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Immune cell Dilemma in Ischemic Cardiomyopathy: To Heal or Not to Heal

Sarita Nehra, PhD[1,2], **Richard J. Gumina, MD, PhD**[1,2,3], **Shyam S. Bansal, PhD**[1,2,*]

[1]Department of Physiology and Cell Biology, The Ohio State University Wexner Medical Center, Columbus, OH

[2]The Dorothy M. Davis Heart & Lung Research Institute, The Ohio State University Wexner Medical Center, Columbus, OH

[3]Division of Cardiovascular Medicine, Department of Internal Medicine, The Ohio State University Wexner Medical Center, Columbus, OH

Abstract

Inflammation is a double-edged sword for sterile tissue injury such as in myocardial infarction (MI). After ischemic injury, inflammatory immune responses activate repair processes, clear tissue-debris, form a stable scar and initiate angiogenesis in the myocardium for efficient wound-healing. However, incomplete immune resolution or sustained low-grade inflammation lead to ischemic cardiomyopathy (IC) characterized by maladaptive tissue remodeling and left-ventricular dilatation. It is clear that a delicate balance of cytokines, chemokines, prostaglandins, resolvins, and the innate and adaptive immune systems is critical for adequate healing as both insufficient- or overt-activation of inflammatory responses can either enhance rupture incidence or exacerbate cardiac dysfunction in the long-term. Among all the players, immune cells are the most critical as they are not only a source for all of the inflammatory protein mediators, but are also a target. However, phenotypic complexities associated with different immune subtypes, their interdependence, phasic-activations and varied functionalities often make it difficult to segregate the effects of one immune cell from another. In this review, we briefly summarize the role of several innate and adaptive immune cells to acquaint readers with complex immune-networks that dictate the extent of wound-healing post-MI and maladaptive remodeling during IC.

Keywords

Immune Cells; Inflammation; Myocardial Infarction; Ischemic Cardiomyopathy; Heart Failure

[*]**Corresponding Author: Address for Correspondence:** Shyam S. Bansal, PhD, Assistant Professor, Department of Physiology and Cell Biology, The Ohio State University Wexner Medical Center, 473 W 12th Avenue, Columbus, OH 43210, Tel: 614-685-0022, shyam.bansal@osumc.edu.

Author Contributions

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Introduction

Inflammatory responses to myocardial infarction (MI) are the protective mechanisms to initiate and regulate repair processes to maintain homeostasis and regain tissue-function. They are indispensable for the overall restorative process to myocardial injury and determine the extent of infarct-healing and the severity of ischemic cardiomyopathy (IC). Several preclinical studies have established that the inflammatory responses immediately after MI are obligatory to clear the dead and apoptotic cells from the injury site, to initiate scar formation and to promote angiogenesis (Figure 1). Moderation of inflammatory responses at this stage interfere with physiological healing mechanisms and often result in significant loss of cardiac function due to inadequate scar formation. Nonetheless, incomplete immune resolution during this acute inflammatory phase can also precipitate into a 2nd wave of slow immune activation, ranging from months to years, that promotes maladaptive LV remodeling [1]. During this sustained low-grade inflammation heart undergoes distinct physiological, structural and functional changes which eventually lead to hemodynamic insufficiency and progressive IC [2]. Inflammatory responses during this chronic phase are phenotypically different than the acute phase and immune-modulation at this stage often dampens maladaptive remodeling and blunts progressive cardiac dysfunction, if not reversal [3]. Since inflammation and immune activation play a complex role during ischemic injury and maladaptive LV remodeling, in this review we briefly summarize various components of the innate and the adaptive immune system as they pertain to MI and IC.

Innate Immune Reponses

Innate immune cells are the first responders to tissue-injury and rapidly mount an escalated response to clear tissue-debris and invoke repair mechanisms, making them vital for the host-defense (Figure 2). In response to pro-inflammatory cytokines such as IL-1β [4], innate immune responses are activated within minutes to hours of injury and are associated with the activation of resident macrophages and infiltration of more diverse circulating immune components including monocytes/macrophages, neutrophils and dendritic cells [5, 6]. Some of the most important players of the innate immune system and their role in MI and IC are described below.

