to Taxol by patients with tumors positive for p53 gene alterations may be variable, depending on the histotype or other genetic abnormalities.

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# Plasminogen and wound healing

*To the editor* — Thompson *et al.*[1] suggest that the impaired wound healing we recently reported in plasminogen-deficient mice[2] could be a result of diminished production of angiogenic fibrin degradation products (FDPs) and a subsequent impairment of cell proliferation including angiogenesis. Although this is certainly a viable hypothesis, it is important to recognize that we did not report and do not know that cell proliferation and angiogenesis are reduced in plasminogen knockout mice. Indeed, at least qualitatively, we observed both abundant formation of granulation tissue and pronounced neovascularization in these animals. In contrast, keratinocyte migration was markedly impaired and we proposed that this may be primarily because of a diminished ability of these cells to proteolytically dissect their way through the provisional fibrin-rich matrix.

A critical linkage between plasmin-generated FDPs and the establishment of vasculature seems generally inconsistent with the fact that both fibrinogen- and plasminogen-deficient mice develop to term and can grow to adulthood[3,4]. Nevertheless, Thompson *et al.*'s hypothesis of a critical role of biologically active FDPs in the context of wound repair, warrants further consideration. One way to discriminate between this concept and our proposal that the chief impediment to wound healing in plasminogen-deficient mice is a fibrin barrier to cell migration is by studying wound healing in mice with a combined deficiency for both plasmin(ogen) and fibrin(ogen). Thompson *et al.*'s hypothesis predicts wound healing will remain impaired in these mice, whereas our hypothesis predicts that the impairment to wound healing observed in plasminogen-deficient mice will be alleviated or corrected if they also lack fibrinogen. Because mice with combined fibrinogen and plasminogen deficiency have been raised and shown to tolerate skin incisions, we expect this issue will be resolved shortly.

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*Thompson* et al. *reply* — The experiments suggested by Rømer *et al.* will certainly be of interest regarding the mechanisms underlying wound healing, but what do we know that might predict the outcome? Plasminogen deficiency in wound healing has been studied in terms of incorporation of inhibitors of fibrinolysis within implanted fibrin clots[5]. Compared with controls, reduced invasion of granulation tissue but increased collagen deposition at the periphery were seen. Such a separation of emerging components of the granulation tissue may be relevant to the range of knockout mouse models now available and it will be important to examine the detailed temporal sequence of histopathological events.

Fibrinogen deficiency has been induced by Arvin defibrinogenation during experimental wound healing[6]. This reduces granulation tissue, which is also a feature of fetal wound healing. Fetal mouse wound closure occurs with minimal clot and macrophages because of the immature fetal coagulation system, by a mechanism of epidermal movement[7]. Another relevant factor is the long recognized chemotactic activity of fibrin degradation products[8]. Therefore, we predict that the fibrinogen knockout mouse will exhibit epidermal closure with minimal true granulation tissue and minimal early inflammatory cell infiltrate. The combined plasminogen fibrinogen knockout should appear similar. However, "adding back" fibrin clot to the wound should restore all normal features to the fibrinogen-deficient mouse but only some of the granulation tissue component to the combined deficiencies mouse. "Adding back" fibrin fragment E, although difficult to envisage technically, should restore normal features to both types of mouse model.

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