MACROPHAGES

Support from the locals

Inflammation that is induced by microorganisms is marked by the rapid recruitment of innate immune cells to the infected tissues. By contrast, a study published in *Science* now shows that helminth-induced tissue inflammation (which is associated with interleukin-4 (IL-4) production) is not associated with the recruitment of monocytes and macrophages, but depends on the proliferation of tissue-resident macrophages.

First, Jenkins *et al.* observed that although few monocytes are recruited to the pleural cavity following infection with the parasite *Litomosoides sigmodontis*, macrophages steadily accumulate. Second, these macrophages shared the F4/80^{hi} phenotype of tissue-resident macrophages and expressed proliferation markers. Third, deletion of blood monocytes and macrophages did not affect the increasing numbers of pleural cavity macrophages in response to *L. sigmodontis* infection. This suggested that helminth infection induces the proliferation of tissue-resident macrophages rather than the recruitment of blood monocytes.

So, how is the proliferation of tissue macrophages induced? IL-4 is produced by innate immune cells and T helper 2 cells during helminth-induced inflammation and has been associated with the accumulation and alternative activation of macrophages. Interestingly, tissue-resident macrophages proliferated less in *L. sigmodontis*-infected *Il4*$^{-/-}$ mice, whereas administration of IL-4 to wild-type mice induced the expansion of populations of peritoneal and pleural macrophages, as well as of Kupffer cells. Thus, IL-4 induces macrophage proliferation in the tissues.

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Next, mixed bone marrow chimaeras were generated, in which pleural macrophages were protected from deletion and were therefore of recipient origin. Following administration of IL-4 or *L. sigmodontis* to these chimaeras, recipient-derived pleural macrophage populations expanded, whereas donor macrophages (which were present in the blood) remained absent from the pleural cavity. This confirmed that IL-4 induces the proliferation of tissue-resident macrophages, and not the recruitment of blood macrophages.

Finally, analyses of mice treated with thioglycollate (which induces macrophage migration to the peritoneal cavity) and IL-4 showed that IL-4 can drive the proliferation and alternative activation of recruited macrophages in the tissue.

So, parasitic infections and possibly allergic responses, which both induce IL-4 production, do not initiate rapid monocyte recruitment, but instead cause the progressive IL-4-driven expansion of tissue-resident macrophage populations. However, in the presence of additional pro-inflammatory stimuli that induce monocyte recruitment, IL-4 drives the proliferation and alternative activation of the recruited cells.

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ORIGINAL RESEARCH PAPER Jenkins, S. J. *et al.* Local macrophage proliferation, rather than recruitment from the blood, is a signature of T_H2 inflammation. *Science* **332**, 1284–1288 (2011)