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Natural Killer Cells as Critical Modulators of Heart Disease: Exploring Pathophysiological Mechanisms and Therapeutic Perspectives

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ABSTRACT

Natural killer (NK) cells are crucial components of the innate immune system and have emerged as significant players in the pathogenesis of heart diseases. This review discusses recent findings regarding the multifaceted roles of NK cells in various cardiac conditions, including coronary artery disease, myocardial infarction, heart failure, myocarditis, and heart transplantation. It outlines the NK cell subsets, particularly CD56-bright and CD56-dim variations, their functional characteristics, cytokine profiles, and the inflammatory pathways they are involved. The review discusses both the beneficial and detrimental effects of NK cell activity on cardiac pathology by underlining their participation in immune regulation, tissue repair, and graft rejection dynamics. Additionally, we have addressed the impact of NK-cell–oriented environmental signals and discussed potential therapeutic approaches, such as immunomodulatory and anti-inflammatory strategies targeting NK cells. This review was therefore geared towards integrating available studies in understanding NK cell dynamics in heart disease and offering insights for future clinical interventions.

Keywords: Natural killer cells; Heart diseases; Coronary artery disease; Myocardial infarctions; Heart transplantations

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INTRODUCTION

Heart disease (HD) is the leading cause of death and is estimated to account for 31% of all deaths worldwide. HD includes a group of heart and blood vessel disorders such as coronary artery disease (CAD) and rheumatic HD. The high cost of treatment and poor health outcomes in HDs are considered major health problems worldwide.[1,2]

Improper cardiac regeneration and inflammatory responses play a pivotal role in the poor outcomes of HD therapies. The interaction between the cardiovascular system and other body systems is disrupted in heart disorders, and it is not easy to identify the exact functional mechanisms owing to the complex relationships between these components.[3] In recent studies, the role of cytokines in chronic heart failure has been investigated, and it has been shown that an increase in the amount of these proinflammatory mediators plays a prominent role in the pathophysiology of several HDs.[4]

Natural killer (NK) cells serve as the first line of defense against various pathogens and are a key component of the innate immune system, representing 5% to 10% of peripheral blood lymphocytes in humans.[5,6] After activation and subsequent proliferation, NK cells mainly interact with other immune system components through cytokine secretion. NK cells are vital components of the innate immune system, possessing the ability to regulate immune responses.[7-10] There are several NK cell subtypes of innate lymphoid cells (ILCs) with different functions in humans and mice. The 2 main subtypes defined by CD56 expression include CD56-bright and CD56-dim cells.[11,12]

Due to the therapeutic potential of NK cells in improving heart regeneration in HDs, further research is needed to investigate the role of these cells as an important component of innate immunity in inflammatory and immune responses. The primary objective of this review is to elaborate on the existing understanding of the role and functionality of NK cells in various heart conditions, including acute MI and coronary heart disease (CHD), while also exploring the therapeutic possibilities of NK cells in enhancing cardiac regeneration. Figure 1 provides a schematic diagram illustrating the key aspects of NK cells discussed in this review.

NK Cell Subsets and Heart Disease

NK cells, as a component of innate immunity, are characterized by the expression of CD56 and the absence of CD3, belonging to group 1 of the innate lymphoid cell family.[13] These cells are divided into 2 main categories based on the density of CD56 (an adhesion molecule) and CD16 (a low-affinity immunoglobulin [Ig] G receptor) on their cell surface: CD56-bright CD16-dim/neg, and CD56-dim $CD16^+$.[12]

Variations in CD16 expression can influence the NK subsets-mediated antibody-dependent cellular cytotoxicity (ADCC), which highlights the role of CD16 in this process. Moreover, these subsets are different in expressing cytokines, chemokine receptors, and adhesion molecules, which impact their response to monocyte-derived cytokines stimulation and trafficking patterns.[12] It has been well established that CD56-bright cells produce a higher level of cytokines after stimulation and could act as a primary source of immunoregulatory cytokines.[13,14] Contrarily, CD56-dim cells are capable of exhibiting both direct and antibody-dependent cytotoxic potential, which is considered the cytotoxic subset. In addition to the more accepted classification, several studies have pointed to other functional and phenotypic intermediate cells, as well as subsets that expand after certain infections. For instance, CD56-neg $CD16^+$ and $NKG2C^+$ expansion is induced following chronic viral infections such as human immunodeficiency virus (HIV) and cytomegalovirus (CMV).[15-18]

