Epidermal integrin α3β1 is a regulator of the macrophage stimulating factor, CSF-1, and of crosstalk from keratinocytes to macrophages during cutaneous wound healing

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Abstract
The development of integrin-targeted wound therapy is hindered by incomplete understanding of integrin function in cutaneous wound healing and the wound microenvironment. Following cutaneous injury, keratinocytes migrate to restore the skin barrier, and macrophages aid in debris clearance. Thus, both keratinocytes and macrophages are critical to the coordination of tissue repair. Keratinocyte integrins have been shown to participate in this coordinated effort by regulating secreted factors, some of which crosstalk to distinct cells in the wound microenvironment. Our earlier findings have identified integrin α3β1 as a key regulator of the keratinocyte secretome and of the skin tumor microenvironment. Previous mass spectrometric analysis of conditioned medium from immortalized keratinocytes indicated that α3β1 positively regulates colony-stimulating factor 1 (CSF-1), a secreted cytokine that is a primary regulator of macrophage differentiation, proliferation, and survival. In our current work, we use an *in vivo* murine model to show that cutaneous wounds deficient in epidermal integrin α3β1 express less epidermal-derived CSF-1. α3β1-deficient wounds also have fewer wound-proximal macrophages, suggesting that keratinocyte α3β1 may stimulate wound macrophages through the regulation of CSF-1. Indeed, using a panel of immortalized keratinocytes, we demonstrate that keratinocyte-derived CSF-1 supports macrophage growth, and that α3β1 regulates *Csf1* expression through YAP-TEAD-mediated transcription. Consistently, α3β1-deficient wounds *in vivo* display a substantially reduced number of keratinocytes with YAP-positive nuclei. Overall, our findings identify a novel role for epidermal integrin α3β1 in regulating the cutaneous wound microenvironment by mediating paracrine crosstalk from keratinocytes to wound macrophages, implicating α3β1 as a potential target of wound therapy.

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