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Complex roles for VEGF in dermal wound healing

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To the Editor:

We read with interest the letter by Stockmann, *et al* entitled "A wound size-dependent effect of myeloid cell-derived vascular endothelial growth factor on wound healing" (Stockmann, *et al*, 2011). The results presented in this paper suggest that myeloid cell-derived VEGF (vascular endothelial growth factor) is important for expedient closure in large excisional wounds, where it contributes significantly to angiogenesis and overall dermal VEGF levels. This does not seem to be the case in incisional wounds, where, at 12 days post-injury there appears to be no significant difference in VEGF levels or dermal scar width. Several years ago, we demonstrated a role for VEGF in scar formation in several models of wound healing (Wilgus, *et al*, 2008). We showed that an increase in total VEGF levels correlate with the transition from scarless to fibrotic healing in fetal skin and that exposure of wounds that normally heal in a scarless fashion to exogenous VEGF leads to scar formation. We also showed in an incisional wound model that antibody neutralization of VEGF throughout the healing process significantly reduces scar size and increases the quality of the collagen that is deposited. These findings are supported by multiple other studies that link VEGF to fibrotic reactions (Choi, *et al*, 2003; Hakroush, *et al*, 2009; Hamada, *et al*, 2005; Karvinen, *et al*, 2011; Lin, *et al*, 2011). While our findings may seem to contradict the study by Stockmann, *et al* at first glance, several important considerations affect the interpretation. Our study employed neutralizing antibodies, administered repeatedly throughout the healing process to inhibit the activity of VEGF. This approach would neutralize VEGF produced not only by myeloid-derived cells, but also from other cellular sources in the wound, including mast cells, fibroblasts, and most notably, keratinocytes, which are thought to be a major source of VEGF after injury (Brown, *et al*, 1992; Rossiter, *et al*, 2004). Furthermore, the repetitive administration of antibodies, as was done in our study, would block the activity of VEGF throughout all phases of healing, while LysM-cre/VEGF$^{+f/+f}$ mice would only exhibit reduced VEGF in the wound during a discrete period when myeloid-derived cells are present at high levels. It is difficult to make direct comparisons between the two studies as different time points and methods were used for analysis. In addition, because detailed

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methods are not included in Letters to the Editor, it is not easy to assess whether other alterations in methodology could contribute to the results presented by Stockmann, *et al*.

The paper by Stockmann and colleagues draws attention to the ongoing struggle that wound healing researchers face when trying to decide what model to use, since results may be quite different depending on whether a large excisional wound or an incisional wound is used. One could argue that because the authors did not find many differences using the incisional wound model, it should be used sparingly for wound healing studies; however, both models are valid and there are well-recognized advantages and limitations for both. Robust inflammation and angiogenesis are hallmarks of the excisional wound model and reepithelialization can be examined more accurately in this model, but large open acute wounds in rodents display a significant amount of contraction. Contraction is less of a consideration with incisional wound models, which more closely represent the clinical situation of acute surgical wounds, and therefore may be a better model of to evaluate cosmesis, despite the smaller scale of the injury response.

The biology of VEGF is gaining in complexity, and this molecule is now known to have many additional roles beyond its original description as an endothelial mitogen and permeability factor. While conditional knockout strategies are valuable, multiple experimental approaches seem warranted to fully understand the function and significance of VEGF in the wound healing process.

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Abbreviations used

VEGF (vascular endothelial growth factor)

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