Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in
Biomedical Engineering

Monocytes and macrophages in heart valves: Uninvited guests or critical performers?

Sraeyes Sridhar, Duc H. Pham, Terence W. Gee, Joanna Hua and Jonathan T. Butcher

Abstract

Monocytes and macrophages are critical components of the myeloid niche of the innate immune system. In addition to traditional roles as phagocytes, this subsection of innate immunity has been implicated in its ability to regulate tissue homeostasis and inflammation across diverse physiological systems. Emergence of discriminatory features within the monocyte/macrophage niche within the last 5 years has helped to clarify specific function(s) of the subpopulations of these cells. It is becoming increasingly aware that these cells are likely implicated in valve development, disease, and tissue engineering outcomes. This review seeks to use current literature and opinions to show the diverse roles and potential contributions of this niche throughout valvulogenic processes, adult homeostatic function, valve disease mechanisms, and tissue engineering approaches.

Addresses

Nancy E. and Peter C. Meinig School of Biomedical Engineering, United States

Corresponding author: Butcher, Jonathan T (jtb47@cornell.edu)

Current Opinion in Biomedical Engineering 2018, **5**:82–89

This review comes from a themed issue on **Futures of Biomedical Engineering: Vascular Biomechanics**

Edited by **Alison L. Marsden**

Received 24 October 2017, revised 31 January 2018, accepted 20 February 2018

https://doi.org/10.1016/j.cobme.2018.02.003

Keywords

Immunology, Calcification, Cardiovascular, Tissue engineering, Valvulogenesis, Aortic valve, Host response.

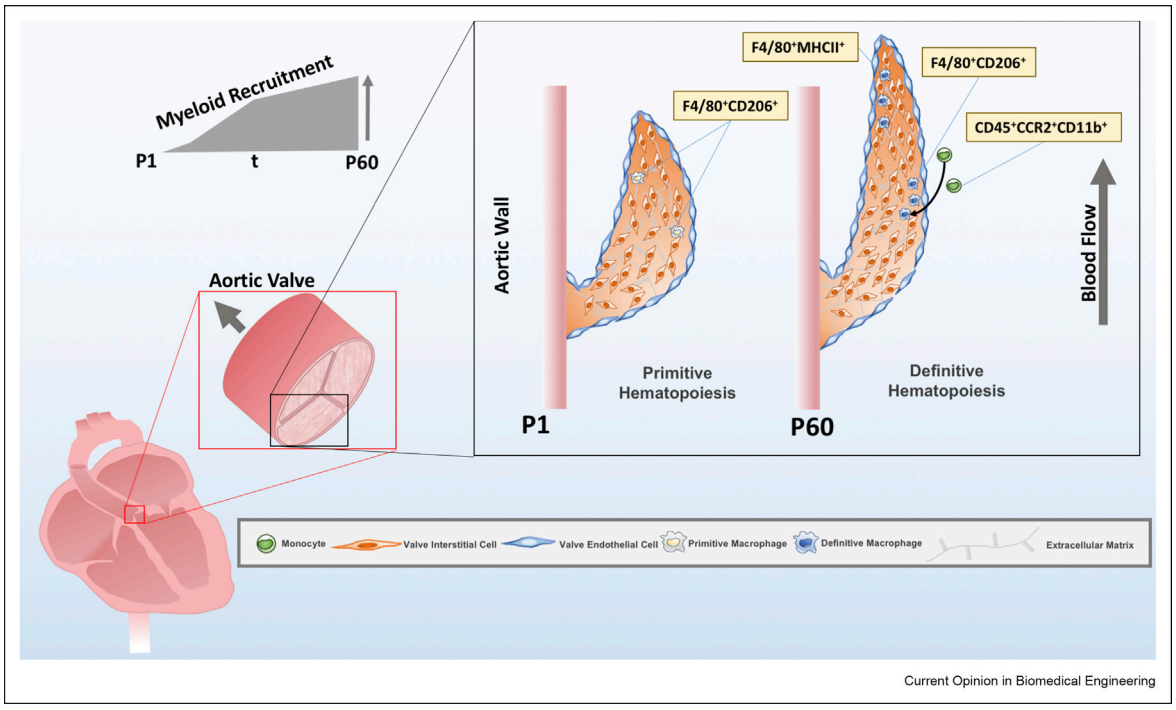
Introduction

Monocytes and macrophages are well known components of the innate immune system that can regulate inflammation, tissue homeostasis, wound repair, and disease [1]. Their ability to regulate not only cytokine/chemokine-mediated inflammatory events, but also actively remodel tissue matrices and regulate fibrosis has been implicated in many disease pathologies [2–4]. The heart valve has shown to be a tissue that is readily associated with hematopoietic-mediated maintenance at homeostasis. While fibrosis and macrophage infiltration during degenerative disease processes are well known hallmarks of valve disease, the specific roles of macrophages in driving disease and facilitating homeostatic function remain elusive [5]. Yet, there is a growing body of literature highlighting an increased awareness of these cells in valvular development and disease. This niche also has great importance in the current and future engineering strategies for valve replacement [6,7]. This review seeks to highlight potential contributions of monocytes and macrophages throughout valvulogenic processes, disease mechanisms, and tissue engineering approaches. (see Figures 1 and 2).

