A multifunctional role of Leucine-rich-alpha 2 glycoprotein 1 in cutaneous wound healing under normal and diabetic conditions

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Abstract

Delayed wound healing is commonly associated with diabetes. It may lead to amputation and death if not treated timely. Limited treatments are available partially due to the poor understanding of the complex disease pathophysiology. Here, we investigated the role of Leucine-rich alpha-2-glycoprotein1 (LRG1) in normal and diabetic wound healing. Firstly, our data showed that LRG1 was significantly increased at the inflammation stage of murine wound healing, and bone marrow-derived cells served as a major source of LRG1. LRG1 deletion causes impaired immune cell infiltration, re-epithelialization and angiogenesis. As a consequence, there is a significant delay in wound closure. On the other hand, LRG1 was markedly induced in diabetic wounds in both humans and mice. LRG1-deficient mice were resistant to diabetes-induced delay in wound repair. We further demonstrated that this could be explained by the mitigation of increased neutrophil extracellular traps (NETs) in diabetic wounds. Mechanistically, LRG1 mediates NETosis in an Akt-dependent manner through TGF-beta type I receptor kinase ALK5. Taken together, our studies demonstrated that LRG1 derived from bone marrow cells is required for normal wound healing, revealing a physiological role for this glycoprotein, but that excess LRG1 expression in diabetes is pathogenic and contributes to chronic wound formation.

Figure

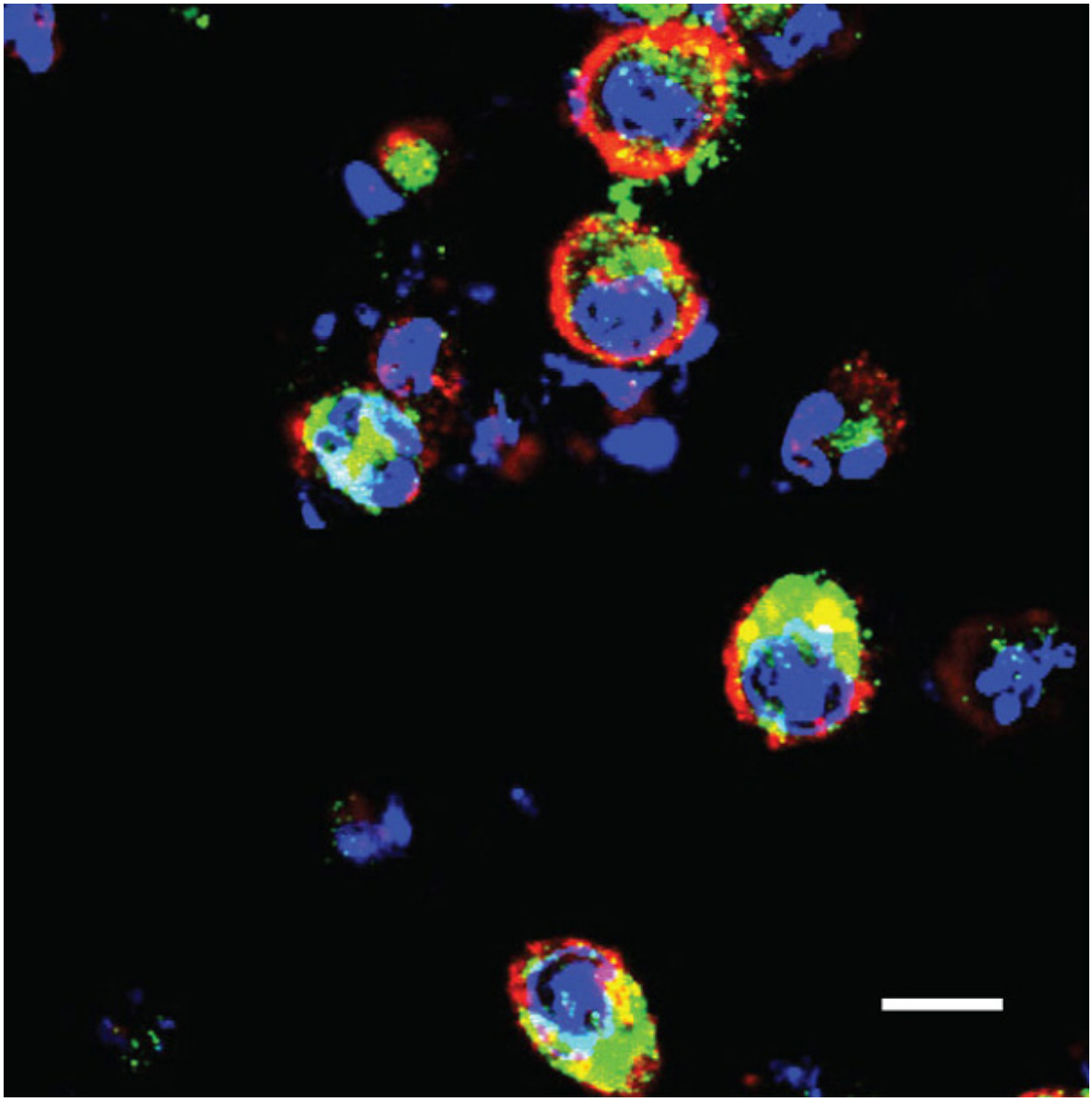

Figure Legend:

Lrg1 is expressed by wound infiltrating bone marrow cells. Immunofluorescence staining detecting LRG1 (green), CD11b (red) or DAPI (4′,6-diamidino-2-phenylindole; blue) in day-one mouse wounds. Scale bar: 120 μm and 20 μm.