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CELL MIGRATION

Pericytes — route planners

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Pericytes wrap around endothelial cells and have important roles in supporting the growth and maintenance of blood vessels. Previous work indicated that venular pericytes facilitate the initial extravasation of immune cells from the blood. A new study has shown that a distinct population of capillary and arteriolar pericytes supports the interstitial migration of myeloid cells and promotes their effector functions at inflamed sites.

Different subsets of pericytes are associated with distinct microvascular sites, and the pericytes that are found along arterioles and capillaries can be distinguished from other pericytes on the basis of their expression of NG2 (also known as chondroitin sulfate proteoglycan 4). Stark *et al.* found that resting NG2$^+$ pericytes expressed tumour necrosis factor (TNF) receptor 1 and various pattern-recognition receptors (PRRs), including Toll-like receptor 2 (TLR2), TLR4, NLRP3 and the formyl peptide receptor FPR2. NG2$^+$ pericytes also expressed intercellular adhesion molecule 1 (ICAM1) and further upregulated ICAM1 expression in response to treatment with TNF or PRR ligands. *In vitro* adhesion experiments showed that neutrophils and monocytes interact with pericytes in an ICAM1-dependent manner. Therefore, arteriolar and capillary pericytes can sense inflammatory stimuli and appear to increase their adhesive interactions with innate leukocytes in response to such signals.

The authors next used intravital two-photon microscopy to explore how pericytes and innate immune cells interact *in vivo*. They found that in a model of sterile skin inflammation, macrophages migrated to the interstitium and closely interacted with NG2$^+$ pericytes. Similar interactions were observed between pericytes and neutrophils in a distinct model of skin inflammation. Neutrophils and macrophages only interacted with NG2$^+$ pericytes following their initial extravasation from the blood, and further imaging studies showed that two distinct types of interaction occurred between these cells: frequent, short interactions of up to 2 minutes in duration, and less frequent, longer interactions that lasted more than 5 minutes. In keeping with a role for ICAM1 in this process, treatment of mice with ICAM1-specific blocking antibodies decreased the frequency and duration of the interactions.

The imaging studies also showed that extravasated macrophages and neutrophils increase their velocity as they approach NG2$^+$ pericytes. This suggests that NG2$^+$ pericytes actively attract innate leukocytes. Indeed, the pericytes were found to constitutively express the chemoattractants CXC-chemokine ligand 1 (CXCL1), CXCL8, macrophage migration inhibitory factor (MIF), CC-chemokine ligand 2 (CCL2) and interleukin-6, and they further increased their production of these chemoattractants following stimulation with PRR ligands. *In vitro* chemotaxis assays suggested that pericytes mainly drive neutrophil and monocyte migration via the production of MIF and CXCL8, and MIF and CCL2, respectively. The authors found that MIF not only promoted the interstitial migration of myeloid cells, but also upregulated their expression of TLRs, integrins and matrix metalloproteinases. In addition, pericyte-derived factors were found to promote neutrophil survival.

Finally, the authors compared the motility profiles of neutrophils that interacted with NG2$^+$ pericytes during extravasation and neutrophils that did not. In response to sterile skin inflammation, pericyte-interacting neutrophils migrated faster and followed straighter paths to the inflammatory foci compared with the non-interacting cells. Similar findings were also observed for macrophages. Pericyte-derived MIF was found to be essential for this more efficient migratory behaviour, as when interstitial MIF was blocked, both interacting and non-interacting leukocytes showed similar patterns of migration. The authors propose that NG2$^+$ pericytes could be an interesting target to explore for future anti-inflammatory therapies.

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ORIGINAL RESEARCH PAPER Stark, K. *et al.* Capillary and arteriolar pericytes attract innate leukocytes exiting through venules and 'instruct' them with pattern-recognition and motility programs. *Nature Immunol.* 25 Nov 2012 (doi:10.1038/ni.2477)