Austin Journal of Clinical Cardiology

Open Access

Austin Publishing Group

Mini Review

Recent Advances in the Pathophysiological Role of Neutrophils and Macrophages following Acute Myocardial Infarction

Shi H* and El Kazzi M

Redox Biology Group, Discipline of Pathology, Faculty of Medicine and Health, Charles Perkins Centre, The University of Sydney, Sydney, Australia

***Corresponding author: Shi H**

Han Shi, Redox Biology Group, Discipline of Pathology, Faculty of Medicine and Health, Charles Perkins Centre, The University of Sydney, Sydney, New South Wales 2006, Australia

Received: January 18, 2023; **Accepted:** February 21, 2023; **Published:** February 28, 2023

Abstract

Acute Myocardial Infarction (AMI) is one of the leading causes of death in the world, and immune cells such as neutrophils and macrophages are implicated in its pathophysiology. Despite decades of research, there is much debate on the roles of these immune cells, however, new concepts are emerging. This review summaries the recent advances in our understanding of the involvement of neutrophils and macrophages in post-AMI cardiac healing. Recently, neutrophils and monocytes were found to begin their phenotypical transformation in the bone marrow following an AMI, before migration to the infarct region. Novel cytokines and feedback loops have been identified in coordinating the process of immune cell recruitment to the heart post-AMI including subsets of pro- and anti-inflammatory neutrophils and new pathways of WNT signalling that alter macrophage phenotypes to a pro-inflammatory phenotype. There is also an interplay between these cells during regulation of immune cell migration as neutrophils are involved in polarising macrophages toward a reparative archetype that promotes clearance of apoptotic cells and cellular debris. Resident macrophages in the pericardial cavity also showed a cardioprotective role which may have important implications in cardiac surgeries that involve removal of the pericardium.

Keywords: Acute myocardial infarction; Neutrophil; Macrophage; Pathophysiology

Introduction

As much as three percent of the global population suffer from Acute Myocardial Infarction (AMI) [1]. AMI can lead to a range of complications such as heart failure and arrhythmias. Immune cells, especially neutrophils and monocytes, are implicated in the development of these adverse outcomes [2]. Immune cells infiltrate the infarct and the peri-infarct zone in the early phase post-AMI, with neutrophils appearing as early as 4 to 6 hours post-AMI [3] and monocytes accumulating in the next 48 to 72 hours [4]. Both beneficial and deleterious effects of neutrophils and monocytes have been described and the conflicting roles are attributable to the heterogeneity among the subsets of immune cells as well as the multiplicity of their cellular activities [5], some of which recognised as potential therapeutic targets. For example, inhibition of myeloperoxidase, an enzyme produced by neutrophils, improves ventricular function and cardiac remodelling post-AMI [6]. Meanwhile, monocytes and their descendant macrophages have displayed a double sided effect as they contribute to the initial myocardial damage by releasing inflammatory mediators, proteolytic enzymes and reactive oxygen species, while also promoting a resolution of inflammation by phagocytosing apoptotic and necrotic myocytes and neutrophils and promoting angiogenesis through the action of vascular endothelial growth factors [4]. Therefore, an unbalanced or unresolved immune reaction might exacerbate the clinical outcomes and understanding the activities of immune cells is crucial for discovering novel targets for intervention.

In this mini-review, we summarise the most recent advances in the understanding of the pathophysiological role of neutrophils, monocytes and macrophages in the post-AMI myocardium and the signalling pathways involved in the regulation of the inflammatory and reparative processes post-AMI. Neutrophil and Macrophage Specialisation Begins in the Bone Marrow

Post-AMI neutrophil and macrophage recruitment starts in the bone marrow, where hematopoietic stem and progenitor cells are activated, resulting in a rapid increase in the produc-

Citation: Shi H, El Kazzi M. Recent Advances in the Pathophysiological Role of Neutrophils and Macrophages following Acute Myocardial Infarction. Austin J Clin Cardiolog. 2023; 9(1): 1104.

tion of neutrophils and monocytes [7,8]. Following cardiac tissue infiltration, these myeloid cells develop their specialised effector functions locally under the stimulation of damage associated molecular patterns (DAMPs) and cytokines in the heart [9,10]. In 2020, Calcagno and colleagues showed that the specialisation of myeloid cells begins in the bone marrow where the type 1 interferon (IFN) response, an innate immune pathway best known for its anti-viral roles, leads to the expression of interferon-stimulated genes, resulting in a range pro-inflammatory phenotypes matching those of immune cells in the heart [11]. This study highlights the role of bone marrow in myelocyte activation prior to the local mediation in the heart, and that the differential phenotypes of immune cells in AMI can be traced back to the origin of myelopoiesis.

