Macrophage Heterogeneity and Functions in Cardiovascular Diseases

Subjects: Cardiac & Cardiovascular Systems

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Cardiovascular diseases (CVDs) are the leading cause of hospitalization and death worldwide, especially in developing countries. The increased prevalence rate and mortality due to CVDs, despite the development of several approaches for prevention and treatment, are alarming trends in global health. Chronic inflammation and macrophage infiltration are key regulators of the initiation and progression of CVDs. Macrophage polarization is a unique phenotypic phenomenon where macrophages exhibit a particular functional response to the microenvironment. Macrophage activation produces distinct functional phenotypes that maintain homeostasis primarily by modulating the release of pro-and anti-inflammatory cytokines.

epigenetics macrophage polarization N6-methyladenosine Cardiovascular diseases

1. Introduction

Cardiovascular diseases (CVDs) are the leading diseases in terms of prevalence and mortality and associated with serious health and socioeconomic burden globally. Despite significant advancements in treatment and prevention, CVDs remain the major cause of death worldwide [1]. It is estimated that more than 17.9 million people die from CVDs each year [2]. CVDs are chronic, progressive diseases that irreversibly alter the myocardial architecture and ultimately lead to complications, such as arterial thrombosis and ischemic stroke [3].

Arterial hypertension, alcoholism, cholesterolemia, diabetes mellitus, obesity, and smoking are the most common risk factors associated with CVDs [4]. Furthermore, infection and inflammatory conditions increase the risk of CVDs. Severe inflammation produces a variety of complications, including atherosclerosis, viral myocarditis, and myocardial damage [5][6][7]. Recent genome-wide association studies (GWAS) and massively parallel sequencing or next-generation DNA sequencing (NGS) have provided insight into the genetic and epigenetic factors underlying CVDs [8][9][10]. In particular, epigenetic modifications refer to chemical modifications of DNA or histones that are associated with changes in gene expression [11], and have recently been linked to macrophage polarization and CVDs.

Cardiac macrophages may also contribute to cardiomyocyte-mediated inflammation and the modulation of electrical conduction in the heart [12][13]. Macrophages are heterogeneous cells found in all organ systems and play significant roles in innate and adaptive immunity, hematopoiesis, vasculogenesis, reproduction, and systemic metabolism [14]. Macrophages exhibit distinct functional phenotypes based upon their activation states [15],

characterized as naïve/non-activated macrophages (M0), classically activated macrophages (M1), and alternatively activated macrophages (M2) [16]. M0 macrophages can be polarized toward pro- or anti-inflammatory phenotypes by different stimuli [17]. M1 macrophages have pro-inflammatory properties and are responsible for host defense and pathogen clearance [18]. M2 macrophages are essential for the resolution of inflammation, wound healing, and tissue repair [18][19]. M1 macrophages can be induced from M0 macrophages by lipopolysaccharides (LPS) and interferon (IFN)-γ; and M2a, M2b, and M2c can be induced from M0 by IL-4/IL-13, immune complexes/LPS/IL-1β, and IL-10/glucocorticoids/transforming growth factor (TGF)-β, respectively [17].

Cardiac macrophages are involved in diverse biological functions, including phagocytosis, antigen presentation, and immune regulation via the production of distinct cytokines and growth factors [20]. Cardiac macrophages not only trigger damaging inflammatory responses but are also involved in tissue repair and myocardial regeneration [21]. In disease, chronic inflammation modulates the macrophage response and induces a phenotypic shift leading more toward a pro-inflammatory phenotype. These changes are associated with epigenetic and transcriptional reprogramming and are modulated by epigenetic enzymes and transcription factors [22]. For example, macrophage dysregulation in atherosclerosis is associated with the complexity of the disease [23]. Recently, studies have shown that epigenetic modifications, such as DNA methylation, histone modifications, and RNA regulation, are significantly involved in the differential activation of macrophages and contribute to macrophage polarization [24], thereby serving as potential therapeutic targets for the treatment of various CVDs [25].

2. Macrophage Heterogeneity and Functions

Macrophage polarization is a unique phenotypic phenomenon where macrophages exhibit a particular functional response to the microenvironment [26]. Macrophage activation produces distinct functional phenotypes that maintain homeostasis primarily by modulating the release of pro-and anti-inflammatory cytokines [27]. The M1 macrophage phenotype is activated by granulocyte-macrophage colony-stimulating factor (GM-CSF), and toll-like receptor (TLR) or IL-1R ligands and secretes pro-inflammatory cytokines, such as interleukin (IL)-1β, IL-6, IL-12, IL-23 [28][29], tumor necrosis factor α (TNF-α) [30], and reactive oxygen intermediates [31]. Furthermore, they express specific biomarkers, including CD86, CD83, CD80, CD68, CD40, and major histocompatibility complex class I (MHC-I) [32]. M2 macrophages produce anti-inflammatory cytokines, including IL-10, IL-4, TGF-β, and arginase-1 (Arg-1); and exhibit elevated expression of CD206, CD204, and CD163 on the cell surface [33]. An imbalance between M1 and M2 macrophage populations is associated with left ventricle (LV) remodeling and heart failure (HF) [34]. Cardiac macrophages maintain a homeostatic population owing to their self-proliferative properties and are independent of monocyte-derived macrophages in the blood [35]. Studies have shown that the heart exhibits a distinct subset of macrophages that can be differentiated by the cell surface expression of C-C chemokine receptor type 2 (CCR2). The presence or absence of CCR2 is considered a robust marker of macrophage origin and phenotype. Further, CCR2 expression distinguishes monocyte-derived cardiac macrophages from those that are embryonic in origin. $CCR2^{+}$ and CCR^{-} macrophage subsets exhibit distinct functions and gene expression profiles [36]. Cardiac $CCR2^{+}$ macrophages originate from bone marrow-derived monocytes and are involved in immune surveillance, neutrophil recruitment, inflammatory cytokine production, and adverse myocardial remodeling,

