IMMUNOLOGY

Specific repair by discerning macrophages

Immune cells recognize organ-specific cues during repair processes

By **Tiffany Bouchery** *and* **Nicola L. Harris**

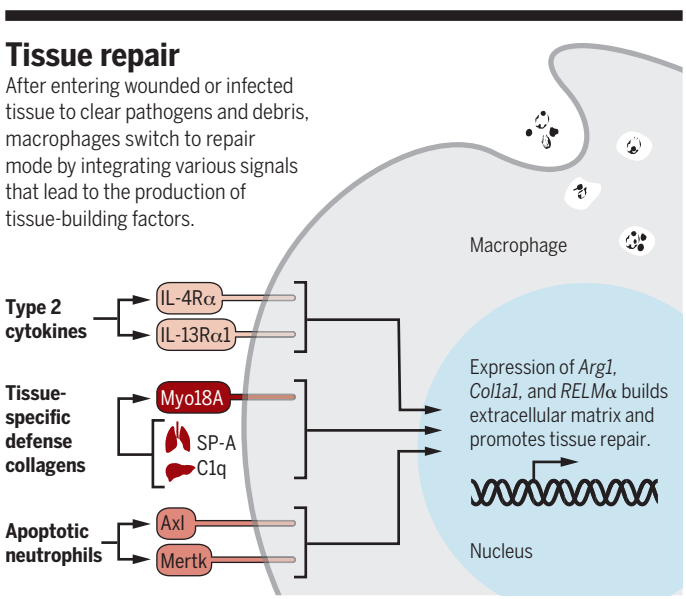
During the inflammatory response to infection or injury, macrophages are deployed to clear pathogens, dead cells, and debris. But macrophages also play a central role in subsequent tissue repair. On pages 1076 and 1072 of this issue, Minutti *et al.* (*1*) and Bosurgi *et al.* (*2*), respectively, expand our understanding of the plasticity of macrophages by demonstrating that these cells integrate signals from specific cytokines and from local "organ-specific" cues, or from sensing dying cells, before activating tissue-repair programs.

The first macrophages to enter a wound or infected area adopt an inflammatory phenotype that enables them to clear cellular debris and bacteria. They then switch phenotype and produce anti-inflammatory cytokines and other factors that dampen inflammation. When activated by the cytokines interleukin-4 (IL-4) and IL-13, macrophages produce factors that are directly involved in repair. These include collagen type I, alpha 1 (Col1a1), which forms the extracellular matrix (a collection of secreted molecules that provide structure to tissues). It also includes resistin-like molecule alpha/found in inflammatory zone (RELMα/FIZZ), which ultimately serves to cross-link collagen with fibrils, providing strength or "stiffness" to the tissue (*3*). In the mouse, arginase-1 (Arg1) is produced in macrophages activated by IL-4.

Although macrophages play a crucial role in each step of the healing process, knowledge of how macrophage plasticity is regulated to ensure efficient and tissue-appropriate repair is lacking. Minutti *et al.* discovered that defense collagens—soluble proteins involved in preventing pathogens from entering the body—enhance IL-4/13–dependent proliferation and tissue-repair functions of macrophages (see the figure). Intriguingly, macrophage tissue location dictated the type of defense collagen required to potentiate this response. In the lung, surfactant protein A (SP-A) played an essential role in a mouse model of lung helminth infection, yet SP-A could not activate macrophages in the peritoneal cavity of mice subjected to peritoneal dialysis. Instead, another defense collagen—C1q, a component of the complement pathway—enhanced peritoneal macrophage activation. C1q also promoted macrophage activation in the liver following infection with a bacterial pathogen. Both SP-A and C1q activate macrophages through the same receptor, myosin 18A (Myo18A), indicating that the tissue-specific functions of these proteins are likely dictated by distinct co-receptors. This finding should initiate a new wave of studies aimed at elucidating specific factors that match the tissue-repair function of macrophages to the specific needs of an organ.

To ensure efficient repair, macrophages must also dampen inflammation, which otherwise prolongs or impairs the process (*4*). Bosurgi *et al.* address this issue by showing that in a mouse model of helminth infection, IL-4/13–stimulated macrophages cannot initiate a tissue-repair program unless they first sense the presence of dying (apoptotic) neutrophils. During infection, neutrophils migrate to the site of injury, directly destroy pathogens, and recruit other immune cell types. The recognition and phagocytosis of apoptotic neutrophils by macrophages—a process called efferocytosis (meaning "to carry to the grave")—triggers macrophages to produce anti-inflammatory cytokines (*5*). Integration of this pathway with IL-4/13 signaling through the type I receptor [IL-4 receptor alpha (IL-4Rα) and IL-13Rα1; see the figure] and/or the type II receptor (IL-4Rα and common gamma chain) may represent a mechanism by which macrophages balance inflammation resolution with tissue repair. Bosurgi *et al.* identified the efferocytosis receptors, AXL receptor tyrosine kinase (Axl) and c-mer proto-oncogene tyrosine kinase (Mertk), as promoting IL-4/13–induced tissue repair. SP-A triggers efferocytosis and C1q increases expression of Mertk (*5*), providing a possible link between the findings of Bosurgi *et al.* and Minutti *et al.*

IL-4/13–activated macrophages can stimulate rapid tissue repair. However, prolonged IL-4/13 production results in fibrosis (scar formation) that ultimately undermines tissue function (*3, 6*). Translating these discoveries into therapeutic applications will require an understanding of how to harness the pro-repair functions of IL-4/13–activated macrophages to promote tissue regeneration (a return to the normal state of a tissue), rather than fibrosis. This will be instrumental for determining how IL-4 regulates the ability of biomaterial scaffolds to stimulate muscle regeneration (*7*) and tissue revascularization (*8*). In mammals, different tissues exhibit remarkable variance in their ability to regenerate. It is tempting to speculate that signals unique to tissues with high regenerative capacity (such as liver, gut, epithelium, and bone marrow) could be used to regulate macrophage plasticity and promote regeneration in other, less pliable tissues. ■



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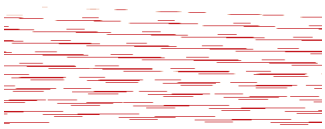

Editor's Summary

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