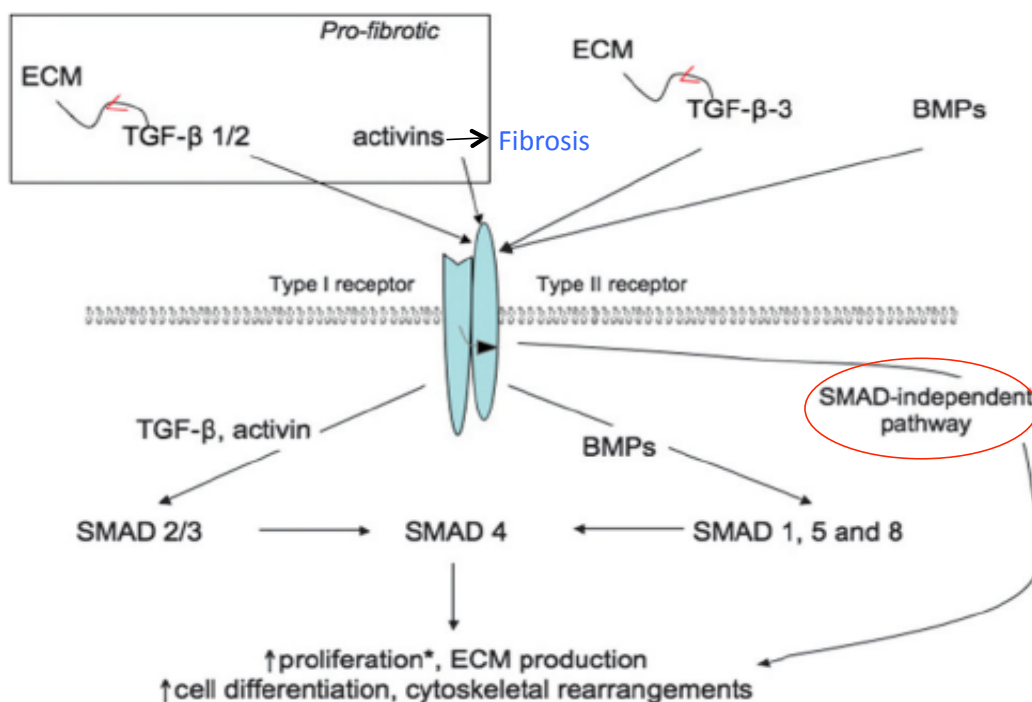


TFGβ signal transduction

The members of the TGFβ family, BMP and activins bind and activate TGFβII receptor. Following injury and during wound healing, Ligand-Receptor interaction lead to the activation of canonical and non canonical pathways.



△ - activating enzymes
MMP2, MMP9, THROMBOSPONDIN-1, AND
INTEGRIN αvβ6

•The effect of TGFβ on cell proliferation are cell type and growth factor concentration dependent

•β1 and β2 are prominent inducers of fibroblast-myofibroblast differentiation, ECM deposition contraction and scar formation, whereas β3 inhibit scarring.

Role of TGF β during wound healing processes

Maturation

TGF- β function:

- Contributes to ECM remodeling by regulating ECM synthesis and degradation
- Regulates expression of matrix-degrading enzymes (e.g. MMPs) and their inhibitors (e.g. TIMPs)
- Increases expression of lysyl oxidases (LOXs) which enhance collagen cross-linking

Proliferation

TGF- β function:

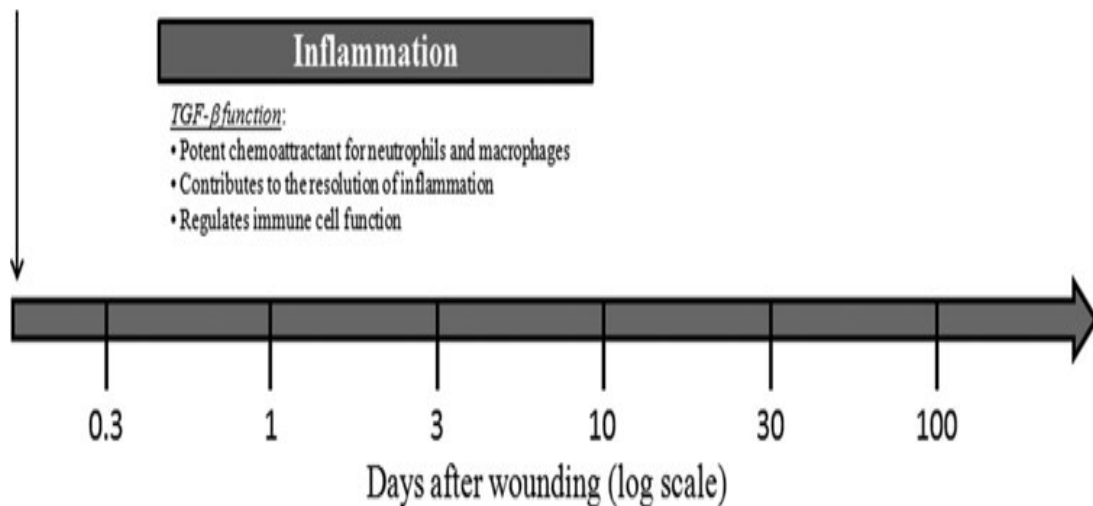
- Promotes angiogenesis by stimulating endothelial cell migration, differentiation and capillary tubule formation
- Increases fibroblast proliferation, promotes fibroblast trans-differentiation into myofibroblasts and stimulates ECM production
- Inhibits keratinocyte proliferation and increases keratinocyte migration during re-epithelialization

Inflammation

TGF- β function:

- Potent chemoattractant for neutrophils and macrophages
- Contributes to the resolution of inflammation
- Regulates immune cell function

Injury



Hypertrophic Scar



Distinguishing features

- Appear as red raised scar tissue
- Scarring does not extend beyond boundary of original wound
- Nodular structures containing α -SMA-producing myofibroblasts
- Promote scar contractures
- Can regress with time

TGF- β involvement

- ↑ TGF- β 1 expression in HTS tissue and HTS fibroblasts (refs 113, 114)
- ↑ T β RI and T β RII expression in HTS fibroblasts (ref. 115)
- ↑ Smad2 nuclear localization in HTS fibroblasts (ref. 116)
- ↑ TGF- β 1 serum levels in burn patients that develop HTS (ref. 119)

Keloid



Distinguishing features

- Often appear as shiny rounded protuberances, color ranges from pink to purple
- Scarring extends beyond boundaries of original wound
- Rarely nodular, no α -SMA producing myofibroblasts
- Do not promote scar contractures
- Do not regress with time

TGF- β involvement

- ↑ TGF- β 1 and TGF- β 2 expression in keloid fibroblasts (refs 125, 126)
- ↑ T β RI and T β RII expression in keloid fibroblasts (refs 127, 128)
- ↑ TGF- β /Smad3 signalling in keloid fibroblasts (refs 127, 128)
- Genetic association of TGF- β 1 and Smad4 variants in etiology of keloid disease (ref. 133)