Pathophysiological Role of Macrophages in AMI

As monocytes accumulate in the myocardium and become macrophages, they differentiate into two distinctive subsets; the pro-inflammatory Ly-6C^{high} and reparative Ly-6C^{low} macrophages. The former is the dominant cell type from day 1 to day 4 post-AMI and clears cellular debris in the infarct, while the latter dominates the later stages and promotes healing by angiogenesis and collagen deposition [12,13]. Importantly, the activity of these two subsets of macrophages are linked to the post-AMI healing process [12,13]. Thus, balancing the pro- and anti-inflammatory activities is crucial for an optimal outcome, and understanding the signalling pathways that regulate these activities may help develop targets for intervention. The canonical WNT pathway is one of the most well-known pathways that hampers infarct healing [14] through increased fibrosis in the infarct, but the role of the non-canonical WNT pathway remained unknown until recently. Meyer and colleagues revealed that the non-canonical WNT signalling shifts the accumulating monocytes toward a pro-inflammatory state and slows healing [15]. However, inhibition of the non-canonical WNT pathway by upregulation of WNT inhibitory factor 1 in cardiomyocytes in response to AMI improves cardiac remodelling and cardiac function, which is associated with reduced number of the Ly-6C^{high} macrophages [15]. These findings suggest that the non-canonical WNT pathway is deleterious, and future studies should consider the potential of targeted therapies on cardiac remodelling.

Traditionally, recruitment of monocytes into the infarcted heart was thought to be a direct result of chemokines from the damaged tissue and infiltrating neutrophils [16,17], but the relevance of signals that maintain the accumulation of appropriate numbers of monocytes and macrophages at sites of cardiac injury was unknown. Lörchner et al. demonstrated that oncostatin M (OSM), a member of the family of IL-6–type cytokines, is synthesized and released by the initial invading myelocytes to trigger the release of Reg3β from cardiomyocytes. Reg3β initiates a positive feedback loop to recruit more OSM-secreting monocytes [18]. Moreover, disruption to this protective pathway leads to ineffective removal of necrotic cardiomyocytes, diminished myofibroblast accumulation, a lack of collagen deposition, vessel formation, and higher incidences of ventricular rupture post-AMI [18]. Subsequent work showed that inactivation of the Reg3β gene prevented the increase of both types of macrophages in the post-AMI myocardium, and the activity of different Reg proteins stimulated the recruitment of different macrophage subsets [19]. These studies highlight the significance of maintenance of cellular signalling.

Besides inter-cellular signalling, macrophages can self-signal to carry out reparative processes through metabolic phagocytic signalling. One such mechanism is via? efferocytosis which results in increased fatty acid levels in macrophages; this fuels mitochondrial respiration and activates an NAD+-dependent signal transduction cascade [20]. The cascade induces interleukin-10 (IL-10) production and release, coordinating wound healing and infarct repair and significantly reducing the risks of ventricular wall rupture [20].

However, blood-derived macrophages are not the only subtype of macrophages involved in post-AMI cardiac remodelling. Pericardial cavity macrophages, resident macrophages normally found in the pericardial cavity, contribute to reparative immune processes as well [21]. These cells migrate into the infarcted myocardium to carry out their anti-fibrotic functions, and, disruption to the activities of these macrophages is associated with worse cardiac function [21]. These findings suggest clinical implications from the removal of pericardial tissue in open-heart surgeries as it could contribute a loss of these beneficial macrophages. Therefore, further studies are warranted to investigate the potential harms of pericardial tissue removal in clinical practice.