Since bacterial and viral infections are potential risk factors for CHD, NK cells, as key components of protective immunity, may play a role in the development and progression of CHD. Hak et al's study on patients with CHD undergoing coronary artery bypass grafting showed a notable reduction in the frequency of peripheral NK cells and the CD56-dim subset.[19] Additionally, NK cells from CHD patients exhibited reduced cytotoxicity and lower intracellular interferon-gamma (IFN-γ) production levels compared to those from healthy controls. The authors argued that peripheral NK cells could migrate to inflammatory sites like artery walls and exacerbate atherosclerosis.[19] Bonaccorsi and colleagues further substantiated this finding by demonstrating the presence of CD56-bright NK cells within human atherosclerotic lesions in symptomatic patients. This observation underscores the pivotal role of NK cells in the progression of atherosclerosis and the instability of carotid atherosclerotic plaques by triggering a proinflammatory response when they recognize specific cellular targets.[20]

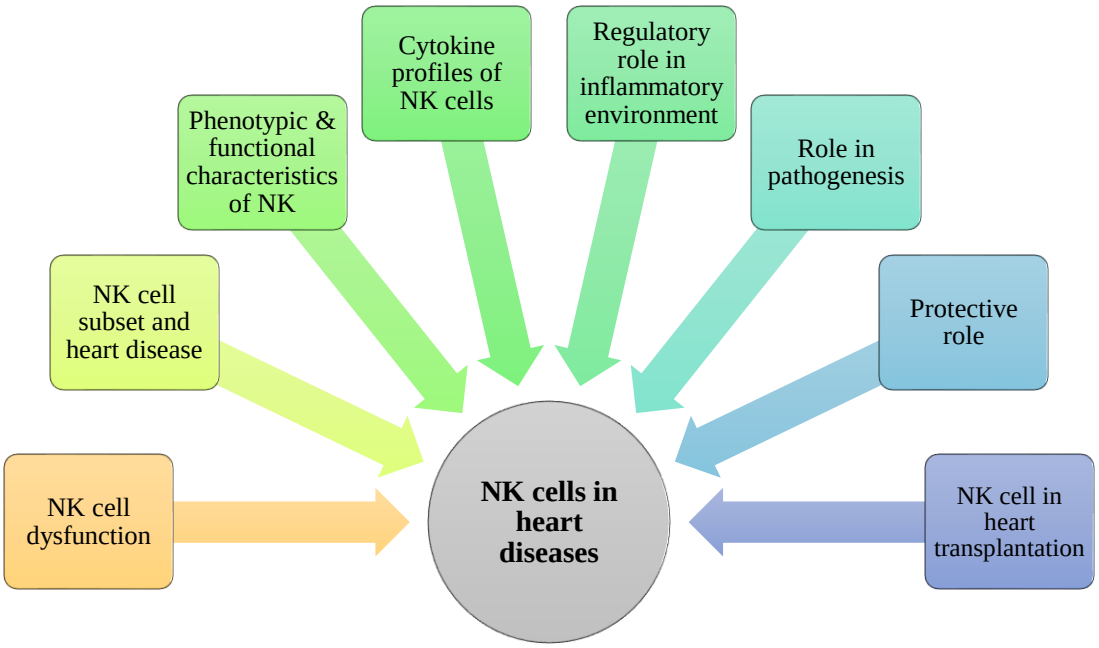

Figure 1. A schematic diagram illustrating the key aspects of NK cells

Similarly, the percentage of total NK cells and CD56-dim cells was substantially lowered in individuals with stable and unstable CAD; however, there was no variation in the CD56-bright subset between groups. The loss of CD56-dim NK cells has been proposed to be mediated by an oxidative imbalance or apoptosis induced by continuous antigen-driven activation of these cells.[21,22] Hou and colleagues investigated the Tim-3 expression on circulating NK cells from atherosclerotic patients compared to healthy individuals. They suggested that Tim-3 upregulation was correlated with NK cell impairment and CD56-dim cell loss in atherosclerosis, suggesting a possible indicator for disease progression.[23]. However, several other studies have reported no substantial difference between NK cell subsets in patients with acute or stable forms of CAD in comparison with healthy controls.[24]

