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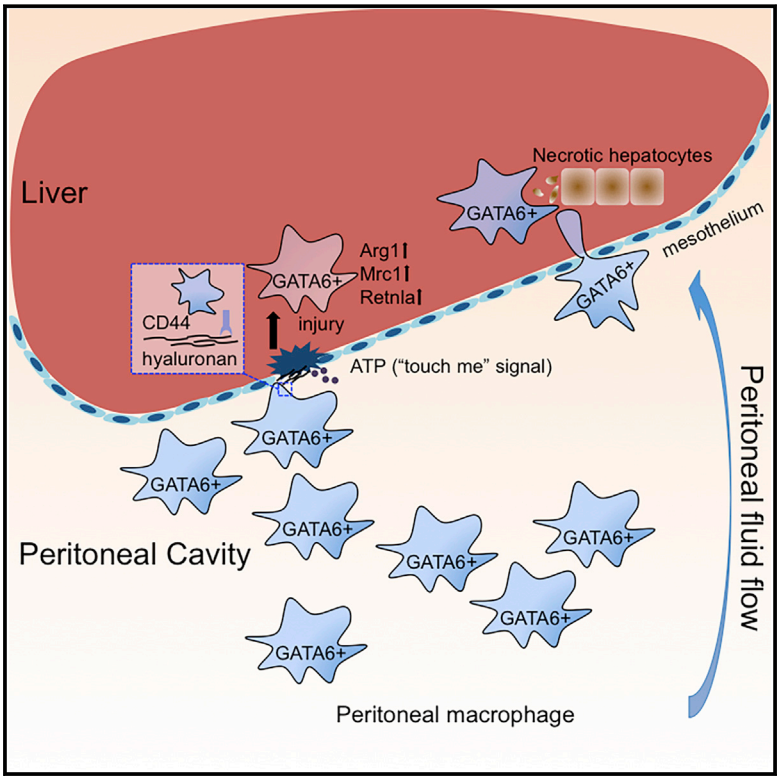
A Reservoir of Mature Cavity Macrophages that Can Rapidly Invade Visceral Organs to Affect Tissue Repair

Graphical Abstract



Highlights

- Peritoneal macrophages rapidly infiltrate an injured visceral organ
- Infiltration occurs via a non-vascular route and can go into deeper tissue
- Peritoneal macrophages in injury site adopt an alternatively activated phenotype
- Depletion of peritoneal macrophages results in lethality in acute liver injury

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In Brief

Following a sterile injury to visceral organs like the liver, a reservoir of fully mature peritoneal cavity macrophages infiltrates the afflicted tissue within an hour via a non-vascular route, isolating the injury and contributing to tissue repair.

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A Reservoir of Mature Cavity Macrophages that Can Rapidly Invade Visceral Organs to Affect Tissue Repair

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SUMMARY

A key feature of inflammation is the timely recruitment of leukocytes, including monocytes, from blood into tissues, the latter maturing into macrophages over a period of 2–3 days. Using multi-channel spinning disk microscopy, we identified a rapid pathway of macrophage recruitment into an injured organ via a non-vascular route requiring no maturation from monocytes. In response to a sterile injury in liver, a reservoir of fully mature F4/80^{hi}GATA6^{+} peritoneal cavity macrophages rapidly invaded into afflicted tissue via direct recruitment across the mesothelium. The invasion was dependent on CD44 and DAMP molecule ATP and resulted in rapid replication and switching of macrophage toward an alternatively activated phenotype. These macrophages dismantled the nuclei of necrotic cells releasing DNA and forming a cover across the injury site. Rapid invasion of mature macrophages from body cavity with capacity for induction of reparative phenotype may impact altered tissues ranging from trauma to infections to cancer.

INTRODUCTION

Inflammation in response to infection or sterile injury has been studied extensively, and certain fundamental principles have been well established. During inflammation, resident tissue macrophages as well as mast cells and other parenchymal cells are activated, stimulating endothelium to express adhesion molecules that then induce the recruitment of multiple cell types (Kim and Luster, 2015). In most cases, neutrophils are the first cells to arrive at the afflicted tissue potentially killing pathogens or clearing debris before they undergo apoptosis. A robust recruitment of monocytes ensues, and these cells are thought to remove dying neutrophils and eventually differentiate into macrophages or dendritic cells over a few days and promote tissue remodeling (Serhan et al., 2007). The tissue resident macrophages are thought to coordinate many of these events, and in some cases these cells can increase their numbers at the source through self-replication (Davies et al., 2013b; Jenkins et al., 2011). The monocyte recruitment and differentiation, however, becomes more essential if tissue is severely damaged eradicating the tissue resident macrophages. For example, *Listeria monocytogenes* infection induces early necroptotic death of the liver resident macrophages, the Kupffer cells. This triggers the proliferation and alternative activation of the recruited monocyte-derived macrophages and ultimately replaces the dead Kupffer cells (Blériot et al., 2015). In sterile inflammation, it has been shown that resident macrophages are lost after adult cardiac injury and are instead replaced by inflammatory monocyte-derived macrophages (Lavine et al., 2014). Since there is no circulating population of macrophages, a rapid recruitment of these cells is thought not to be possible.

Most vertebrates have a number of defined body cavities, surrounding the internal organs including the peritoneal cavity in which the visceral organs reside, the pleural cavity in which the lung is found and the pericardial cavity where the heart is situated. Macrophages in the peritoneal cavity have been studied extensively for their ability to phagocytose and kill invading pathogens. Recently, two physically, functionally, and developmentally different peritoneal macrophage subsets have been described (Ghosn et al., 2010). The small peritoneal macrophages (SPMs) are F4/80 low, CD11b low, and Ly6C positive, and bone marrow derived and are present as a small population under basal conditions but can be recruited from a pool of circulating monocytes into the peritoneum upon infection. SPMs phagocytose bacteria and make large amounts of nitric oxide. By contrast the large peritoneal macrophages (LPMs) are F4/80 high, CD11b high, and Ly6C negative. LPMs are maintained in the peritoneal cavity through self-renewal and are capable of undergoing rapid proliferation upon inflammation (Jenkins et al., 2011). Compared to SPMs, LPMs make much less nitric oxide and have less capacity to phagocytose bacteria. However, LPMs phagocytose apoptotic cells more effectively (Uderhardt et al., 2012). Recently, further characterization of the peritoneal macrophages revealed that LPMs but not SPMs selectively express the zinc finger transcription factor GATA-binding protein 6 (GATA6) (Gautier et al., 2014; Okabe and Medzhitov, 2014; Rosas et al., 2014). Gata6-deficient mice have fewer LPMs, and Gata6 appears to be involved in