TGFβ-Mediated Epithelial Mesenchymal Transition and Metastasis in Skin and Head-and-Neck Cancer

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Summary. In human skin and head and neck cancers, cancer cells frequently overexpress TGFβ but decrease expression of TGFβ signaling components. We generated several genetically engineered mouse models to investigate how these changes affect cancer progression. Overexpression of TGFβ1 in the skin or head and neck epithelia rapidly induced inflammation, suggesting that inflammation is a direct effect of TGFβ1 overexpression. Given the importance of inflammation in cancer development, our data suggest that in certain tissue types, TGFβ1-induced inflammation may override its tumor suppressive effect, even at early stages of carcinogenesis. This notion is further supported by our finding that deletion of TGFβ type II receptor (TGFβRII) in head and neck epithelia resulted in an elevated

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Abbreviations: TGFβ, transforming growth factor beta; SCC, squamous cell carcinoma; TGFβRII, TGFβ type II receptor; TGFβRI, TGFβ type I receptor; R-Smads, receptor-specific Smads; Co-Smad, common Smad; I-Smads, inhibitory Smads; ALK, activin receptor-like kinase; PAI-1, plasminogen activator inhibitor I; MMP, matrix metalloproteinases; TPA, phorbol 12-myristate 13-acetate.
endogenous TGFβ1, which was correlated with severe inflammation and angiogenesis in head and neck tissue. In combination with an activated Ras oncogene in TGFβRII null epithelial cells, these mice developed head and neck squamous cell carcinoma (HNSCC). Considering that most late-stage HNSCC cells are resistant to TGFβ1-mediated growth inhibition via loss of TGFβRII or other molecular alterations, our study suggests that inhibition of the effect of TGFβ1 on tumor stroma in combination with therapy targeting cancer epithelia may provide an effective therapeutic strategy for HNSCC. Our study also revealed that dominant negative TGFβRII blocks TGFβ1-mediated EMT but not metastasis. Consistent with this finding, deletion of a common TGFβ signaling mediator, Smad4, in keratinocytes resulted in SCC formation but not EMT-type tumors. This result suggests that Smad4 loss abrogates TGFβ-mediated EMT, but not TGFβ-mediated invasion, the latter of which may be mediated by Smad3. This notion is further supported by our findings that Smad3 knockout mice are resistant to experimental skin carcinogenesis, and that Smad3 is rarely lost in SCCs. Taken together, our study suggests that SCCs that have both increased TGFβ1, and reduced TGFβRII or Smad4 in tumor epithelia will have a poorer prognosis than those with TGFβ1 overexpression alone or loss of TGFβRII/Smad4 alone.

**Key words.** transforming growth factor beta, skin carcinogenesis, epidermis, Smads, inflammation

**Introduction**

Transforming growth factor beta (TGFβ) represents a family of multifunctional cytokines that play a pivotal role in the maintenance of tissue homeostasis through regulation of biological processes including cell growth, differentiation, apoptosis, extracellular matrix formation, inflammation, and angiogenesis (Feng and Derynck, 2005). The TGFβ superfamily consists of three major subfamilies: TGFβ, activins/inhibins, and bone morphogenetic proteins (BMPs). These family members signal through type II and type I transmembrane serine/threonine kinase receptors. Three TGFβ isoforms,