Examination of NK cell inhibitory and activating receptors in patients with acute MI and stable angina revealed NK cell quantitative loss in both disorders and dysfunction of NK cell receptors.[25] Moreover, the reduced number and impairment of NK cells have been confirmed in viral and idiopathic myocarditis.[26] Evaluating NK cells in non-infected and coxsackievirus B3 (CVB3)-infected cocultured RAW/Hela cells in the presence/absence of myeloid-derived suppressor cells (MDSC) from infected A.BY/SnJ mice revealed that MDSCs contribute to the development of chronic CVB3 myocarditis through suppression of NK cell functional activity in myocarditis.[27] Notably, the frequency of granulysin-expressing NK cells (both CD56-bright and CD56-dim subsets) was elevated on day 7 post-MI and returned to basal level in healthy individuals on day 28.[28] Furthermore, analyzing the distribution of NK cell receptors revealed a higher LILRB1$^+$ NK cell proportion in patients with acute MI as compared to healthy controls.[29] According to another study by Yao and colleagues, the number and cytotoxic activity of circulating NK cells in patients with chronic heart failure are reduced, and treatment with interleukin (IL)-2 could elevate their cytotoxic activity in vitro.[30]

The Role of NK Cells in Solid Allograft and Heart Rejection

Figure 2 depicts a schematic diagram illustrating the behavior of NK cells after heart transplantation. The first evidence for NK cell involvement in solid allograft rejection was presented by studies in the early 1980s. [31]

Given the pivotal role of NK cells in discriminating self from non-self (defined as missing self-hypothesis), any disparity in MHC I or downregulation of autologous MHC I molecules could lead to NK cell activation and subsequent allograft rejection. Additionally, NK cells could become activated and target transplanted endothelium via the FcγRIII (low-affinity receptor for IgG) and ADCC activity after an adaptive immune response.[32,33]

Analyzing the cellular components of rejecting liver allografts demonstrated recipient NK cell infiltration as early as 12 hours after transplantation.[34] Additionally, a study has demonstrated that alloreactive NK cell activity plays a significant role in the rejection of heart allografts, indicating their role in the rejection of solid organ transplants This study not only indicates that cardiac allografts can trigger the activation of alloreactive NK cells but also suggests that these NK cells may function similarly to classic cytotoxic T lymphocytes (CTLs) in specific combinations during the rejection of solid organ transplants.[35]

Allograft-infiltrating $NKG2D^+$ $NK1.1^+$ cells may contribute to cardiac rejection by interacting with upregulated NKG2D ligands (e.g., HAE-1, Mult1, and H60) in mice.[36,37] This NKG2D ligand upregulation may occur due to trauma, cellular stress, and ischemia/reperfusion (I/R) injury, as well as an adaptive immune response.[36] Likewise, Wei and colleagues elucidated that HIF-1α overexpression in response to I/R injury elevates the expression of the NKG2D ligand MICA/B on human cardiomyocytes, which is correlated with NK cell cytotoxicity.[38] In this context, NKG2D blockade combined with anti-CTLA-4 treatment reduces chronic allograft vasculopathy (CAV) by lowering alloantibody production, impeding IL-6 expression, and increasing the number of regulatory T cells.[39]

According to the study conducted on CD28-deficient mice, the $NK1.1^+/CD3^-$ NK cells are rapidly infiltrated into the cardiac allograft and are involved in acute rejection by activating alloreactive T cells in the absence of CD28-costimulation signals.[40] Although the activating Ly49D receptors for H-2 molecules were expressed in a higher proportion of infiltrated NK cells on day 6 post-transplantation (the peak of NK cell infiltration) compared to splenic NK cells, these receptors are not essential for cardiac allograft rejection mediated by NK cells.[41] Hence, long-term graft acceptance can be achieved by combining CD28-blocking strategies with NK cell inhibition. [40,41]

Hirohashi and colleagues highlighted that, beyond acute rejection, NK cell Fcγ receptors play a significant role in antibody-mediated rejection and CAV. These processes are critical factors limiting long-term allograft acceptance.[42] Other positive and negative signals from inhibitory and/or activating receptors may also regulate NK cell functions. For instance, higher expression of Rea-1 on recipient cardiac endothelial cells could influence the NK cell-mediated allograft vasculopathy through interaction with NKG2D activating receptors.[43] Paul and colleagues demonstrated that elevated CD16 (FCGR3A) expression and NK cell ADCC function were correlated to the FCGR3A-VV genotype that is more frequent in CAV^+ patients. Hence, it could be considered an independent predictor of CAV development in heart transplant recipients.[44] On the other hand, the absence of self-MHC I molecules on allograft endothelium induced recipient NK cell-mediated microvascular inflammation (MVI) in an antibody-independent manner. It has been suggested that mTOR inhibition could be beneficial in attenuating MVI lesions and preventing self-induced NK cell activation.[45]

