The Inflammation–Fibrosis Link? A Jekyll and Hyde Role for Blood Cells during Wound Repair

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The healing of a skin wound is a complex process involving many cell lineages. In adult tissues, repair is always accompanied by a robust inflammatory response, which is necessary to counter the potential for infection at any site where the skin barrier is breached. Unlike embryonic tissues that can repair perfectly without a remnant scar at the wound site, adult tissue repair always leads to formation of a fibrotic scar where the wound has healed. In recent years, it has become clear that the wound inflammatory response may be, at least in part, responsible for fibrosis at sites of tissue repair. In this review, we consider the beneficial *vs* the detrimental functions of inflammatory cells during the repair response and compare data from other tissues, the lung, and liver, where fibrosis and its resolution may be related to a damage-triggered inflammatory response. We also consider how it may be possible to molecularly disentangle the potentially good from the bad influences of inflammatory cells during tissue repair and how fundamental studies in inflammatory cell biology may prove the way forward for development of drug targets in this respect.

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Introduction

Recruitment of inflammatory cells and the subsequent laying down of extracellular matrix during wound repair is a normal and healthy response to tissue damage as cells in the vicinity of the wound become activated and migrate to fill the breach (Figure 1). These rapid and robust reparative events have clearly been selected for so that an animal can survive in hostile environments. However, it seems, in part, that we are victims of our evolutionary success, because the general end point of repair is excessive and poorly ordered matrix deposition and fibrosis, which affects normal-tissue architecture and ultimately can disable proper functioning of tissues. For this reason, there has been much investigation into the molecular events underlying fibrosis after tissue insult and much of the data, as described in this review, implicate the infiltrating leukocyte – the inflammatory response – as being the causal agent.

Wherever adult skin is damaged, there is a massive influx of leukocytes in order to prevent infection. However, along with their involvement in innate immunity, leukocytes also release factors that influence the behavior of other cells around them. Early in the last century, it was observed that inflammatory cells secrete factors that stimulate fibroblast growth (Carrel, 1921), and since then many other studies have indicated that inflammation may be beneficial to the repair process (Leibovich and Ross, 1975; DiPietro *et al.*, 1998; Nagaoka *et al.*, 2000). For example, an early study of the messenger RNAs expressed by activated macrophages at a wound site indicated transforming growth factor (TGF)α, platelet-derived growth factor (PDGF), and TGFβ as growth factors that are delivered by recruited macrophages (Rappolee *et al.*, 1988), and each one of these growth factors has been shown in some way or other to be beneficial in wound healing (Mustoe *et al.*, 1987; Hebda, 1988). We now know of many more such factors released by one or more of the infiltrating leukocytic lineages and almost all of these factors will possibly have some positive effect on some aspect of repair, be it keratinocyte motility, fibroblast proliferation or contraction, or the wound angiogenic response. However, in recent years there has been increasing evidence to suggest that, at least in some respects, leukocytes can also be bad for repair and may actually promote fibrosis.

Insight into the role of inflammation during repair comes not only from studies in skin but from other organ systems as well. Fibrosis is certainly not unique to repair of skin tissues. Every organ of the body can mount a repair response that generally results in a fibrotic lesion. Lung fibrosis as a result of chronic obstructive pulmonary disease and liver fibrosis because of hepatitis infection are just two exam-

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Abbreviations: PDGF, platelet-derived growth factor; TGF, transforming growth factor

