Permissive environment in postnatal wounds induced by adenoviral-mediated overexpression of the anti-inflammatory cytokine interleukin-10 prevents scar formation

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ABSTRACT

Wound healing in the mid-gestation fetus is scarless with minimal inflammation and a unique extracellular matrix. We have previously documented the relative lack of inflammatory cytokines in this environment. We demonstrate that interleukin (IL)-10 is highly expressed in mid-gestation human fetal skin but is absent in postnatal human skin. We hypothesize that overexpression of IL-10 in postnatal skin may create a permissive environment for scarless healing. To study the mechanism underlying this process we performed immunohistochemistry for IL-10 in human mid-gestation fetal and postnatal skin. We also determined if adenoviral-mediated overexpression of IL-10 could allow for scarless wound healing in a murine incisional wound model. Wounds were analyzed at 1–90 days postwounding for effects on scar formation, inflammatory response, and biomechanical properties. Ad-IL-10 reconstitutes a permissive environment for scarless healing as shown by reconstitution of a normal dermal reticular collagen pattern and distribution of dermal elements. Compared with controls, Ad-IL-10 treated wounds showed reduced inflammatory response and no difference in biomechanical parameters. Therefore, overexpression of IL-10 in postnatal wounds results in a permissive environment for scarless wound repair, possibly by replicating a fetal wound environment.

The healing of mid-gestation fetal skin is characterized by scarless repair, with restoration of normal dermal architecture.1–2 The precise mechanisms that account for scarless fetal wound healing are poorly understood. The most striking characteristics of what is known about fetal wound healing include a markedly diminished cellular inflammatory response, an altered wound extracellular matrix (ECM) composition, and a characteristic pattern of TGF-β isoform expression.5 Although diminished inflammation in fetal wounds is well shown, most work in this area has been limited to the cellular and humoral inflammatory response. Previous work in our laboratory suggests there is a decrease in the pro-inflammatory cytokines interleukin (IL)-6 and IL-8 in fetal wound repair,5,9 as well as a role for the anti-inflammatory cytokine IL-10 in fetal wound healing.10 Cutaneous wound repair in fetal IL-10 knockout mice occurs with scar formation. In contrast, wounds in the skin of wild-type fetal mice heal scars less. This suggests there may be a significant role for IL-10 in scarless fetal wound repair.10 This led us to develop a cytokine hypothesis for fetal wound healing. Simply stated, the cytokine hypothesis posits that fetal tissue is permissive of scarless wound healing as a consequence of a shift toward increased anti-inflammatory cytokine expression and decreased pro-inflammatory cytokine expression. The mechanisms, by which the balance is tipped towards anti-inflammatory cytokines that results in a permissive environment for scarless healing, are not known.

IL-10, originally termed cytokine inhibitory factor, is a 35 kDa homodimeric cytokine product of Th2 cells, B cells, and macrophages. It is a potent anti-inflammatory cytokine that has been implicated in preventing a maternal immune response to the fetus and its “foreign” antigens.11–13 Levels of IL-10 are known to be elevated in amniotic fluid.14 IL-10 has also been shown to deactivate macrophages and neutrophils, and diminish the production of pro-inflammatory cytokines IL-6 and 8.3,15–17 In postnatal tissue repair, levels of IL-10 have been shown to be inversely correlated with fibrotic processes.18 We hypothesized that overexpression of IL-10 in postnatal wounds may replicate the permissive fetal environment enabling scarless wound repair. The effects of IL-10...