Neutrophils

Circulating neutrophils constitute the first-line of defense and predominantly dictate initial 24-h post-MI [7] as they follow chemokine gradients to transmigrate across the endothelial walls and infiltrate into the ischemic myocardium [8]. This rapid response to tissue-injury also makes them excellent prognostic markers for acute cardiac injury [9]. Increased G-CSF levels in the circulation (and their concomitant decrease in the bone marrow; BM) facilitate neutrophil emigration into the circulation as well as their differentiation from BM progenitors to ensure constant supply during this period [7]. Once at the site of myocardial injury, neutrophils amplify the resident cardiac immune response and release proteolytic enzymes to either kill evading pathogens or clear dead cells [10, 11]. Activated neutrophils also produce significantly higher levels of reactive oxygen species and IL-1β that are potent

chemo-attractants for the recruitment of other immune cells, and hence also regulate subsequent immune responses [7]. During acute inflammation, they undergo significant temporally-determined phenotypic alterations [10] and dynamically modulate their ability to alter macrophage activity and dampen inflammation [12] favoring reparative processes [11]. Thus, early-phase neutrophil response during cardiac injury is critical for efficient wound-healing; failure of which promotes uncontrolled inflammatory response, maladaptive fibrotic myopathy and progressive heart failure [12]. Much is known about acute-phase pro-inflammatory role of neutrophils in myocardial injury, but their direct involvement in ischemic cardiomyopathy remains poorly understood and require detailed temporal immunomodulation studies.

Monocytes

Monocytes are the circulating phagocytic cells that upon injury extravasate into the tissues and differentiate to replenish pro- and anti-inflammatory macrophages and dendritic cells (DCs) [13]. Based on their Ly6C expression, murine monocytes can be characterized to either have high- ($Ly6C^{high}$) or low LY6C ($Ly6C^{low}$) expression [13]. Analogues to these, human monocytes can either be classical ($CD14^{+}CD16^{-}$) or non-classical ($CD14^{-}CD16^{+}$) monocytes, respectively [13]. Despite having a phagocytic activity similar to the neutrophils, monocytes are much less cytotoxic for tissues and possess specific mechanisms for antigen/pathogen recognition due to which acute injuries, including MI, strongly rely upon their rapid infiltration, and subsequent differentiation into other professional antigen-presenting cells. Studies have shown that monocytes are sequentially recruited into the injured myocardium with predominantly $Ly6C^{high}$ monocyte infiltration from 1-3d post-MI (pro-inflammatory phase) followed by $Ly6C^{low}$ monocytes from 4-7d (reparative/resolution phase) [14]. $Ly6C^{high}$ monocytes are recruited using CCR2/CCL2 signaling, express pro-inflammatory cytokines such as TNFα and IL-1β, clear tissue-debris and promote tissue-granulation [14]. $Ly6C^{low}$ monocytes, on the other hand, infiltrate using CX3CR1-fractalkine mediated pathways, express pro-angiogenic factors such as VEGF [14] and promote TGF-mediated fibrotic scar formation [15]. Reparative phase (4-7 days post-MI) is, thus, marked with the sublimation of pro-inflammation and augmentation of TGFβ and VEGF mediated tissue-regenerative and angiogenic responses [14]. However, a 2^{nd} wave of monocyte influx characterized by heightened $Ly6C^{high}$ monocytes, primarily derived from the spleen, has also been reported during IC [16]. Adoptive transfer studies using splenocytes harvested from HF mice further suggest a pathological role of these monocytes in mediating LV remodeling, interstitial fibrosis and progressive cardiac dysfunction [16]. This pathological transition from being protective during MI and pathological during IC could largely be triggered by the sustained inflammatory processes and is associated with continuous cardiomyocyte apoptosis [17], hypertrophy and interstitial fibrosis, thereby emphasizing the necessity of a balanced inflammatory response for reparative cardiac remodeling.