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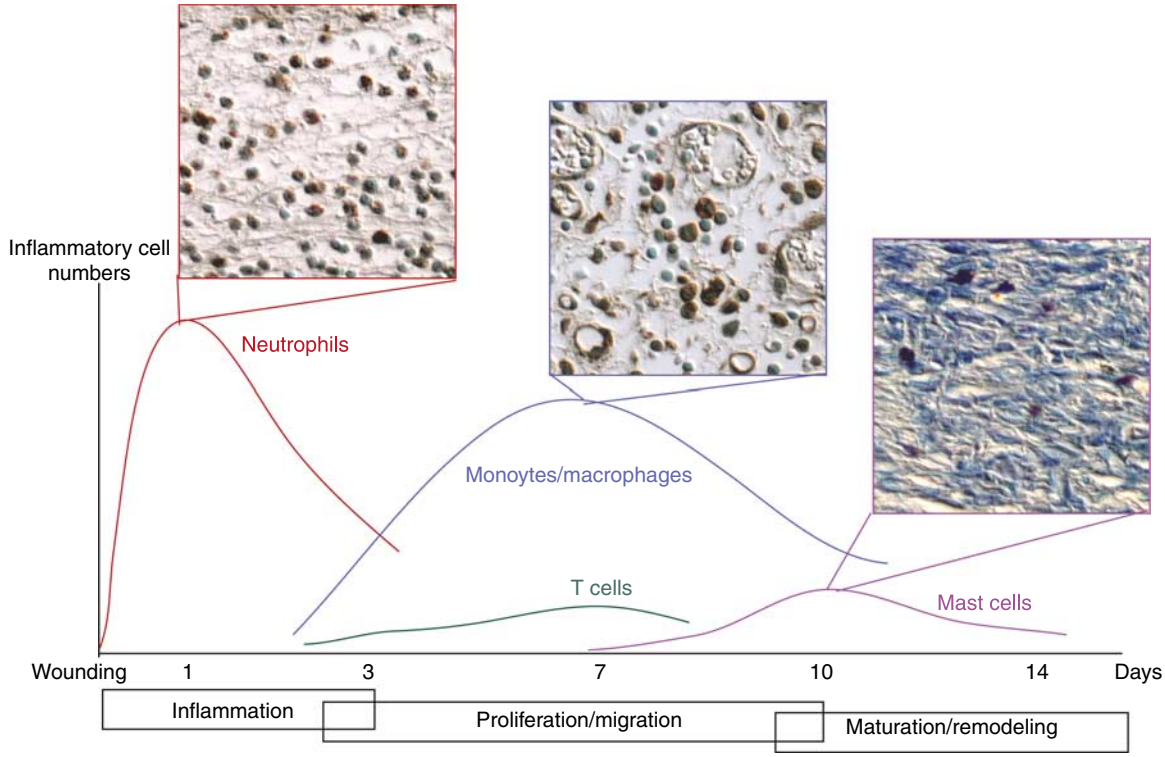

Figure 1. Relative time course of inflammatory cell recruitment to sites of tissue damage. Graphs indicate the approximate time course of influx and dispersal of neutrophils, macrophages, T lymphocytes, and mast cells in a typical murine wound response, superimposed on the three classically considered and overlapping phases of tissue repair (inflammation, proliferation/migration, and maturation/remodeling). The insets show neutrophil and macrophage immunohistochemistry at the wound site at times of peak numbers of these two cell types and mast cells revealed by toluidine blue histochemistry.

ples. This review will discuss both the positive and negative aspects of inflammation as a constituent component of the repair process drawing on parallels from other organ models besides the skin. Unfortunately, as with most scientific questions, the answers turn out to be more complex than we might initially have hoped.

Correlative indicators of an inflammation–fibrosis link in skin repair

At early stages of embryonic development when tissue repair is very rapid and recapitulates embryo morphogenesis, there is no inflammatory response because the inflammatory lineages have yet to be born (Hopkinson-Woolley *et al.*, 1994). Even at limb bud stages of organogenesis, when the first macrophages appear in loose connective tissues there is still no major recruitment of these cells to wounds (Hopkinson-Woolley *et al.*, 1994). Not until much later in development, equivalent to the later stages of organogenesis, do wounds trigger a significant inflammatory response in the fetus and this correlates with the first stage in development when tissue repair leads to a fibrotic scar at the healed wound site. This correlative link between inflammation and fibrosis, with a coincident transition onset time for both, has been observed in several organisms from mouse to man; in mouse, the developmental transition stage appears to be about embryonic days 15–16, beyond which stage considerably more macrophages are drawn to wounds and their activation state also appears increased (Whitby and Ferguson, 1991; Hopkinson-Woolley *et al.*, 1994; Cowin *et al.*, 1998). Studies in rat and rabbit fetuses suggest similar correlations for neutrophil recruitment (Dixon, 1960; Adzick *et al.*, 1985), whereas human fetal surgeons generally find that their lesions only heal without scars in operations performed before the onset of the third trimester (Adzick and Longaker, 1992). Curiously, this transition need not necessarily be during the *in utero* period, and thus is not necessarily linked to a sterile environment or exposure of tissues to amniotic fluid, because studies in marsupials that are born developmentally immature reveal that they neither raise an inflammatory response nor scar at the wound site until 9 days in the pouch (Armstrong and Ferguson, 1995).

It has been proposed that the key difference between embryonic and adult wounds that may explain why the one scars and the other does not, is the differing level of various ''profibrotic'' growth factors – in particular the TGFβs – released into the wound milieu. Certainly, it seems that TGFβ1 levels are reduced and this growth factor is more rapidly cleared in embryonic wounds (Whitby and Ferguson, 1991; Martin *et al.*, 1993) than during adult tissue repair (Frank *et al.*, 1996), and experiments to knock down TGFβ1 levels at the adult wound site in order to more resemble those seen during embryonic and fetal repair, appear to dramatically reduce scar formation in the healed wound (Shah *et al.*, 1992, 1994, 1995). Although a large bolus of TGFβ1 is delivered to the wound by