In addition to the cytotoxic and activating roles of NK cells in allograft rejection, several studies have pointed to their regulatory effects on alloimmune responses.[46-50] For instance, they could promote the induction of allograft tolerance from skin allograft rejection by inhibiting the survival and dissemination of the donor's antigen-presenting cells.

In the absence of NK cells and their cytotoxic activity, donor antigen-presenting cells (APCs) can migrate to extralymphoid sites, where they effectively activate alloreactive T cells. This activation plays a critical role in transplant rejection, as these T cells mount a robust immune response against the transplanted tissue. These alloreactive T cells are more resistant to the immunosuppressive regime (such as CD28/CD154/OX40 blockade). In this situation, NK cell impairment makes tolerance induction against mismatched MHC I transplants more difficult.[47] Similarly, Beilke and colleagues proposed that NK cells are required for tolerance induction in islet allografts via regulating the cellular components of the host immune system.[48] It is pertinent to point out that the immunoregulatory effects of NK cells in the course of heart allograft rejection are dependent on the degree of allogeneic immune activation, and such rejection occurs when T-cell stimulation is moderate. NK cells were found to be capable of reducing the first trigger of the

immune response, which in turn results in the establishment of the regulatory function, leading to the promotion of graft tolerance.[49] Diverse and somewhat conflicting results have been postulated in assessing the role of NK cells in transplant rejection (no involvement, involvement over T cells, and active involvement. The diversity of animal models used in this regard might be capable of providing appropriate explanations.[20,35,41,47,51,52]