whereas CCR2^{-} macrophages originate from fetal monocyte progenitors and the primitive yolk sac and are involved in the clearance of apoptotic cells, production of anti-inflammatory cytokines, angiogenesis, and cardiomyocyte proliferation [20][37]. The distinct sets of CCR2^{+} and CCR^{-} tissue-resident macrophages have been reported in the human myocardium (**Figure 1**). In the adult heart, two resident cardiac macrophage subsets (MHC-IIlowCCR2^{-} and MHC-IIhighCCR2^{-}), a monocyte-derived macrophage population (MHC-IIhiCCR2^{+}) and a monocyte population (MHC-IIloCCR2^{+}), have been identified by a combination of flow cytometry and genetic lineage tracing techniques; the injured adult heart selectively recruits monocytes and MHC-IIhiCCR2^{+} monocyte-derived macrophages [20]. Furthermore, cardiac macrophages facilitate electrical conduction in the heart, and their depletion can exacerbate myocardial remodeling and dysfunction, highlighting the role of resident cardiac macrophages in the pathophysiology of CVDs [21].

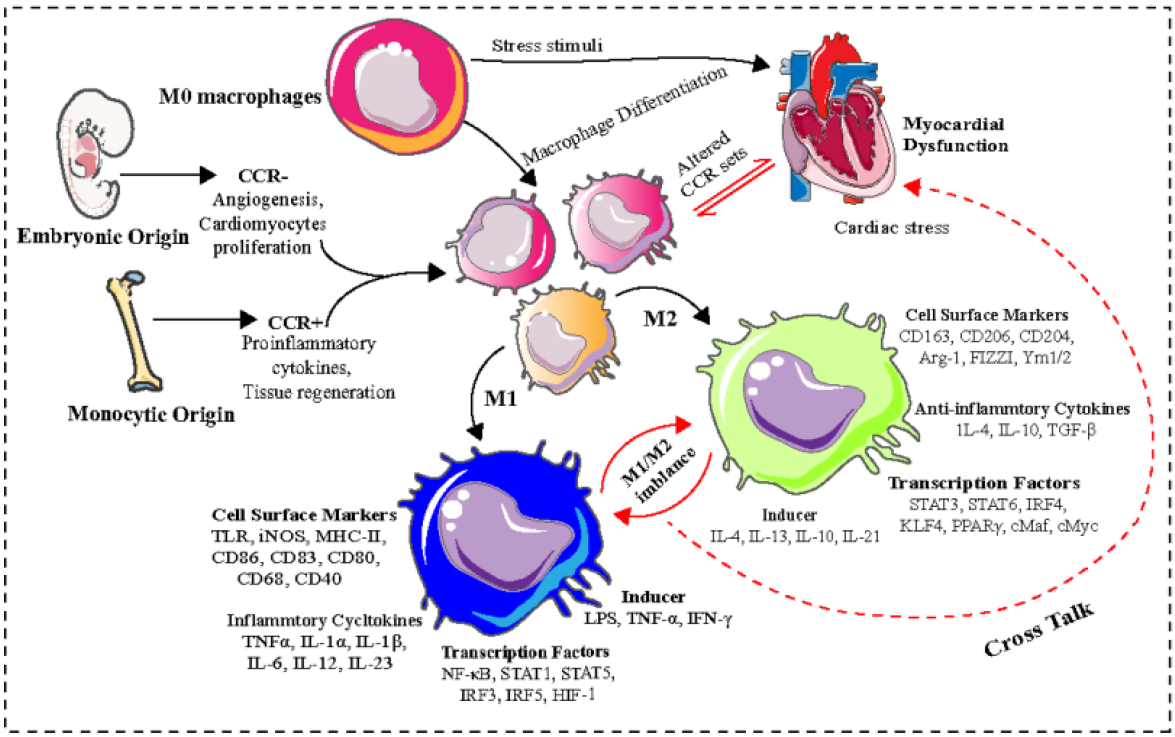

Figure 1. Macrophage polarization and its association with myocardial dysfunction. Macrophage polarization is a unique phenotypic expression wherein macrophages exhibit a particular functional response to the host immune system in both healthy and pathological conditions. Macrophages are also involved in triggering an inflammatory response, immune control, and adaptive immune response; whereas the imbalance between M1/M2 macrophage populations has been reported to be associated with ventricle remodeling and myocardial dysfunction. Abbreviations: CCR, C-C chemokine receptor type; M0, naïve/non-activated macrophages; LPS, Lipopolysaccharides; TNF-α, Tumor necrosis factor alpha; IFN-γ, Interferon gamma; TLR, Toll-like receptors, iNOS, Inducible nitric oxide synthase; MHC, Histocompatibility complex; CD, Cluster of differentiation; IL, Interleukin; Arg-1, Arginase 1; FIZZ1, Resistin-like molecule alpha1; TGF-β, Transforming growth factor beta; M1/M2, Macrophages; NF-κB, Nuclear factor kappa-light-chain-enhancer of activated B-cells; STAT, Signal transducer and activator of transcription; IRF, IFN regulatory factor; HIF-1, Hypoxia-inducible factor 1; KLF4, Krüppel-like factor 4;

PPAR, Peroxisome proliferator- activated receptor; cMaf, transcription factor c-Maf; cMyc, c-Myc multifunctional transcription factor.

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