Macrophages

Macrophages are the professional antigen-presenting cells and are either derived from embryonic or hematopoietic lineages. Embryonically-derived macrophages are the tissue-

resident macrophages (RMs) and hematopoietic lineages differentiate into ‘infiltrating’ monocyte-derived macrophages (MDMs) [18]. Proliferation of local embryonic progenitor cells maintain RMs during steady-state, and infiltration of Ly6C^{high} monocytes during acute inflammation contribute to inflammatory MDMs [19]. While MDMs induce pro-inflammatory milieu, RMs regulate atrio-ventricular conduction [20], and promote myocardial repair [21], neo-vascularization and tissue-regeneration [22] post-MI emphasizing their protective role in tissue-healing. RMs and MDMs, thus, belong to disparate lineages, undergo distinctive activation processes and regulate different signaling cascades to control inflammation [18].

Like monocytes, macrophages also demonstrate a functionally distinct biphasic response during cardiac injury. RMs, owing to their close proximity to the cardiomyocytes, are especially suited to promptly sense myocyte-injury, proliferate to clear tissue debris and activate systemic immune responses [23]. They also release significant amounts of IL-1β to recruit initial wave of neutrophils [23]. Studies have shown that RM activity and proliferation predominate the early phase of injury-response (0-2d post-MI) [23]. However, as monocytes take over the injury site (3-5d post-MI), RMs are replaced (and inhibited) by MDMs marking an ontogenic shift from reparative to pro-inflammatory macrophages [18]. MDMs mediate NLRP3 inflammasome activation, clear dead cells, and, produce several chemokines (CxCl1, Cxcl2, CCL2 and CCL9) and pro-inflammatory cytokines (IL-1β, TNFα) necessary to initiate wound-healing processes [18, 23]. Phenotypically heterogeneous embryonically-derived RMs (CCR2−) and infiltrating MDMs (CCR2+) have also been reported in the failing human hearts, the latter being directly associated with pro-inflammation and ischemic cardiomyopathy [24]. Although, ‘M1- and M2-like’ macrophages have also been described in the pro-inflammatory and resolution phases, respectively; due to controversies associated with this phenotype-based characterization, these are not discussed here.

Dendritic Cells

Dendritic cells (DCs) are the professional antigen-presenting cells and by modulating adaptive immune responses play a vital role in IC. Phenotypically, DCs are similar to macrophages and share ontogeny but are superior in regulating T-cells to induce either immunogenic or tolerogenic responses [25]. Broadly, DCs can be categorized as conventional DCs (cDC1 and cDC2) or plasmacytoid DCs (pDCs) and all of these subsets have been shown to reside in non-injured hearts mostly in close proximity to RMs [26]. Resident DCs process proteins released during the regular wear and tear of cardiomyocytes and maintain immune-homeostasis by activating regulatory T-cells to induce tolerogenic responses. However, during MI, resident DCs also escort cardiac-specific self-antigens to the LNs and activate effector CD4+ T-cells, thereby waning self-tolerance and inducing auto-immunity [27]. Studies have shown that at around 5d post-MI, cDC2s are maximal in the ischemic hearts and promote pro-inflammation to aid in the clearance of cellular debris. However, by day 7 post-MI, cDC2s are replaced by cDC1s to induce Treg-mediated tolerance, promote fibrotic scar-formation and initiate angiogenesis during the reparative phase [26]. Although, the exact function and role of tolerogenic pDCs is not clear but they also have been found to infiltrate the injured heart by 3d post-MI [26]. Due to their

phenotypic diversity, it is not trivial to conclusively ascertain the function of each DC subset in MI and IC. However, it is clear that cDCs are important for tissue-healing as their depletion immediately after MI improves cardiac function, reduce myocyte hypertrophy and blunt IC by curbing pro-inflammation (cDC2 mediated), and T-cell infiltration during resolution (7d post-MI) [26]. Similarly, adoptive transfer of tolerogenic pDCs also subside pro-inflammatory responses by inducing immune-suppressive Tregs [28]. It, therefore, appears that DCs exert indirect effects on ischemic cardiomyopathy by altering T-cell mediated pro-inflammation and/or favoring Treg-mediated wound-resolution.