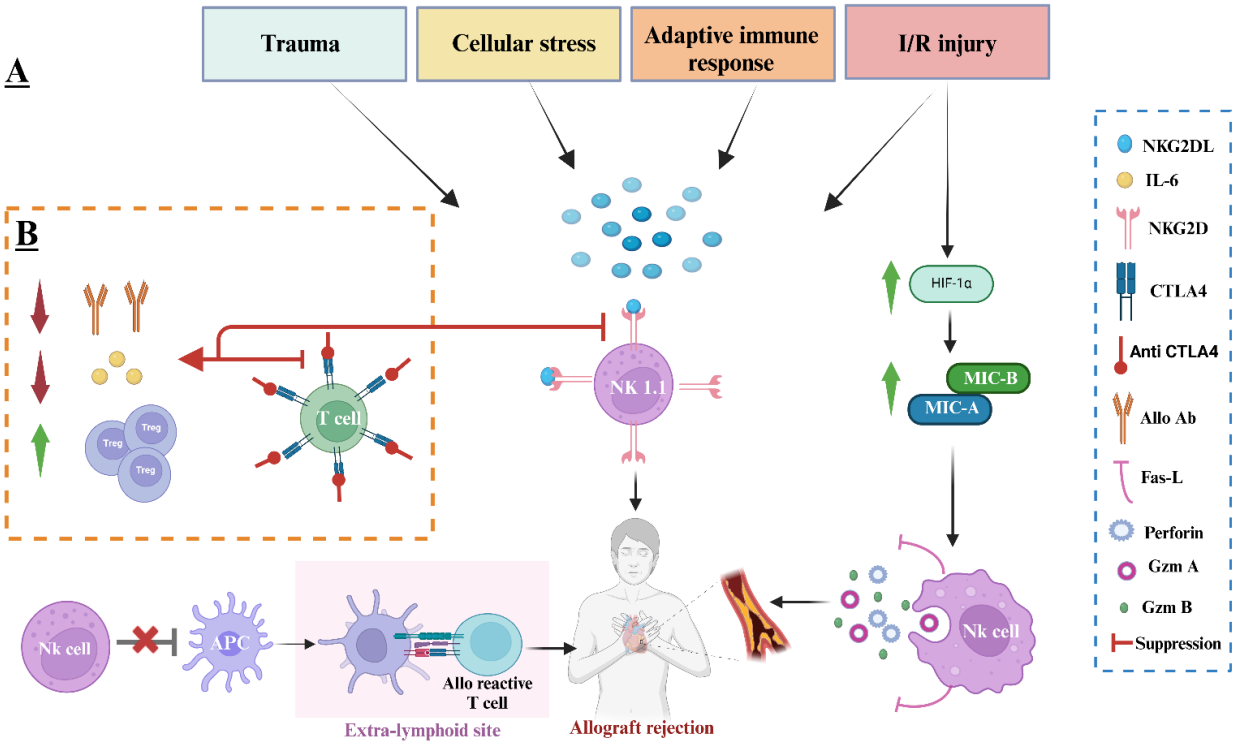

Figure 2. Schematic diagram illustrating the behavior of natural killer (NK) cells after heart transplantation. A. Natural killer group 2D (NKG2D) ligands are increased by trauma, cellular stress, ischemia-reperfusion (I/R) injury, and adaptive immune response, which results in the activation of natural killer group 2D-positive natural killer 1.1-positive ($NKG2D^{+}NK1.1^{+}$) cell and cardiac rejection. After I/R injury and overexpression of hypoxia-inducible factor 1-alpha (HIF-1α), MHC class I chain-related protein A (MICA), and MHC class I chain-related protein B (MICB) are expressed on human cardiomyocytes, which cause heart allograft rejection via the activation of NK cells cytotoxicity. The inhibition of donor antigen-presenting cells (APC) by NK cells is a key factor in favor of heart transplantation. By migrating donor APCs into the extra-lymphoid sites, they cause the activation of alloreactive T cells and subsequently cause rejection of transplanted tissue. B. Simultaneous inhibition of NK cells and T cells through NKG2D blockade and anti-cytotoxic T-lymphocyte associated protein 4 (CTLA-4) treatment respectively, leads to decreasing alloantibody and interleukin-6 (IL-6) production and also increasing regulatory T cells, which cause chronic allograft vasculopathy reduction. NKG2DL: natural killer group 2D ligand; IL-6: interleukin-6; Gzm: granzymeB; Fas-L: Fas ligand; Treg: regulatory T cell; Allo Ab: alloantibody; APC: antigen-presenting cell; HIF-1α: hypoxia-inducible factor 1-alpha; MICA-A: MHC class I chain-related protein A; MICA-B: MHC class I chain-related protein B

NK cell Dysfunction in Heart Failure and Cytokine Profile of NK Cells in Heart Disease

NK cells play indispensable regulatory roles in several heart-related complications, such as coronary artery and ischemic conditions, pulmonary arterial hypertension (PAH), myocarditis, cardiac fibrosis, and transplant rejection.[53] Also, NK cells may influence cardiovascular complications associated with various

pathogenic conditions. HD is one of the proven and dangerous complications of obesity, in which the transition of macrophage phenotypes leads to the recruitment of NK cells.[54]. Also, preeclampsia is a distinct pregnancy-related condition, and women who have experienced it are 12 times more likely to develop cardiovascular diseases later in life. Since NK cells are the most abundant immune cells in the uterus, a group of researchers have suggested that these cells may play a role in the cardiovascular complications of this disease.[55-57] NK cells are shown to present organ-specific phenotypes based on cytotoxic properties, chemokine receptor expression, and cytokine expression profiles.[58,59] According to the signals received, mature NK cells are capable of secreting various cytokine and inflammatory mediators such as type I interferons, tumor necrosis factor-alpha (TNF-α), IFN-γ, and IL-13.[60]

Inflammation is a vital physiological process where immune cells and tissues interact to restore tissue function and maintain homeostasis. However, chronic or excessive inflammation can contribute to the development of cardiovascular disease (CVD). Acute local inflammation in the heart can arise from various causes, including infections (particularly viral), toxins, and MI.[61] One key inflammatory mediator involved is TNF-α, which is often elevated in patients with heart failure. Elevated TNF-α levels indicate impaired cardiac function and are associated with a poor prognosis.[62,63] Elevated levels of TNF-α can induce cell apoptosis and disrupt the balance between matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs). This imbalance contributes to adverse cardiac remodeling, resulting in ventricular hypertrophy and dilation, as well as decreased ejection fraction. The mechanisms by which TNF-α affects these processes underscore its role in heart failure progression and highlight the potential for therapeutic strategies targeting inflammatory pathways to mitigate cardiac damage.[64,65] Overexpression of TNF-α also activates both inflammatory and humoral immune responses in transgenic hearts, resulting in the progression of autoimmune myocarditis in TNF1.6 mice.[65] Moreover, chronic hypoxia is capable of inducing IL-1 production in cardiomyocytes.[66] Hampering IL-1 could be associated with the restoration of calcium homeostasis, reduction of inflammatory infiltration, and improvement of cardiac dysfunction.[67,68]