Monocytes

Monocytes are circulatory precursors to macrophage populations, originating either from the yolk sac or the fetal liver [8]. These cells arise from myeloid progenitors, such as common monocyte progenitors (cMoP) or monocyte and dendritic progenitors (MDP) [9,10]. Beyond their involvement in phagocytic processes, they undergo both inflammatory and anti-inflammatory cytokine production and contribute to endothelial regulation [11]. Monocytes are currently categorized into three functional states: classical, non-classical, and intermediate [12]. Classical, or inflammatory, monocytes (IMs) are functionally considered to be $CD14^{+}$ (lipopolysaccharide [LPS] receptor) and $CD16^{-}$ (Fcγ receptor III) in humans, $CCR2^{high}$ (chemokine receptor 2), $Ly6C^{high}$, and $CX3CR1^{low}$ (chemokine receptor of CX3CL1) in mice, and $CD43^{low}$ in rat [1,13]. These cells account for 80–90% of all circulating monocytes in blood [14]. Non-classical, or anti-inflammatory, monocytes (AMs) are considered to be $CD14^{+}$ and $CD16^{+}$ in humans, $CCR2^{low}$, $Ly6C^{low}$, and $CX3CR1^{high}$ in mice, and $CD43^{high}$ in rat [1]. Unlike their inflammatory counterparts, these cells are implicated in their ability to regulate matrix remodeling and anti-fibrotic activity [15]. $CD14^{+}CD16^{+}$ monocytes have also been shown to be $CD32^{+}$ (Fcγ receptor II), $CD64^{+}$ (Fcγ receptor I). Some literature points to a third monocyte subset that is $CD16^{+}$ but $CD14^{-}$ [16]. These are referred to as intermediate monocytes, with low Fc receptor expression, low phagocytic activity, and decreased antigen presentation capacity [17]. Although no studies have demonstrated the roles of these monocyte subtypes in pathology, some have shown that these cells are upregulated during sepsis [18].

Figure 1



Valve development. Macrophages localize themselves in the interstitial layer of the valve leaflet at the commissure and distal tip. During post-natal maturation, embryonically derived macrophages display CD206+ markers in early on and later MHCII+ populations emerge at the distal tip after the establishment of definitive hematopoiesis. Between P1 to P60 leukocyte presence in the valve increases from ~5% to ~12% in the aortic valve. CD206+ and MHCII+ macrophages are believed to have analogues M2 and M1 macrophages respectively, which may have functions in post-natal maturation processes or local leukocyte response to variable hemodynamic loading.

Macrophages

In mice, embryonic macrophages in the heart arise from two hematopoietic events. During primitive hematopoiesis (E7.5-E11.5), yolk sac progenitors develop into macrophages that populate throughout the embryo [8]. By means of definitive hematopoiesis (E11.5 and E16.5), fetal liver hematopoietic stem cells (HSCs) differentiate into monocytes that circulate, take residence, and give rise to tissue-specific macrophages [19]. In the heart, yolk sac-derived macrophages are present as early as E9.5[19]. At E13.5, fetal liver monocytes begin to invade cardiac tissue, differentiate into a small contingent of resident macrophages, and proliferate [20]. By E18.5, the population of primitive macrophages becomes overwhelmingly diluted by cardiac-specific monocyte-derived macrophages [21]. Bone marrow-derived monocytes replace yolk sac and fetal macrophages soon after human birth in many systems [22]. There are some tissues that retain yolk-sac derived macrophage populations into adulthood. It has been shown that in some cardiac diseases such as myocardial infarction, tissue-resident macrophages are outcompeted by bone marrow-derived macrophages, which facilitate a loss of niche homeostatic function [23].

Postnatally, $CCR2^{high}Ly6C^{+}$ inflammatory and $CCR2^{low}Ly6C^{-}$ anti-inflammatory monocytes differentiate into classical, inflammatory, or M1 macrophages and non-classical, anti-inflammatory, or M2 macrophages from hematopoietic origins. Viewing M1/M2 phenotypes as a lineage dichotomy greatly oversimplifies actual macrophage phenotypic fluidity and context dependent functionality. For example, early studies have shown that macrophages can transdifferentiate between phenotypes [24]. Further, it is not just M2 phenotypes that are beneficial for tissue healing and reparative remodeling, but combinations of M1 and M2 act synergistically to improve tissue healing speed and ECM characteristics [25]. Subpopulations within the M2 spectrum have shown to be valid *in vitro* targets or extremes with functional differences such as M2a (inflammatory resolution), M2b (immunoregulatory), and M2c (tissue remodeling). M1 inflammatory macrophages exposed to classic activation signals, such as IFNγ and LPS, express opsonic receptors, while M2 anti-inflammatory macrophages express more non-opsonic receptors. M1 polarization involves the synthesis of pro-inflammatory cytokines, such as tumor necrosis factor α (TNFα), interleukin 1-β (IL1β), interleukin 6 (IL6), and expression of surface markers,