In summary, a distinct innate immune-cell landscape involving several players is activated during acute ischemic insult with the purpose of activating phasic responses to clear apoptotic cells and induce pro-inflammation followed by repair and immune resolution. However, sustained inflammation or eventual re-activation of these innate immune components fuel pathological cardiac responses leading to progressive cardiac dysfunction and maladaptive LV remodeling during IC [30].

Adaptive Immune Response

Helper T-cells

$CD4^+$ helper (Th) T-lymphocytes play a critical role in mediating transition from the pro-inflammatory to immune-resolution phase. By reacting to a variety of tissue-cytokines, they can polarize into a spectrum of subsets, such as Th1, Th2, Th9, Th17, Th22, follicular helper (Tfh) or regulatory T-cells (Tregs) capable of exerting varied effects ranging from inflammation to fibrosis and angiogenesis [29]. T-cell activation is the most stringently controlled immune activation mechanism requiring strong interaction between the cognate T-cell receptors (TCRs), the antigens presented in conjunction with MHC molecules expressed on the APCs (RMs, MDMs and DCs) and other appropriate co-stimulatory signals [30]. Studies with reporter mice expressing mCherry protein under the cardiac-specific αMyHC, have clearly shown the migration of $mCherry^+$ myeloid cells to the mediastinal lymph nodes (mLNs) and spleens of infarcted mice [31]. These findings suggest that intracellular cardiac-antigens or neo-antigens formed during MI are phagocytosed and processed by the APCs and are shuttled to the mLNs/spleens to effect T-cell activation and proliferation. Several independent groups have shown that T-cell activation follows innate immune activation and cardiac T-cell levels are maximal in 3-7 days post-MI, return to baseline levels by day 14 [32] and exhibit a 2^{nd} wave of T-cell activation during IC [3]. Moreover, T-cell subsets exhibit phase-dependent plasticity and interconvert from pro-inflammatory (Th1 and Th17) to pro-fibrotic (Th2 and Treg) subsets during the transition from pro-inflammatory to resolution phase [33]. Ischemic and non-ischemic models of HF also show that T-cells can modulate fibroblast activity and collagen secretion as well. While defective scar formation with disarrayed collagen fibers has been observed in $CD4^{-/-}$ [34] and $TCR^{-/-}$ [35] mice during ischemic and non-ischemic injury, respectively; T-cell depletion during ischemic cardiomyopathy results in reduced fibrosis and LV remodeling [3]. These contradictory findings suggest that T-cells are indispensable for wound healing and immune resolution early after injury but during IC undergo a phenotypically pathological shift (presumably owing to persistent low-grade inflammation) that by

accentuating pro-inflammation and fibrotic LV remodeling aggravate cardiac dysfunction [3]. Furthermore, this T-cell activation is directed against specific cardiac antigens such as MyHCA [36] as OT-II mice exhibit significant protection from T-cell induced autoimmune damage. Analogues to these preclinical studies, T-cells with distinct TCR repertoires [37] or specificity against cardiac antigens, such as αMyHC and troponin have also been reported in clinical studies [38].

Among all Th subsets, Tregs demand a specific mention due to their potent immune-suppressive potential. Tregs are critical to regulate immune responses, promote cardiac repair and initiate immune resolution [39]. Similar to effector CD4+ T-cells, Tregs also infiltrate the myocardium immediately after MI (day 1), reach maximal levels by day 3 and return to baseline by day 14 post-MI. These Tregs promote 'M2-like' macrophage phenotype characterized by arginase-1, IL-13, TGF-β and osteopontin expression thereby suggesting cardio-protective effects of Tregs during the acute phase [40]. This is also consistent with the fact that adoptive transfer of Tregs during MI subside inflammation and promote cardiac repair [41]. However due to chronic inflammation during IC, Tregs have also been shown to undergo a temporal phenotypic shift with expression of pro-inflammatory cytokines and loss of immunosuppressive potential [42]. Importantly, their partial depletion and subsequent reconstitution resets their phenotype and immunosuppressive potential leading to improved cardiac function, reduced LV remodeling and partial reversal of IC [42].

