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<td>Ku, Chee Wai</td>
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**Paracrine Regulation of Epidermal Growth via Smad3**

### Introduction

Skin is the largest organ in the body and it serves as a protective barrier. It is made up of an outermost epidermal layer and an underlying dermal layer. The formation and maintenance of the epidermis depend on the precise regulation of keratinocyte proliferation, differentiation and apoptosis. This homeostasis relies on a network of cytokines and growth factors, one of the most important being transforming growth factor β (TGFβ). TGFβ regulates cell growth, apoptosis, differentiation, migration and extracellular matrix production. TGFβ signals via Smad proteins in the canonical signaling pathway (Figure 1). TGFβ is an important growth inhibitor of epithelial cells, but it is also one of the most pro-fibrotic cytokine in vivo. However, the role of TGFβ signaling in fibroblasts in the dermis and the paracrine regulation of keratinocytes in the epidermis remain unclear.

### Aims

To construct organotypic cocultures with wild type and Smad3−/− mouse fibroblasts and investigate the paracrine effect of Smad signaling on epidermal keratinocytes.

### Methods

**Extraction of mouse fibroblast**

**Genotype using tail from pups**

**Organotypic coculture**

**Cryosectioning, Staining and Immunofluorescence**

### Results

**Fig 1. TGFβ signal transduction.**

**Fig 2. Genotyping of wild type (WT), heterozygous (Smad3+/−) and Smad3 knockout (Smad3−/−) mice.**

**Fig 3. Graph of the number of proliferative and apoptotic cells in WT and Smad−/− cultures.**

**Fig 4. H & E staining shows a thicker suprabasal layer in Smad3−/− as compared to WT. CK5 staining reveals impaired early differentiation in keratinocytes. There is increased proliferation and apoptosis of keratinocytes as indicated by Ki67 staining and TUNEL assay respectively.**

### Discussion

TGFβ is one of the most important cytokines in regulating skin homeostasis. Fibroblasts deficient in Smad3 resulted in increased epidermal proliferation, increased apoptosis and impaired cellular differentiation. These results revealed for the first time the impact of TGFβ signaling on epithelial-mesenchymal communication. The delicate balance between cell proliferation and apoptosis is crucial in many pathophysiological diseases, such as cancer and wound healing. The implications are far-reaching, as the elucidation of effects mediated by specific pathways downstream of TGFβ can contribute to the design of drugs that battle cancer or enhance wound healing.