IL-6 levels are elevated in advanced heart failure, potentially contributing to the underlying pathophysiology of this condition.[69,70] Blockade of IL-6 in angiotensin II-treated mice could decrease cardiac hypertrophy and fibrosis.[71] NK cells, in addition to their role as killer cells, are significantly involved in the repair process of damaged tissues and modulating tissue homeostasis.[72] NK cells play a crucial role in regulating the cardiac inflammatory environment by both promoting and inhibiting various inflammatory responses. They facilitate monocyte maturation and eosinophil apoptosis, while also halting viral replication, autoreactive T cells, ILC-derived T_H2 cytokines, and activated cardiac fibroblasts. This regulatory function is achieved through the release of perforin and IFN-γ.[73] Some key roles of NK cells in HDs are mentioned in Figure 3.

Previous studies have demonstrated a decreased total number and/or function of NK cells in the CAD and ischemic HD.[19,21]

In CHD, it is revealed that NK cells are less cytotoxic in comparison to healthy controls, which may be associated with the proinflammatory effect of cytokines.[19] Additionally, a notable link has been observed between the inability to restore NK cell levels and low-grade cardiac inflammation. This suggests that reduced NK cell counts act as a negative indicator in CAD while also providing a protective function.[24] However, there is inconsistency in the data regarding the peripheral blood NK cell number in acute coronary syndrome,[24,74-77] while other investigations have reported an increased number of NK cells.[78,79] However, whether these phenomena are causative or merely coincidental remains to be elucidated. Besides, NK cells are not accelerators or inhibitors of atherosclerosis in mouse models but are considered to be more like bystanders, awaiting further experimental tests.[80,81] NK cell cytolytic defect is correlated with higher levels of IL-6 in patients with heart failure, though the underlying mechanisms have not been elucidated.[82] Furthermore, it has been shown that NK cells in patients with PAH exhibit functional deficits, characterized by reduced production of macrophage inflammatory protein-1β and elevated levels of MMP-9. This suggests that NK cells play a role in vascular remodeling,[83] indicating their potential therapeutic effects on the pathogenesis of PAH.[84] Moreover, it is indicated that NK cells have a protective role in myocarditis, where they are capable of limiting cardiac inflammation and fibrosis by inhibiting eosinophil infiltration.[85] Cardiac fibroblasts and cardiomyocytes are both susceptible to CVB3 infection.

Among these, cardiac fibroblasts are crucial to the pathology of CVB3-induced myocarditis, serving as significant facilitators of virus replication that worsen the condition.[86] Host cells are capable of promoting an inflammatory environment in response to infection by producing proinflammatory cytokines like IL-1α, IL-6, TNF-α, and IFN-γ, as well as monocyte and NK cell activation, leading to apoptosis of infected cells.[61,87] NK cell presence is essential for the elimination of viral infection-related myocarditis.[88] NK cells along with macrophages effectively eliminate the virus by releasing perforin to kill infected cardiomyocytes and by stimulating adaptive immunity via IFN-γ production.[89] Moreover, a significant decrease in NK cell number and function has been reported in idiopathic myocarditis, where depressed NK cell activity may be linked to recurrent attacks in viral myocarditis.[26] In one study, perforin-related pores were found on virally infected myocytes in patients with myocarditis.[90]