CD8+ cytotoxic T-cells are also significantly increased by day 1 with a peak observed by 5-7 days post MI [32]. Like Th cells, CD8+ T-cells are also known to be increased at 8 weeks post-MI during IC [3]. Increased incidence of cardiac rupture, compromised scar formation and exacerbated pro-inflammation at 7 days post-MI have been observed in the absence of functional CD8+ T-cells. Paradoxically, the cardiac function improves significantly in CD8 deficient mice also at 7d post-MI suggesting their protective role in adequate scar formation but an overall pathological effect on cardiac physiology [43] immediately after MI. *In-vitro* co-culture studies have shown that during late stages of MI (2-3 weeks post-infarction) CD8+ T-cells exert antigen-specific cytotoxic effects on cardiomyocytes and escalate their apoptotic death [44]. Despite this knowledge, the exact role of CD8+ T-cells in mediating LV remodeling during IC is not known and require further studies to adequately discern their spatio-temporal effects on cardiac pathophysiology.

γδT-cells

Inherent complexity of T-cell responses can also be appreciated from the fact that several unconventional T-cells that do not require MHC-restriction (and hence antigen-presenting cells) for their activation have also been identified in humans and rodents [45]. These T-cells i) recognize proteins that are outside the MHC locus such as MR1, and CD1a-d, ii) are apt for rapid responses (hour to days), iii) bridge innate and adaptive immune responses iv) do not recognize classical antigens, v) are not donor-specific and, last but not the least, vi) most individuals respond similarly as opposed to conventional T-cells where the degree and extent of activation can be different in different individuals [45]. Innate natural killer T-cells (iNKT), γδT-cells and mucosal-associated invariant T-cells (MAIT) are some important

members of this class [45, 46]. To maintain brevity and focus only γδT-cells are discussed below and readers are recommended to explore other detailed reviews discussing the role of iNKT cells in cardiovascular diseases [47] and MAIT cells in autoimmune responses [48].

It is well-established that unconventional T-cells are poised to mount a rapid immune response during ischemic [49] and non-ischemic tissue injuries [46] as they directly recognize lipidic- and phosphatidic-antigens in the environment and do not need antigen-presentation by other cells. Indeed, studies have shown that γδT-cells quickly respond to ischemic cardiac injury, and using CCL20-CCR6 signaling infiltrate the myocardium within 1 day post-MI, peak levels being observed by 7 days [49]. Moreover, these T-cells are a major source of IL-17A which is known to alter endothelial cell activation, regulate neutrophil recruitment, mediate pro-inflammatory macrophage phenotype, facilitate myofibroblast activation and exert pro-apoptotic effects on cardiomyocytes [50]. Consequently, mice deficient in γδT-cells exhibit higher survival during the initial 7 days, and significantly reduced IC characterized by blunted LV remodeling, decreased fibrosis and improved cardiac function at 28 days post-MI [49]. Similar results have also been observed by direct IL-17A neutralization using selective antibodies [50]. Considering that IL-17A expression is regulated by IL-23 and IL-1β [51], it is possible that during acute MI these cytokines directly bolster IL-17A production in γδT-cells which then act on the cardiomyocytes, fibroblasts and innate immune cells to pathologically alter their function, and overall inflammatory/reparative milieu.

B-cells

B-lymphocytes mediate humoral immunity by generating antibodies against self or non-self antigens. Presence of auto-antibodies against cardiac antigens such as actin, myosin, troponin I, Na^+K^+ATPase, in humans [52] as well as in rodents [53], therefore, points to B-cell mediated adaptive responses in cardiac diseases. Naïve murine heart contains two different populations of $B220^+$ B-cells characterized by $IgM^{high}IgD^{low}$ (larger fraction) and $IgM^{low}IgD^{high}$ (smaller fraction) expression [54]. Although, the ontogeny of these populations is not known, they populate the heart by E13.5 and despite certain phenotypic differences reside in equilibrium with circulating and splenic B-cells [55]. During ischemic injury, B220+ and $CD19^+IgD^+IgM^{loW}$ cells are actively recruited into the infarcted myocardium, reach maximal levels by day 3-5 post-MI and return to baseline levels by day 14 [56]. It appears that B-cells exert a pathological role in cardiac wound healing post-ischemic injury as their anti-CD20 mediated depletion confer a protective response by decreasing LV remodeling and improving cardiac function by day 14 post-MI [56]. Since, anti-CD20 only depletes B2 and B1b cells without affecting B1a levels [57] it is possible that more complex subset-specific effects exist for different B-cell subtypes. Several mechanisms, such as reduction in cell apoptosis, ischemic damage, pro-inflammatory cytokines and $Ly6C^{high}$ monocyte recruitment, appears to play a role in this protective response. Moreover, these effects are CCL7 (a ligand for CCR2) dependent as B-cell specific CCL7 gene knockout results in negation of these effects [56]. Moreover, owing to the complex interactions of B-cells with other components of the innate and adaptive immune responses, and lack of appropriate pre-clinical and clinical studies, much remains to be investigated to better understand the role of B-cells in IC.

