INFECTION

Monocytes regulate wound healing after infection via appetite hormones

Kratofil, R.M. et al. *Nature* (2022) https://doi.org/10.1038/s41586-022-05044-x

Infection, the invasion of pathogens such as bacteria into the body, triggers inflammation and the recruitment of white blood cells to the afflicted tissue. While neutrophils are essential to fight bacterial infection, the role of monocytes is less clear. In a new study published in *Nature*, Rachel Kratofil and colleagues (University of Calgary, Canada) discovered a monocyte-mediated pathway that is critical for wound repair following bacterial infection.

During infection, neutrophils are the first leukocytes to arrive in the area, followed by monocytes. "Monocytes were not clearing bacteria, they were not regulating neutrophil recruitment or clearance, they were not even migrating around when I imaged immune cell behavior," comments Kratofil. "However, we previously showed that monocytes help facilitate tissue repair after sterile injury in the liver, so we wondered whether they have a similar role in tissue repair during infection," she adds.

Using a foreign body coated with *Staphylococcus aureus* inserted in the skin of wild-type or genetically modified mice, the researchers imitated the skin-penetrating route of bacterial invasion and used imaging over time to investigate the role of monocytes in infection. They found that the recruited monocytes do not eliminate bacteria in the infected skin, but instead contribute to the elimination of infection by regulating angiogenenesis and tissue repair. Knocking-out *Ccr2*, a gene mediating monocyte attraction to the wound during infection, delayed wound healing and increased angiogenesis in the wound. "When we imaged the wounds, the vasculature perfusing the wounds was striking in the monocyte-deficient mice. We figured the monocytes must have had some turn-off mechanism (proteases etc.) to inactivate angiogenic factors", explains lead investigator Paul Kubes.

The investigators observed that impaired tissue healing in the skin of CCR2-deficient mice was accompanied by an increase in skin fat cell numbers. Adipocytes secrete peptides, such as leptin, which have a critical role in wound healing and angiogenesis but also in appetite. The researchers found that leptin blockade at the infection site of CCR2-deficient mice rescued the excessive blood vessel formation, while treatment with leptin resulted in elevated vessel growth in non-healing wounds. By contrast, treatment with ghrelin, an opposite hormone to leptin in hunger, reversed the harmful effects of leptin on angiogenesis and improved wound healing. Altogether these findings suggest that monocyte-derived ghrelin drives skin repair post-infection.

"Moving forward, we are looking at vascular growth in skin cancer to see whether leptin and monocytes affect tumor growth. We also are thinking how our story fits into poor wound healing in metabolic disorders such as diabetes and obesity," comments Kubes.

Ioannis Bakoyiannis

Published online: 15 September 2022
https://doi.org/10.1038/s41684-022-01060-6