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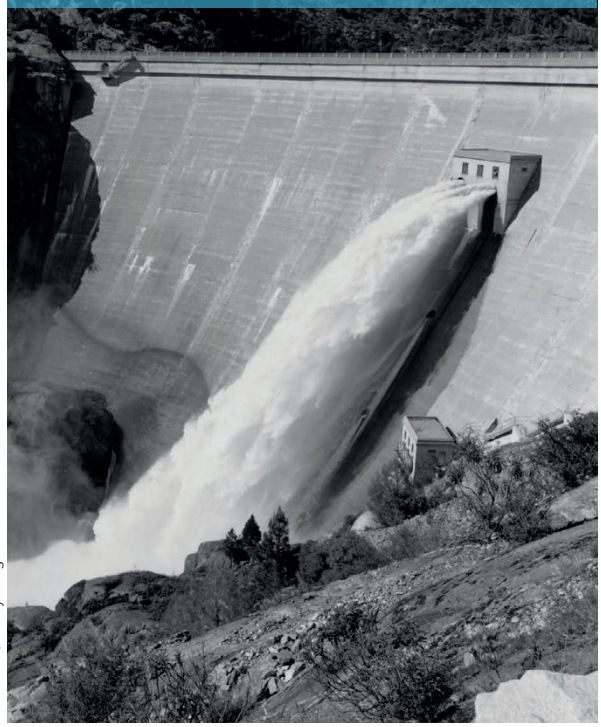
MACROPHAGES

Reservoir reinforcements



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> non-vascular recruitment of macrophages from the peritoneal cavity into the injured liver

A typical inflammatory response to tissue injury first involves the activation of tissue-resident macrophages, which then stimulate the vascular endothelium within the tissue to induce the recruitment of circulating immune cells. These include monocytes that differentiate in the tissue into additional macrophages to promote tissue repair. However, this two-step process takes time and would be affected by severe tissue damage that eradicates the tissue-resident macrophage population. Wang and Kubes now describe a new pathway for the rapid, non-vascular recruitment of macrophages from the peritoneal cavity into the injured liver.

In a mouse model of sterile, thermal injury to the liver, an F4/80^{hi} population of cells accumulated on top of the injury site, associated with necrotic hepatocytes as early as 1 hour after injury and persisted for at least 48 hours. These F4/80^{hi} cells did not move intravascularly into the injury site and were shown, using cell-depletion experiments, not to be derived from monocytes or liver-resident macrophages (Kupffer cells). Further analysis of the population confirmed the expression of several other macrophage-related (but not Kupffer cell-related) surface markers, including CD102, as well as the transcription factor GATA6, which are markers for resident peritoneal macrophages. When peritoneal macrophages were depleted, no F4/80^{hi} macrophages were found in the liver lesion. Furthermore, adoptive transfer of labelled peritoneal macrophages into the peritoneum, but not the vasculature, resulted in their recruitment to the injury site.

The recruitment of peritoneal macrophages to sites of liver injury did not depend on chemokine receptor signalling or β1 or β2 integrins, which indicates that the mechanism differs from the intravascular recruitment of immune cells. Instead, macrophage recruitment depended on ATP and expression of the adhesion molecule CD44 by macrophages. Hyaluronan, the ligand for CD44, was exposed in the injured tissue but not in the surrounding healthy tissue, and pretreatment of mice with hyaluronidase prevented the recruitment of macrophages to the injured liver.

In keeping with recent evidence that hyaluronan can induce macrophages to switch to an alternatively activated phenotype, macrophages from the liver injury site had increased levels of proliferation compared with those taken from the peritoneal cavity, and they had increased expression of markers of alternative activation, such as arginase 1. This phenotype suggests that macrophages that are recruited from the peritoneal cavity mediate tissue repair. Indeed, in the absence of macrophage influx, the revascularization and healing of the affected tissue was significantly delayed. The peritoneal macrophages were observed to pull away pieces of nuclei from necrotic cells, resulting in the release of DNA that covered the wounded area.

Thus, in contrast to the current view of tissue-resident macrophages as stationary populations, Wang and Kubes have shown that those macrophages that reside in the peritoneal cavity can be rapidly recruited by a non-vascular route to the liver to mediate tissue repair. Similar pro-repair functions were observed in a chemically induced model of liver injury, in which peritoneal macrophages adhered to the surface of the liver and penetrated into the tissue. It will be important to determine whether this new recruitment pathway can be generalized to other organs and body cavities, and possibly to other cell types such as B1 cells in the peritoneal cavity.

Kirsty Minton

ORIGINAL ARTICLE Wang, J. & Kubes, P. A reservoir of mature cavity macrophages that can rapidly invade visceral organs to affect tissue repair. *Cell* http://dx.doi.org/10.1016/j.cell.2016.03.009 (2016)