Conclusion

Considerable evidence suggests direct and indirect protective effects of immune activation during MI and overall pathological response during IC. Several players of the innate and adaptive immune systems form a complex interconnected network that can exert beneficial as well as detrimental effects depending upon the cues received from the tissue-milieu, the nature and extent of the injury and the previous history of cardiac insults. Although, highly specific pre-clinical models compel to appreciate the therapeutic benefits of immunomodulation during IC, direct evidence from clinical studies are scant and require carefully planned studies to dissect acute vs chronic effects to devise efficient immune cell based therapeutic strategies for cardiac repair.

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Abbreviations:

MI	Myocardial Infarction
IC	Ischemic cardiomyopathy
BM	Bone marrow
CCL7	Chemokine (C-C motif) ligand 7
CCR2/CCL2	C-C chemokine receptor type 2/Chemokine (C-C motif) ligand 2
cDC	Conventional dendritic cells
CX3CR1	CX3C chemokine receptor 1
DC	Dendritic cells
IL-1β	Interleukin 1β
Ly6C	Lymphocyte antigen 6 complex
MDM	Monocyte derived macrophages
mLN	Mediastinal lymph nodes
MyHCA	Myosin heavy chain alpha
pDC	Plasmacytoid dendritic cell
RM	Resident macrophages
TCR	T-cell receptor

TGF	Transforming growth factor
TNFα	Tumor necrosis factor alpha
VEGF	Vascular endothelial growth factor