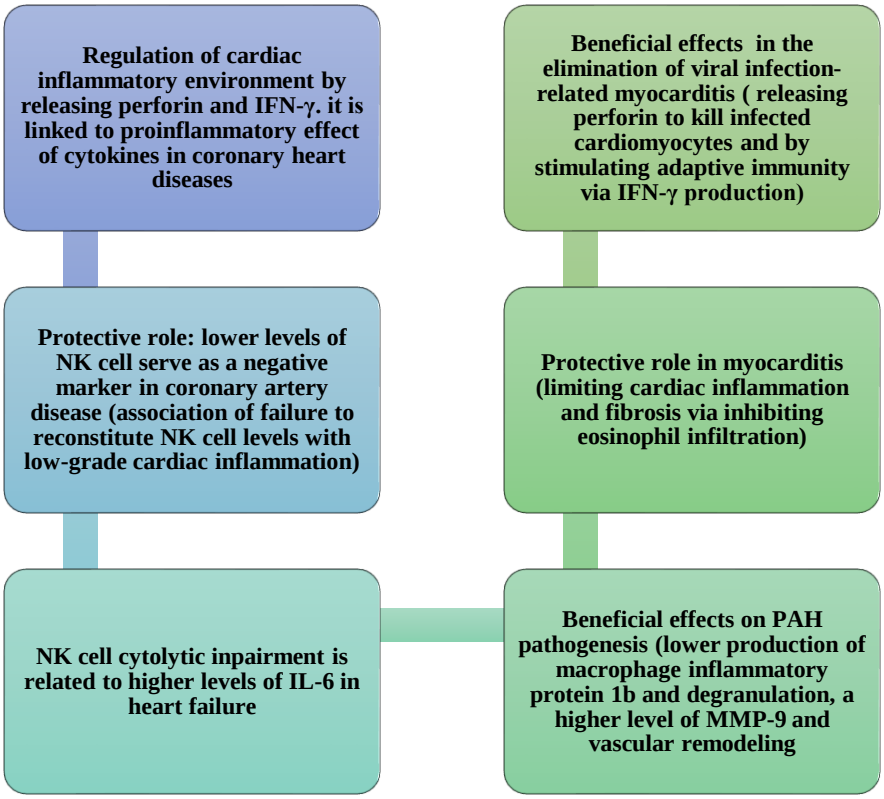

Figure 3. The key roles of natural killer cells in heart disease. IFN-γ: interferon gamma; IL-6: interleukin-6; PAH: pulmonary arterial hypertension; MMP-9: matrix metalloproteinase-9

Even though the precise role of NK cells in MI has yet to be completely understood, some studies have reported crosstalk between monocytes and NK cells through the T-bet/IFN-γ/IL-12 signaling loop, which in turn results in NK cell and monocyte activation, leading to the recruitment of inflammatory cells to inflammation sites.[91] The IL-18/IL-12 axis is involved in the regulation of the T_H1 response and promotes high-level IFN-γ production, leading to the enhancement of B-cell responses, i.e., maturation and isotype switching, indicating the role of inflammatory activation as a bridge between innate and adaptive responses in the development of heart failure.[92]

Another study demonstrated that c-kit signaling can inhibit ventricular dilation and hypertrophy while preserving cardiac function in c-kit–deficient mice. This signaling pathway is involved in mediating the mobilization of bone marrow-derived NK and angiogenic cells following MI. The aforementioned study indicated the role of inflammatory pathways, particularly NK cell-mediated mobilization after MI, in rescued hearts.[93]

Moreover, NK cells play a consequential role in cardiac transplant outcomes in patients, both in the short and long term. This positions them as a promising therapeutic target to enhance clinical results following transplantation and engraftment. The infiltration of NK cells into cardiac donor tissue, combined with the recognition of mismatched HLA class I molecules by KIRs in the innate immune system, as well as antigen-specific responses from the adaptive immune system, all play critical roles in the acute rejection of cardiac transplants and grafts.[23,34]

NK Cells and CHD/NK Cells in Acute Myocardial Infarction

Acute MI ranks among the leading cardiovascular diseases contributing to global morbidity and mortality. Despite all medical advances in reperfusion methods and greatly improved survival rates, patients may still suffer from the remodeling of the ventricle following MI, which in turn puts them at risk of ischemic heart failure and further long-term complications.[94]

Many studies have demonstrated the importance of NK cell malfunction in the pathology of cardiovascular diseases such as CAD. This defect is primarily attributed to a reduced number of NK cells, likely resulting from spontaneous apoptosis.

