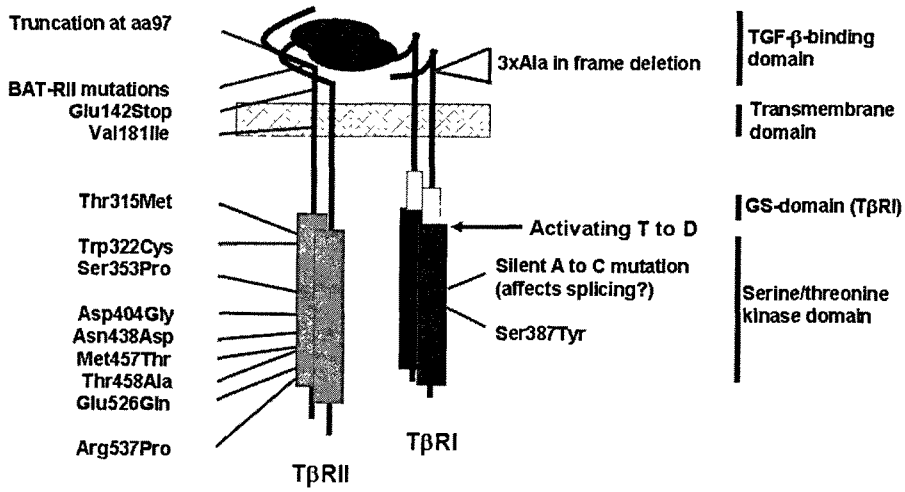
The TGF-β Superfamily



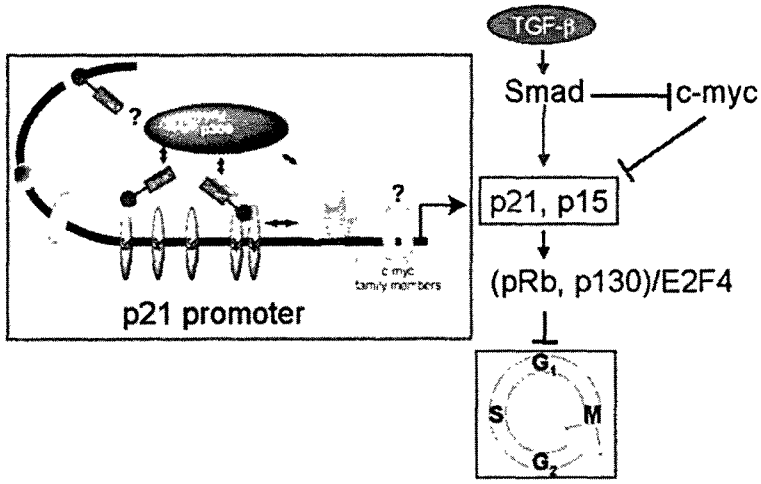


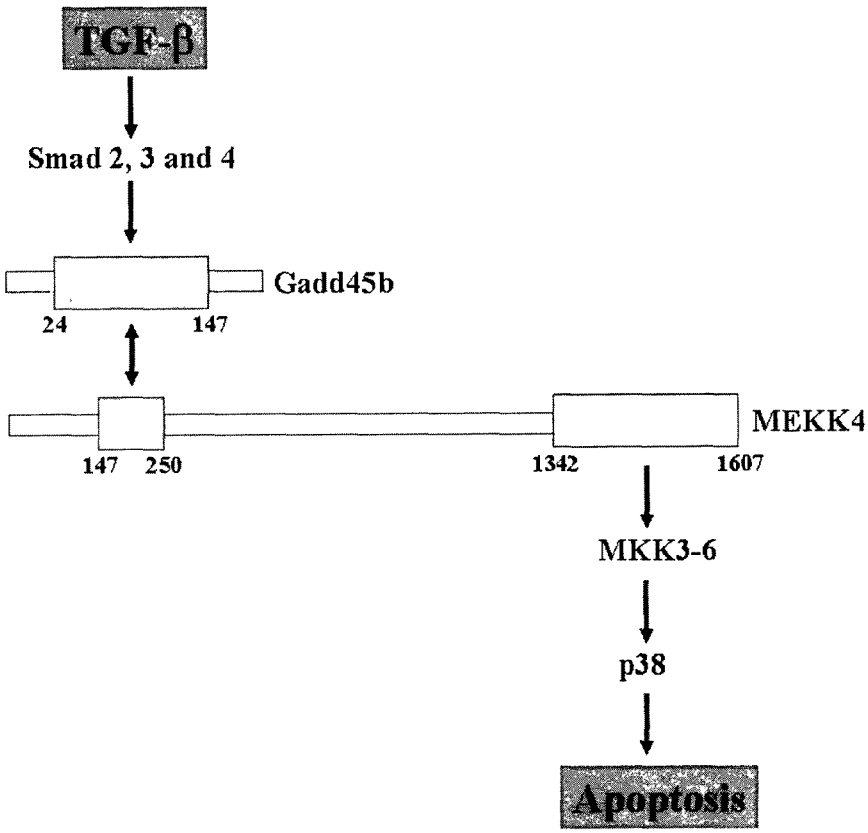
Wakefield and Roberts, Current Opinion in Genetics and Development, 2001

Mutations in the TGF-β receptors found in human cancer



Mechanism of TGF-β-induced growth inhibition





Mechanism of Fas-induced apoptosis