Pathophysiological Role of Neutrophils in AMI

Neutrophils have been believed to contribute to myocardial damage during AMI for decades through the production of reactive oxygen species and proteases which exacerbate local vascular and tissue injury [22]. Clinically, neutrophil cell counts in the peripheral blood are associated with worse clinical outcomes in ischaemic heart disease [23,24]. Myriads of signalling molecules and enzymes that contribute to the neutrophil-mediated myocardial damage have been identified, such as neutrophil enzyme myeloperoxidase, but the exact pathways are often unknown, partially due to high costs associated with knockout studies. A study published in 2022 documented an image-based quantitative protocol that utilises multiplex imaging tools, namely imaging mass cytometry, to study the expression of subcellular markers of interest [25]. Among a panel of inflammatory and oxidative damage markers, the authors highlighted the ones that are potentially involved with neutrophil activities based on the spatial relationship between the markers and neutrophils. This is a cost-effective method can be applied on numerous markers simultaneously in order to screen and determine the key players that might be implicated in the pathology of AMI, before moving on to knockout studies.

Neutrophils are not entirely detrimental. A comprehensive understanding of the neutrophils requires an accurate classification of their subsets. Ma and colleagues were the first group of scientists to propose that two distinct subclasses of neutrophils exist, namely the proinflammatory N1 neutrophils and anti-inflammatory N2 neutrophils, by combining analysis on cell surface markers and mRNA expression [26]. Additionally, the number of N2 neutrophils continues to increase with time from day 1 to day 7 post-AMI, reflecting the course of resolution of the inflammatory processes, while DAMPs in the infarct polarise neutrophils to the N1 phenotype by activating toll-like receptor-4. Functionally, N1 neutrophil activity results in infarct wall thinning. Hence future interventions targeting the N1 subgroup are warranted.The significance of the reparative role of neutrophils was corroborated by another study that showed neutrophil-depletion in AMI results in diminished cardiac function and increased fibrosis [27]. In this study, however, the authors demonstrated that the protective role of neutrophils stems partially from the ability of neutrophils to polarise macrophages to-

ward a reparative phenotype (M2c macrophage). This process is mediated by neutrophil gelatinase-associated lipocalin, and its inhibition reduces the number of M2c macrophages, whose role is to clear the apoptotic cells, culminating in increased the number of TUNEL-positive cells within the infarct [27].

Conclusion

This review summarises the recent publications that describe the involvement of myeloid cells in AMI. It should be noted, however, that most of the data are based on experimental murine models. Translating the above conclusions to the clinical settings will require experiments using human samples, where applicable. Another limitation of this review is that the studies cited used different models of AMI. Specifically, the cellular component in the infarct resulted from a permanent left anterior descending artery ligation could differ from that in the ligation-and-reperfusion model. Besides, there is no consensus on the exact protocol of the ligation-and-reperfusion model as the temporary ligation phase varied anytime from 30 minutes to 24 hours among different studies. Nevertheless, this review outlines the newly recognised molecular pathways and cellular subgroups, and a better knowledge of the immune cells in AMI may help develop more targeted therapies in the future.

