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TISSUE REPAIR

Biological scaffolds modulate immune cells

The immune system has an important role in wound healing and tissue repair, and the use of biomaterial scaffolds is an emerging way to drive immune-mediated tissue regeneration. Now, Sadtler *et al.* show that, in response to traumatic tissue injury, biological scaffolds induce an immune microenvironment that depends on T helper 2 (T_H2) cells to reduce inflammation and support tissue regeneration.

The authors induced muscle injury in mice and treated these mice with biological scaffolds composed of collagen or tissue-derived extracellular matrix (ECM) to investigate their immunomodulatory properties. The presence of biological scaffolds in a muscle wound dramatically increased the number of myeloid cells and lymphocytes at the injured site compared with saline-treated control mice. Furthermore, wounds treated with biological scaffolds were associated with an increased ratio of $CD4^+$ T cells to $CD8^+$ T cells. The expression of *Il4* — which encodes the canonical T_H2 cell cytokine interleukin-4 (IL-4) — increased in the presence of scaffolds, and this effect was lost in mice deficient in recombination-activating gene 1 (RAG1), which lack mature B cells and T cells. Furthermore, the expression of genes encoding proteins that are associated with T_H1 cell responses, such as interferon-γ, decreased in response to scaffold implantation. Thus, T_H2 cells seem to drive the immune microenvironment induced by the biological scaffolds.

Biological scaffolds are known to become associated with M2 macrophages during tissue regeneration. Indeed, macrophages isolated from the wounds of scaffold-treated mice showed increased expression of hallmark genes of M2 macrophages and more specifically of IL-4-activated macrophages. Expression of the M2 macrophage marker CD206 was lower in the wounds of *Rag1*$^{-/-}$ mice compared with controls; this phenotype was rescued after transfer of wild-type $CD4^+$ T cells but not when mice received T_H2-deficient T cell populations. Furthermore, the gene expression profile associated with scaffold-associated macrophages was lost in *Rag1*$^{-/-}$ mice, and the expression of several genes implicated in muscle regeneration was substantially decreased in these mice. In addition, myeloid cells from scaffold-treated *Il4*$^{-/-}$ mice expressed decreased levels of CD206 compared with those from control mice. Thus, IL-4 is required for T_H2 cell-dependent macrophage polarization to support tissue regeneration.

Finally, the authors investigated the functional effects of scaffold-induced tissue regeneration. After 6 weeks, injured and scaffold-treated wild-type mice could run similar distances as uninjured control mice. However, this effect was abolished in injured and scaffold-treated *Rag1*$^{-/-}$ mice but the effect was restored after transfer of wild-type $CD4^+$ T cells. Histological analysis showed that injured muscle treated with a tissue-derived ECM scaffold was similar to uninjured muscle after 6 weeks, whereas the injured muscle from *Rag1*$^{-/-}$ mice showed a defect in tissue regeneration.

So, in response to muscle injury, tissue-derived biological scaffolds support muscle regeneration by developing a supportive immune microenvironment that depends on T_H2 cells.

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