Primary Actor: **TGF-beta**
Pre-conditions: TGF-beta and receptors must be present.
Post-conditions: SMAD 2 is phosphorylated and released from TGF-beta receptor I.

Main Success Scenario (or Basic Flow):

1. TGF-beta homodimerizes (GO:0042803)
2. TGF-beta binds TbRI-TbRII complexes (1) (GO:0050431)
3. Type I and II receptors tetramerize (2 type II receptors and 2 type I receptors) (2-4) (GO:0046982)
4. Constitutively activated Type II receptor phosphorylates and activates type I receptor (GO:0016740, GO:0042301)
5. TGF-beta and receptors are internalized
6. Type I receptor propagates signal by phosphorylating Smad 2 (GO:0046332, GO:0016740, GO:0042301)
7. The phosphorylation of Smad2 and formation of the Smad complex results in the release of activated Smads from TGF beta RI

Extensions (or Alternative Flows):

2a. Dimerized TGF-beta 1 binds to homodimeric TGF-beta receptor III (GO:0042803, GO:0046982)

1. TGF-beta receptor III presents TGF-beta to Type II receptor and Type I receptor (1)
2. TGF-beta receptor III can be phosphorylated by TGF beta RII (GO:0016740, GO:0042301)
    a. TGF-beta receptor III interacts with beta-arrestin, which mediates endocytosis of TGF-beta receptor III and TGF-beta RII (5)

3a. In an allosteric model, binding of ligand to the type II receptor is required to induce a conformational change in the ligand, which leads to exposure of the binding epitope of the type I receptor (6)

3b. In a cooperative model, the ectodomain of the type I receptor interacts with an extended surface that relies on the formation of the type II receptor-ligand complex (6)

4a. FKBP12 inhibits TGF-beta signaling by binding to the unphosphorylated type I receptor (7)

5a. Internalization via lipid raft-caveolar compartments containing receptor bound to Smad7-Smurf2

1. results in accelerated receptor turnover by promoting poly-ubiquitination (8)

5b. Clathrin-dependent TGF-beta receptor internalization

1. activated TGF-beta receptor complex is internalized via coated vesicles to SARA-containing early endosomes promoting Smad signaling (8)

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