References

1. Sanchis-Gomar F, Perez-Quilis C, Leischik R, Lucia A. Epidemiology of coronary heart disease and acute coronary syndrome. Ann Transl Med. 2016; 4: 256.
2. Swirski FK, Nahrendorf M. Cardioimmunology: the immune system in cardiac homeostasis and disease. Nat Rev Immunol. 2018; 18: 733-744.
3. Jordan JE, Zhao ZQ, Vinten-Johansen J. The role of neutrophils in myocardial ischemia-reperfusion injury. Cardiovasc Res. 1999; 43: 860-878.
4. Nahrendorf M, Pittet MJ, Swirski FK. Monocytes: protagonists of infarct inflammation and repair after myocardial infarction. Circulation. 2010; 121: 2437-2445.
5. Swirski FK, Nahrendorf M. Leukocyte behavior in atherosclerosis, myocardial infarction, and heart failure. Science. 2013; 339: 161-166.
6. Ali M, Pulli B, Courties G, Tricot B, Sebas M, et al. Myeloperoxidase Inhibition Improves Ventricular Function and Remodeling After Experimental Myocardial Infarction. JACC Basic Transl Sci. 2016; 1: 633-643.
7. Dutta P, Sager HB, Stengel KR, Naxerova K, Courties G, et al. Myocardial Infarction Activates CCR2(+) Hematopoietic Stem and Progenitor Cells. Cell Stem Cell. 2015; 16: 477-487.
8. Herault A, Binnewies M, Leong S, Calero-Nieto FJ, Zhang SY, et al. Myeloid progenitor cluster formation drives emergency and leukaemic myelopoiesis. Nature. 2017; 544: 53-58.
9. Kaczmarek A, Vandenabeele P, Krysko DV. Necroptosis: the release of damage-associated molecular patterns and its physiological relevance. Immunity. 2013; 38: 209-223.
10. Arslan F, de Kleijn DP, Pasterkamp G. Innate immune signaling in cardiac ischemia. Nat Rev Cardiol. 2011; 8: 292-300.
11. Calcagno DM, Ng RP, Toomu A, Zhang C, Huang K, et al. The myeloid type I interferon response to myocardial infarction begins in bone marrow and is regulated by Nrf2-activated macrophages. Sci Immunol. 2020; 5.
12. Nahrendorf M, Swirski FK, Aikawa E, Stangenberg L, Wurdinger T, et al. The healing myocardium sequentially mobilizes two monocyte subsets with divergent and complementary functions. J Exp Med. 2007; 204: 3037-3047.
13. Hilgendorf I, Gerhardt LM, Tan TC, Winter C, Holderried TA, et al. Ly-6Chigh monocytes depend on Nr4a1 to balance both inflammatory and reparative phases in the infarcted myocardium. Circ Res. 2014; 114: 1611-1622.
14. Daskalopoulos EP, Hermans KC, Janssen BJ, Matthijs Blankesteijn W. Targeting the Wnt/frizzled signaling pathway after myocardial infarction: a new tool in the therapeutic toolbox? Trends Cardiovasc Med. 2013; 23: 121-127.
15. Meyer IS, Jungmann A, Dieterich C, Zhang M, Lasitschka F, et al. The cardiac microenvironment uses non-canonical WNT signaling to activate monocytes after myocardial infarction. EMBO Mol Med. 2017; 9: 1279-1293.
16. Baggiolini M. Chemokines and leukocyte traffic. Nature. 1998; 392: 565-568.
17. Frangogiannis NG. Chemokines in the ischemic myocardium: from inflammation to fibrosis. Inflamm Res. 2004; 53: 585-595.
18. Lorchner H, Poling J, Gajawada P, Hou Y, Polyakova V, et al. Myocardial healing requires Reg3beta-dependent accumulation of macrophages in the ischemic heart. Nat Med. 2015; 21: 353-362.
19. Lorchner H, Hou Y, Adrian-Segarra JM, Kulhei J, Detzer J, et al. Reg proteins direct accumulation of functionally distinct macrophage subsets after myocardial infarction. Cardiovasc Res. 2018; 114: 1667-1679.
20. Zhang S, Weinberg S, DeBerge M, Gainullina A, Schipma M, et al. Efferocytosis Fuels Requirements of Fatty Acid Oxidation and the Electron Transport Chain to Polarize Macrophages for Tissue Repair. Cell Metab. 2019; 29: 443-56 e5.
21. Deniset JF, Belke D, Lee WY, Jorch SK, Deppermann C, et al. Gata6(+) Pericardial Cavity Macrophages Relocate to the Injured Heart and Prevent Cardiac Fibrosis. Immunity. 2019; 51: 131-40 e5.
22. Ma Y, Yabluchanskiy A, Lindsey ML. Neutrophil roles in left ventricular remodeling following myocardial infarction. Fibrogenesis Tissue Repair. 2013; 6: 11.
23. Cannon CP, McCabe CH, Wilcox RG, Bentley JH, Braunwald E. Association of white blood cell count with increased mortality in acute myocardial infarction and unstable angina pectoris. OPUS-TIMI 16 Investigators. Am J Cardiol. 2001; 87: 636-9, A10.
24. Zhang S, Wan Z, Zhang Y, Fan Y, Gu W, et al. Neutrophil count improves the GRACE risk score prediction of clinical outcomes in patients with ST-elevation myocardial infarction. Atherosclerosis. 2015; 241: 723-728.
25. Shi H, El Kazzi M, Liu Y, Gao A, Schroder AL, et al. Multiplex analysis of mass imaging data: Application to the pathology of experimental myocardial infarction. Acta Physiol (Oxf). 2022; 235: e13790.
26. Ma Y, Yabluchanskiy A, Iyer RP, Cannon PL, Flynn ER, et al. Temporal neutrophil polarization following myocardial infarction. Cardiovasc Res. 2016; 110: 51-61.
27. Horckmans M, Ring L, Duchene J, Santovito D, Schloss MJ, et al. Neutrophils orchestrate post-myocardial infarction healing by polarizing macrophages towards a reparative phenotype. Eur Heart J. 2017; 38: 187-197.