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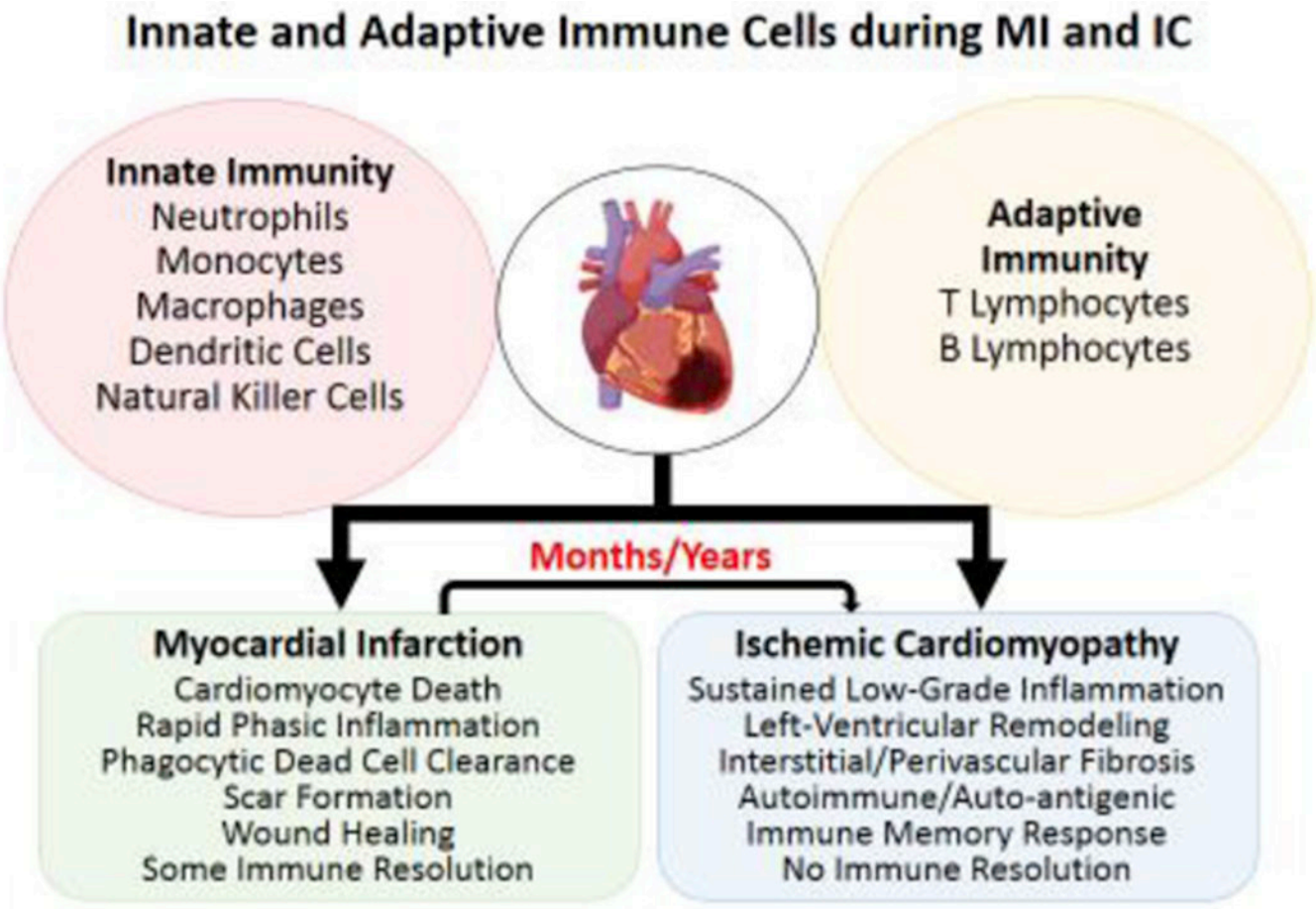

Figure 1:

Schematic showing several key players of the innate and adaptive immune system known to play an important role in wound-healing post-myocardial infarction (MI), and mediating left-ventricular remodeling during ischemic cardiomyopathy (IC) in preclinical studies. Both innate and adaptive immune cells function in an interdependent complex network where one cell-type regulates and influences the behavior of others to achieve an overall goal of wound-healing, scar formation and ultimately immune resolution post-MI. However, the same network of immune cells responds differently to sustained low-grade inflammation and undergo a phenotypic change to mediate maladaptive tissue-remodeling during IC. If one player is more pathological/critical than the others is not known. Some of the components were designed using ‘Biorender’.

