Key role for ubiquitin protein modification in TGFβ signal transduction.

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Abstract

The transforming growth factor β (TGFβ) superfamily of signal transduction molecules plays crucial roles in the regulation of cell behavior. TGFβ regulates gene transcription through Smad proteins and signals via non-Smad pathways. The TGFβ pathway is strictly regulated, and perturbations lead to tumorigenesis. Several pathway components are known to be targeted for proteasomal degradation via ubiquitination by E3 ligases. Smurfs are well known negative regulators of TGFβ, which function as E3 ligases recruited by adaptors such as I-Smads. TGFβ signaling can also be enhanced by E3 ligases, such as Arkadia, that target repressors for degradation. It is becoming clear that E3 ligases often target multiple pathways, thereby acting as mediators of signaling cross-talk. Regulation via ubiquitination involves a complex network of E3 ligases, adaptor proteins, and deubiquitinating enzymes (DUBs), the last-mentioned acting by removing ubiquitin from its targets. Interestingly, also non-degradative ubiquitin modifications are known to play important roles in TGFβ signaling. Ubiquitin modifications thus play a key role in TGFβ signal transduction, and in this review we provide an overview of known players, focusing on recent advances.

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