Wound Healing Society Annual Meeting
May 2002. Baltimore, Maryland

THE CONDITIONAL KNOCK-OUT OF THE TRANSFORMING GROWTH FACTOR TYPE II RECEPTOR IN FIBROBLASTS RESULTS IN IMPAIRED WOUND HEALING

Neil A. Bhowmick[1], Anna Chytil[1], Cher Carlisle[2], Eric Neilson[3], Jeffrey M. Davidson[2*], Harold L. Moses[1]. Departments of [1]Cancer Biology, [2]Pathology, and [3]Medicine, Vanderbilt University, and [*]VA Medical Center, Nashville, TN 37232 neil.bhowmick@mcmail.vanderbilt.edu

The transforming growth factor-beta isoforms (TGF-ß1, TGF-ß2, and TGF-ß3) regulate wound healing through autocrine and paracrine signaling. TGF-ß signaling is initiated by its binding to cell surface receptors that form a heterotetrameric complex of two type I and two type II serine/threonine kinase receptors. Based on our previous TGF-ß studies identifying signaling pathways crucial for epithelial-to-mesenchymal transdifferentiation progression, we developed a mouse model that exhibited a conditional knock-out of the TGF-ß type II receptor (TßRII) in fibroblastic cells. Using a Cre-lox approach, targeted fibroblastic recombination was achieved by crossbreeding transgenic mice having both floxed TßRII alleles with those expressing Cre under the FSP-1 (fibroblast specific protein) promoter. FSP-1 is expressed in the mesenchymal cells of fibroblastic origin beginning at embryonic day 9. Analysis of various tissues of the bigenic mice with the intended knock-out, *Tgfbr2*^{fspko}, show mesenchymal recombination of the *Tgfbr2* gene, including the skin.

Keratinocytes are recognized as key regulators of skin remodeling, however their interaction with the underlying dermal fibroblasts during wound healing is less clear. The *Tgfbr2*^{fspko} mouse model uniquely permits such studies. These animals were tested for excision and linear incision wound healing properties through a 7-10 day period, at which time the mice were sacrificed for histological analysis. The keratinocyte organization and the closure of the excisional wound in *Tgfbr2*^{fspko} mice were similar to that of wild type C57BL/SV6 mice. However there were diminished numbers of cells in the suprabasal layer in the remodeled excision wound of the conditionally knocked-out mice. Interestingly, tensile strength analysis showed that there was essentially no healing of the incisional wound in *Tgfbr2*^{fspko} mice seven days after wounding. We investigated the expression and distribution of TGF-ß1, integrin, and extracellular matrix proteins. Our findings suggest TGF-ß signaling is important in stromal remodeling and keratinocyte expression.