Inflammation, Healing, and Genes: A Preface

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THE FOCUS OF this volume entitled “Genetic Drivers of Regeneration” is the roles inflammation plays in wound repair and regeneration.

We begin by examining the Murphy Roths Large (MRL) mouse, an autoimmune mouse with intrinsic inflammatory properties. This mouse, originally bred by crossing four different mouse strains to maintain the achondroplasia gene *cn*, is unique in its healing properties, many of which are shared with amphibian regenerative responses. Specifically, holes made in the ear pinna close unlike most other mice whose holes serve as lifelong markers. In the review by Gourevitch *et al.*¹, entitled “Inflammation and its correlates in regenerative wound healing: an alternate perspective,” an analysis of steady-state genes in the regenerative MRL and the nonregenerative B6, which heals by repair, shows that the majority of genes that are differentially expressed are involved in inflammation, tissue remodeling, metabolism, and cell cycle. Many of the inflammatory genes are mast cell associated and the data presented point to an unusual and potentially regenerative mast cell. Also, HIF1a target genes are overexpressed.

Canhamero *et al.*², in their review entitled “Acute inflammation loci are involved in wound healing in the mouse ear punch model,” present an amazing biological convergence. In

their studies of AIRmax and AIRmin mice, specifically bred and selected for high and low inflammatory responses, respectively, a parallel regenerative phenotype to that seen between the MRL and B6 was observed. AIRmax mice thus confirm a central regulatory role for inflammation in mammalian regeneration. They identify genes responsible for this function and point to the neutrophil.

The third study by Morales *et al.*³, entitled “Mapping novel subcutaneous angiogenesis quantitative trait loci in [B6×MRL]F2 mice,” focuses on angiogenesis in skin explant cultures. Explants have the obvious benefit of isolating tissue intrinsic effects, but also the less obvious advantage of isolating the target tissue from the mechanical forces of wound contracture imposed upon a punch biopsy flank skin wound, *in situ*. Again, we seen a further convergence with many similar molecules identified in MRL ear tissue, including VEGF involved in angiogenesis, a molecule induced by HIF1a as well as molecules showing differences in mast cells.

Finally, in the contribution from Long *et al.*⁴, entitled “Tight skin 2 mice exhibit delayed wound healing caused by increased elastic fibers in fibrotic skin,” a spontaneous inflammatory fibrotic condition is shown to affect wound repair. In this delayed

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healing model, two components associated with wound healing are studied. The authors show that deletion of the NLRP3 inflammasome did not remedy slow healing, but genetic deletion of elastic fibers led to normal repair in the fibrotic mice. The

lack of NLRP3 inflammasomes would be likely to reduce inflammation in the skin, and supporting the notion that inflammation is needed for good skin repair, NLRP3KO mice healed more slowly on average and in two cohorts, significantly less well.

REFERENCES

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