REVIEW ARTICLE

Cardiac macrophage biology in the steady-state heart, the aging heart, and following myocardial infarction

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Macrophages play critical roles in homeostatic maintenance of the myocardium under normal conditions and in tissue repair after injury. In the steady-state heart, resident cardiac macrophages remove senescent and dying cells and facilitate electrical conduction. In the aging heart, the shift in macrophage phenotype to a proinflammatory subtype leads to inflammaging. Following myocardial infarction (MI), macrophages recruited to the infarct produce both proinflammatory and anti-inflammatory mediators (cytokines, chemokines, matrix metalloproteinases, and growth factors), phagocytize dead cells, and promote angiogenesis and scar formation. These diverse properties are attributed to distinct macrophage subtypes and polarization status. Infarct macrophages exhibit a proinflammatory M1 phenotype early and become polarized toward an anti-inflammatory M2 phenotype later post-MI. Although this classification system is oversimplified and needs to be refined to accommodate the multiple different macrophage subtypes that have been recently identified, general concepts on macrophage roles are independent of subtype classification. This review summarizes current knowledge about cardiac macrophage origins, roles, and phenotypes in the steady state, with aging, and after MI, as well as highlights outstanding areas of investigation. (Translational Research 2017;■:1–14)

Abbreviations: AV = atrioventricular; CCL = chemokine C-C motif ligand; CCR = chemokine C-C motif receptor; CXCL = chemokine C-X-C motif ligand; CX3CR = chemokine C-X3-C motif receptor; ECM = extracellular matrix; GM-CSF = granulocyte macrophage colony-stimulating factor; HSC = hematopoietic stem cell; IFN = interferon; IL = interleukin; LPS = lipopolysaccharide; MERTK = myeloid epithelial reproductive tyrosine kinase; MHCII = major histocompatibility complex class II; MI = myocardial infarction; MMPs = matrix metalloproteinases; TGF-β1 = transforming growth factor-β1; TNF = tumor necrosis factor

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INTRODUCTION

Macrophages were first identified by Ilya Ilyich Mechnikov in 1882 and belong to the vertebrate first-line defense system against infection and injury.[1] With the advent of genetic fate mapping and tracing techniques (cell reporter lines, parabiosis, bone marrow transplant, and intravital microscopy), our understanding of macrophage physiology has been revolutionized over the past decade. We now know that macrophages reside in all organs in the steady state.[2] Tissue resident macrophages persist from embryogenesis into adulthood and minimally rely on monocyte infiltration for renewal, with the exception of skin and gut macrophages that depend on monocyte entry to maintain numbers.[3,4] In response to infection or injury, circulating monocytes are mobilized to inflamed tissue and differentiate into macrophages, which constitute the majority of the macrophage population during the acute inflammatory phase.[5]

In the steady state, tissue resident macrophages exert homeostatic functions, including defending against infection and removing senescent or damaged cells. Moreover, macrophages exhibit distinct organ and tissue-specific physiological functions. For instance, skin macrophages participate in regulating salt-dependent extracellular volume and blood pressure homeostasis.[6] In adipose tissue, macrophages generate catecholamines to sustain adaptive thermogenesis and promote insulin resistance by nuclear receptor co-repressor–dependent mechanisms.[7,8] Peritoneal macrophages orchestrate migration of immunoglobulin A-producing B cells to the intestine, where they play a key role in the early response to pathogens.[9] Macrophages are also involved in erythrocyte removal and iron recycling in the liver, synaptic pruning and normal brain development, and hematopoietic control in the bone marrow and spleen.[10-12]

In addition to maintaining equilibrium, the macrophage plays an indispensable role in response to injury, including myocardial infarction (MI) both in the presence and absence of reperfusion. The importance of macrophages during post-MI remodeling has been highlighted by studies in which depletion of macrophages by clodronate liposomes compromises cardiac repair in mouse MI models.[13,14] Following MI, macrophages can secrete proinflammatory, anti-inflammatory, proangiogenic, or proreparative factors; can phagocytize dying cells; and can directly interact with other cell types to orchestrate the repair response.[15,16] The diverse functions of macrophages are partially attributed to their different phenotypes and polarization status. Macrophage polarization is a process by which macrophages exhibit vastly different gene expression profiles and functions in response to extremes in environmental signals. Post-MI macrophages show a proinflammatory M1 phenotype early and an anti-inflammatory M2 phenotype later, with these phenotypes playing distinct and even opposite roles.[17,18] In this review, we will discuss current literature regarding cardiac macrophage origins, roles, and phenotypes in the steady state, the aging heart, and post-MI, as well as emphasize outstanding areas of investigation to complete our understanding of macrophage polarization in the heart.

MONOCYTE/MACROPHAGE MARKERS

Monocytes and macrophages have been assessed by multiple approaches using a variety of markers to label cells and cell subtypes. Table I provides a comprehensive list of monocyte and macrophage markers that have been used. Ly6C/Gr-1 is expressed in rodents, but not in humans, whereas all other markers in Table I are expressed in both rodents and humans. Single-marker labeling is commonly used in experiments with immunohistochemistry, immunoblotting, or immunofluorescence approaches. One underappreciated concept is the fact that the marker used to identify cell type by itself has biological functions. For instance, the most commonly used macrophage marker F4/80 has proinflammatory properties and can induce antigen-specific regulatory T cells (Tregs).[33] Distinct gating strategies using flow cytometry can delineate monocyte and macrophage origin and subset types based on marker expression patterns. Table II summarizes current gating strategies to discriminate distinct blood and cardiac monocyte and macrophage phenotypes under steady state and after injury. In addition, the Macrophage Community Website (www.macrophages.com)[51] and the Immunological Genome Project (www.immgen.org) provide excellent macrophage database resources.

MACROPHAGES IN THE STEADY STATE HEART

Macrophage origins. The earlier dogma that macrophages are exclusively derived from circulating monocytes generated by the bone marrow and spleen has been challenged.[52] In the past decade, a growing body of literature demonstrates that tissue resident macrophages, in the brain, spleen, liver, lung, bone marrow, kidney, pancreas, peritoneum, and heart are established prenatally, persist throughout the life span, and self-renew locally.[53,54] In the steady state, resident cardiac macrophages in mice are reported to account for approximately 5%–10% of nonmyocytes in the heart.[43,55] Resident macrophages adopt a spindle-like shape and intermingle closely with myocytes, endothelial cells, and fibroblasts.[43] Genetic fate