Yan and colleagues demonstrated that both quantitative loss and dysfunction of NK cells in AMI patients are linked to the activity of inhibitory and activating NK cell receptors. Therefore, improving NK cell immunity may represent a potential therapeutic strategy for patients with AMI.[25] A reduced number of NK cells has also been reported in various forms of MI.[95] Consistently, in another study by Zhao and colleagues, activated NK cells were found among other immune cells to infiltrate infarcted tissues of the heart and probably play a part in MI development.[96] Although the persistent mild inflammation in CAD patients following altered NK cell levels confirmed the protective effects of these cells in atherosclerosis, not much data is available on the exact role of NK cells in AMI. In this regard, the number of $NKG2D^+$ NK cells in circulation decreased in patients with acute MI, which may indicate that these cells are migrating to the injured tissue. Meanwhile, other NK cell phenotypes are likely moving from tissues into circulation to regulate the inflammatory immune response.[97]

On the other hand, the restoration of NK cell levels to normal may be impeded by proinflammatory conditions, such as elevated IL-6 in patients with CAD. Low-grade inflammation has been associated with the inability to reconstitute NK cells,[24] implying that NK cell deficiency serves as a negative indicator in CAD.

IFN-γ and TNF-α produced by NK cells are linked to a worse survival prognosis following MI.[98] This aligns with findings from Ortega-Rodríguez and colleagues, who demonstrated that the migration of certain NK cell subtypes to the bloodstream helps regulate inflammation.[97]

Since the introduction of cell-based therapies, MI has also become an interesting target among other pathologies. Autologous bone marrow-derived cells[94] and mesenchymal stem cells (MSCs) have been used clinically as adjuvant therapies.[99] Although NK cells, their activating and inhibitory receptors, and signaling cascades have been long studied and exploited for most solid tumors and hematologic malignancies and transplant rejection management, the therapeutic potential of these innate immune cells in MI has been quite overlooked. Therefore, it appears highly beneficial to conduct further investigations in this area.

CONCLUSION

Different immune cells contribute to the pathogenesis of different inflammatory and non-inflammatory CVDs such as MI, heart failure (HF), CAD, etc.[7,100] NK cells are recognized as the primary effector lymphocytes in the innate immune response, equipped with constitutive cytolytic capabilities. They are involved in the repair of damaged tissues and play a role in maintaining tissue homeostasis.[72] Furthermore, NK cells play a crucial role in modulating the immune system through receptor-ligand interactions and the release of cytokines and chemokines.[63] It has been shown that circulating NK cells are significantly reduced in number and lose their cytolytic function in HF as well as in coronary and ischemic heart disease.[63] In MI, NK cells are the first lymphocytes that infiltrate the heart and play several roles to protect the injured heart tissue. NK cells limit the infiltration of innate immune cells and their activity by decreasing chemokine production and secretion of IFN-γ, perforin, and anti-inflammatory chemokines.[101] NK cell cytolytic impairment was found to be associated with unstimulated levels of IL-6 in the peripheral bone marrow-derived cells of patients suffering from heart failure. It was also reported that NK cells are drastically decreased in patients with coronary artery and ischemic heart disease.[24]

In the human body, NK cells are recruited to the arterial wall by many chemokines such as Monocyte chemoattractant protein-1(MCP1) and fractalkine, and their continuous activation leads to the secretion of proatherogenic cytokines like IFN-γ.[7] In the arterial wall, NK cells' interaction with dendritic cells in the presence of oxidized low-density lipoprotein results in enhanced activation of NK and dendritic cells, promoting the inflammatory properties of both cells and exacerbating the atherosclerotic lesion.[102]

PAH is a sort of pulmonary hypertension, specified by pulmonary arterial remodeling.[103] A study of 14 patients with PAH demonstrated that the insufficiency of NK cells is probably related to an increased risk of death in PAH patients.[24] NK cells from PAH patients showed functional impairment with a decrease in macrophage inflammatory protein-1 beta (MIP-1β) production and degranulation. Additionally, NK cells from patients with PAH showed elevated gene expression and enzymatic activity of MMP-9. This suggests a potential mechanism through which these cells can directly impact the pathological pulmonary vascular remodeling,[83] highlighting the protective response of NK cells in the pathogenesis of PAH.[83,84]

In the mouse model of myocarditis, NK cells play a key role in limiting the spread of viral infection and reducing cardiac eosinophilic infiltration.[53] NK cells demonstrate a protective effect against the development of cardiac fibrosis by limiting collagen formation in cardiac fibroblast cells and preventing specific inflammatory population accumulation in the heart.[53]

Several clinical investigations have shown that NK cells are significantly decreased in patients with coronary artery and ischemic heart disease through either total numbers or phenotypic ability.[21,23]

STATEMENT OF ETHICS

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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DATA AVAILABILITY

All the data are available in the article.

AI ASSISTANCE DISCLOSURE

Not applicable.

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