Inflammation and repair in the ischaemic myocardium

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Summary
Shortly after myocardial infarction, various circulating leukocyte subsets accumulate in the heart. Leukocyte recruitment is highly coordinated and relies on cell production in the bone marrow, mobilization to the blood, and chemokine-mediated infiltration to the destination tissue. Neutrophils, which are phagocytic and inflammatory, are among the first leukocytes to accumulate in large numbers. Within a day, neutrophils disappear and are replaced by a subset of monocytes that further contribute to inflammation and phagocytosis. After a few days, monocyte-derived reparative macrophages accrue, quell inflammation, and foster angiogenesis and tissue remodelling. Studies suggest a well-balanced response comprising these three waves is essential to optimal infarct healing.

Myocardial infarction (MI) is a leading cause of death worldwide (1, 2). Although the MI mortality rate has declined over the last 50 years thanks to medical innovations, scientific discoveries, and public health improvements, the total number of MI deaths is rising. Patients who initially survive MI must endure a major obstacle: ischaemia damages the heart, and effective cardiac repair likely requires a precise balance between removal of debris and formation of a scar that is compatible with sufficient heart function.

Within the first year, MI survivors frequently develop heart failure, and while many therapeutics are beneficial, the continued high mortality indicates an unmet clinical need that requires a better understanding of the disease’s pathophysiology.

Decades of research have detailed the underlying biology of heart failure, with particular emphasis on cardiomyocytes, cardiac fibroblasts, and stem cells (3–27). By comparison, we know little about how leukocytes, the circulating white blood cells that respond to injury and infection, participate in infarct healing. Recent studies show, however, that leukocytes are more important than previously thought. Here, I take a closer look at leukocytes belonging to the myeloid lineage, although lymphocytes have also been receiving attention (28, 29).

The three waves
Neutrophils

Neutrophils are the first leukocytes to accumulate at sites of injury or infection. Produced in the bone marrow and recruited to tissue from the blood, neutrophils are in many ways the quintessential inflammatory cells. They are large, abundant, short-lived, and can be easily identified morphologically by their characteristic segmented nuclei. Neutrophils are highly phagocytic cells containing granules filled with various defensins, elastases, cathepsins, cathelicidins, phosphatases, oxidases, and collagenases, and their primary function is to amplify the inflammatory response. As producers of neutrophil extracellular traps (NETs), neutrophils can ensnare bacteria to limit infection. In response to myocardial infarction, neutrophils accumulate copiously in the heart, peaking within 24 hours of injury. In this setting neutrophils likely phagocytose dead cardiomyocytes, digest debris, and augment the inflammatory response, although this is yet to be conclusively shown.

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Monocytes

At the height of the neutrophil peak, a different leukocyte type invades the infarcted myocardium. We have known since the 1980s that the human blood contains at least two subsets of monocytes, which are large, bone marrow-derived myeloid leukocytes capable of differentiating to macrophages in tissue (30). Importantly, identifying monocyte heterogeneity suggested that monocytes are predisposed to enter specific tissue and thus are more committed to particular fates than previously believed.

The concept was tested experimentally following recognition that mouse blood likewise contains monocyte subsets that can be distinguished from one another by their differential migratory properties and expression of various surface markers (31). In the infarcted myocardium, bone marrow-derived Ly-6C<sup>high</sup> monocytes, expressing the glycoprotein Ly-6C and the chemokine receptor Ccr2 at high levels, infiltrate the heart when neutrophil numbers begin to wane. Upon tissue accumulation, Ly-6C<sup>high</sup> monocyte scavenge dead cells and debris and produce inflammatory cytokines (e.g. IL-1β, TNFα, IL-6) and proteases; it is helpful to think of Ly-6C<sup>high</sup> monocytes as a “clean-up” crew that removes dead tissue to make way for the formation of a durable scar. Ly-6C<sup>high</sup> monocytes are important because their depletion dramatically compromises the heart’s ability to heal (32). Not only are Ly-6C<sup>high</sup> monocytes needed, but they are needed in sufficient numbers to replace their predecessors, which have already died or exited.

Perhaps because of this increased demand for continuous supply, the bone marrow outsources Ly-6C<sup>high</sup> monocyte production to the spleen (33). Compared to the neutrophil peak, which is sharp and narrow, Ly-6C<sup>high</sup> monocytes persist in the myocardium for several days.

Macrophages

Approximately 5 days after myocardial infarction (in the mouse), there is a third leukocyte wave, this time consisting of Ly-6C<sup>low</sup> macrophages. These cells are bigger than monocytes and less inflammatory, and they produce generous amounts of the anti-inflammatory IL-10, profibrotic TGFβ, and angiogenic VEGF. Consequently, Ly-6C<sup>low</sup> macrophages are reparative, resolve inflammation, and contribute to new blood vessel formation. They are also proficient efferocytes (34), expressing the classic macrophage marker and efferocytosis mediator, MerTK (35). Ly-6C<sup>low</sup> macrophages persist in the myocardium for many more days and perhaps never entirely disappear, although their numbers return to steady-state levels two weeks after MI. Despite their similar Ly-6C expression, Ly-6C<sup>low</sup> macrophages are not produced by Ly-6C<sup>low</sup> monocytes. Careful fate-mapping studies using Nr4a1 deficient mice have recently shown that Ly-6C<sup>high</sup> monocytes differentiate to Ly-6C<sup>low</sup> macrophages in the heart (36). Ly-6C<sup>low</sup> macrophages, on the other hand, infiltrate the heart at low levels but do not differentiate to macrophages. We can confidently conclude that Ly-6C<sup>low</sup> macrophages do not derive from Ly-6C<sup>low</sup> monocytes because the Nr4a1-deficient mouse lacks Ly-6C<sup>low</sup> monocytes (37), yet still produces Ly-6C<sup>low</sup> macrophages in the tissue.

### Conclusion

Three sequential myeloid accumulation waves occur in the infarcted myocardium.

- Neutrophils infiltrate on the first day and disappear shortly after.
- Next, Ly-6C<sup>high</sup> monocytes arrive from the bone marrow and spleen and peak on day 3.
- Finally, Ly-6C<sup>high</sup> inflammatory monocytes differentiate to reparative Ly-6C<sup>low</sup> macrophages and dominate on day 7 (32, 33, 38–42) (Fig. 1).

Although the precise role of Ly-6C<sup>low</sup> monocytes is still undetermined, it is possible these cells patrol the vasculature, as has been shown in other contexts (43).

### Future Perspectives

Recent studies show that macrophages are essential to both cardiac recovery following injury (44) and limb regeneration (45). Balance is key to macrophage function during healing. On one hand, infarcted hearts in mice depleted of macrophages rupture and the host, likely due to impaired collagen deposition, defective clearance of necrotic cells, and poor angiogenesis. On the other hand, heightened monocyte/macrophage numbers are harmful and may cause post-MI heart failure.

Because monocytes/macrophages are functionally heterogeneous — i.e. are they inflammatory and proteolytic or reparative and angiogenic? — attempts at indiscriminate depletion are likely to fail (42, 46–50). Therapeutic strategies targeting myeloid cells to ameliorate post-MI heart failure must carefully consider cell heterogeneity, timing, and tissue localization.

### Conflict of interest

The author declares that he has no conflict of interest.
References