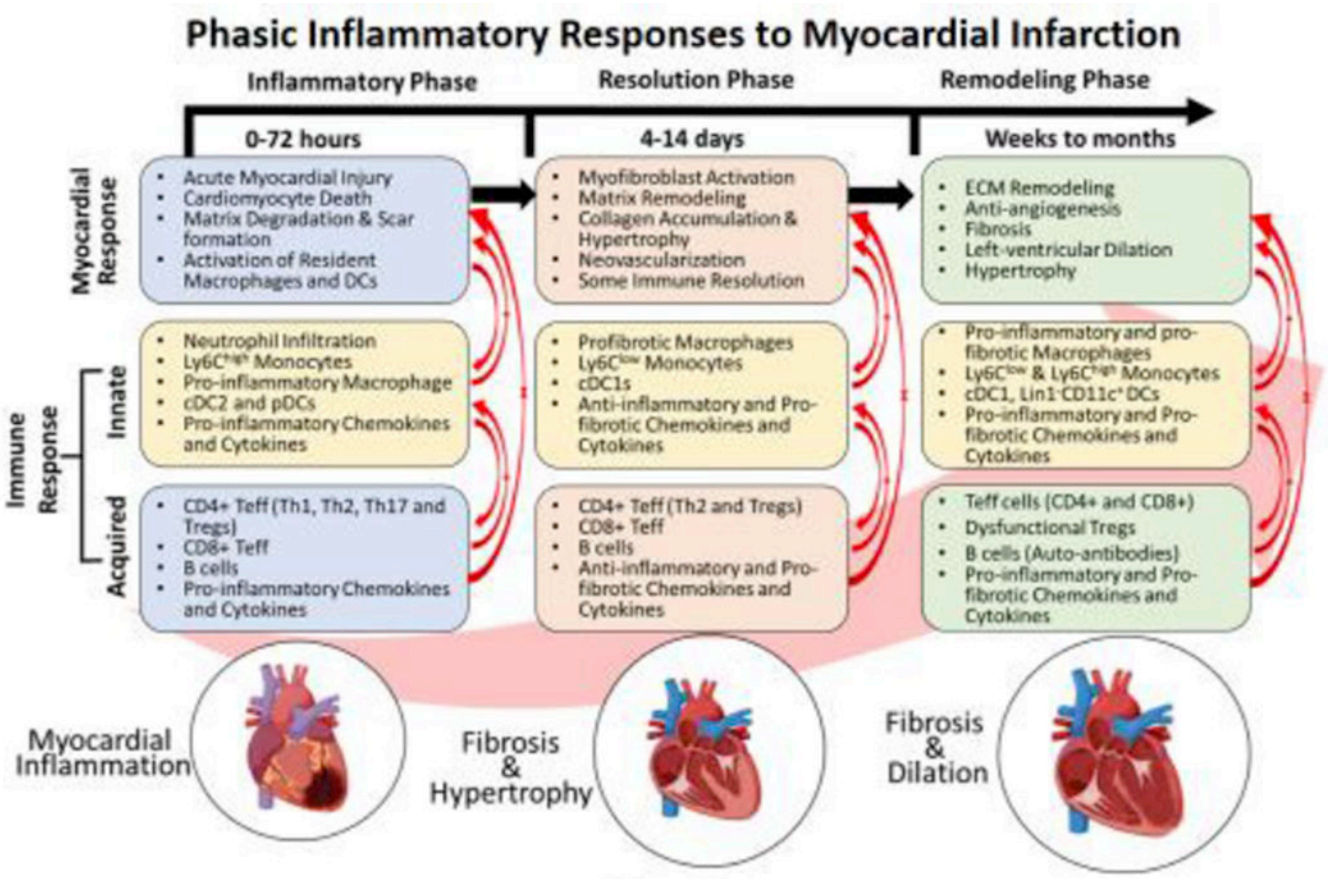

Figure 2:

Different phases of immune activation post-MI are temporally regulated to induce intense pro-inflammation from 0-72 h post-injury to clear the damaged cells followed by scar-formation and somewhat immune-resolution from 4-14 days. While the first phase is predominated by the phagocytic and pro-inflammatory cells, 2nd phase is dictated by anti-inflammatory and pro-fibrotic cells. Phase-1 specific chemokines are CXCR2/KC, CXCR4/SDF1α, CCR1/MIP1α, CCR2/MCP1, CXCL1, CXCL12, CXCL13, and CXCL9 whereas cytokines are TNFα, IFNγ, IL-6, and IL-1β. In contrast, phase-II specific chemokines are CCR2/MCP1, CXCR2/CXCR4/MIF, CCR1/MIP1α, CCR5/RANTES, CX3CR1/Fractalkine, CXCL2, CXCL5, CXCL8, and CXCL12, and cytokines are IL-10, TGFβ, CTGF, IL-4, IL-13, IL-6 and eotaxin. Ischemic cardiomyopathy (IC) is associated with low-grade inflammation that over a period of months to years (post-MI) lead to extensive extracellular matrix remodeling, inhibit angiogenesis, and promote LV-remodeling. Both pro- and anti-inflammatory immune responses have been found to be active during this phase suggesting disparate local networks of functionally-similar immune cells. This phase is also associated with several chemokines (CX3CR1/Fractalkine, CXCR4/SDF1α, CCR2/MCP1, CXCL1, CXCL2, CXCL5, and CXCL8) and cytokines (TNFα, IFNγ, TGFβ, IL-10, IL-12, IL-6, and eotaxin). Some of the components were designed using ‘Biorender’.