Functional Impact of Macrophages during tissue repair and aging

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Macrophages are innate immune cells acting as frontline sentinels against infection, but they are also involved in tissue homeostasis and repair. Infiltrating macrophages differentiate from circulating monocytes that in turn continuously renew from hematopoietic stem cells (HSC) in the adult bone marrow. However, in most tissue types and organs, resident macrophages have a different ontogeny than infiltrating macrophages: they are generated from HSC-independent progenitors and they seed their tissue of residency during embryonic development, where they persist during adulthood. While the role of macrophages in the tissue repair process, both through the initiation and the termination of inflammation, has been demonstrated, such findings need to be re-examined in the light of the existence of these two macrophage lineages, as their different times of residency in the liver and/or their ontogeny may account for the heterogeneity of macrophage functions in wound healing.

To investigate the role of the two lineages of macrophages in tissue repair, we characterized a model of acetaminophen-induced acute liver injury coupled with non-genetic and genetic pulse labelling methods to distinguish between the two macrophage lineages.

After acute injury, liver resident macrophages self-maintain by local proliferation without input from monocyte-derived infiltrating macrophages recruited to the injury site. Moreover, as the ability to repair injured tissues is altered with aging, we investigated whether macrophage function is impaired during aging and if the origin of resident macrophages changes with time, as proposed in the heart. We report that while there is a decrease in the density of HSC-independent resident macrophages in most tissues, we do not observe significant changes in gene expression patterns or in phagocytosis ability with age in liver resident macrophages. We then demonstrated that proliferative exhaustion is not responsible for macrophage loss but that sustained inflammation (over time) is one of the mechanisms driving resident macrophage loss without replacement from monocytes.

This uncompensated decrease in macrophage density could play a role in the impairment of tissue repair with ageing. We propose that exploring the relationship between macrophage origin and functions could provide insights into tissue homeostasis and repair mechanisms and help design tools to improve these processes.

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