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Natural Killer Cells in Post-Infarction Angiogenesis: Mechanisms, Evidence, and Translational Prospects

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ABSTRACT

Myocardial infarction (MI) is leading cause of cardiovascular morbidity and mortality in developed and developing countries. Deep insight into the cellular and molecular mechanisms governing cardiac infarction may foster the translation of emerging therapeutic approaches into clinical practice. The promotion of angiogenesis and blood perfusion into the ischemic myocardium is essential for restoring functional cardiomyocytes after infarction. It has been indicated that different immune cell subsets can regulate the angiogenic switch in ischemic myocardium via close interaction with vascular cells and production of various pro-angiogenesis cytokines. Natural killer cells are innate lymphocytes that may influence inflammatory and reparative responses after MI. Depending on their phenotype and the stage of injury, NK cells may aggravate tissue damage or contribute to repair. These cells have capacity to be recruited into the inured sites with the capacity to mediate several molecular and cellular mechanisms associated with healing process by collaborating with other immune cells, production of various cytokines. However, the precise role of NK cells in regulating angiogenesis following myocardial infarction remains incompletely understood. In this regard, the elucidation of NK cell function and activity may pave the way for the development of long-term, efficient therapeutics with minimal side effects in MI patients. Here, we aimed to collect the recent data related to the activity of NK cells within the ischemic myocardium and the regulatory role of these cells in healing processes.

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1. Introduction

MI is the leading cause of human mortality in industrialized and developing societies during the last few decades. Acute myocardial infarction remains a major cause of morbidity and mortality; the relevant contemporary estimate should be cited accurately.[1] Under chronic conditions, the formation of myofibroblasts, inappropriate collagen deposition, and ventricular wall thinning are the main causes of heart insufficiency.[2] It is widely accepted that the recruitment of various immune cell subsets can exacerbate the inflammatory response, leading to the death of vulnerable cardiomyocytes in the vicinity of ischemic regions.[3]

Among various immune cells, the critical role of NK cells has been indicated following ischemic changes, especially within the myocardium.[4] NK cells are key components of the innate immune system with a prominent role in the regulation of inflammation, tissue repair, and the immune response, especially after MI.[5,6] Experimental and observational studies have linked altered NK-cell number or function with several cardiovascular conditions, although causality is not established in all settings, such as myocardial tissue inflammation, atherosclerosis, coronary artery disease (CAD), and AMI. [7,8] As an critical component of the immune system, NK cells can be effective cells in the subsequent phases of inflammatory responses and cardiac tissue repair.[9] It was suggested that NK cells can produce and release cytokines such as interferon-γ (IFN-γ) which may promote the recruitment of other immune cell types into the infarcted area.[9] Along with these changes, the type of NK cell-fibroblast interaction may influence the prevention of collagen fiber production and control of cardiac tissue fibrosis.[10] The induction of vascularization and restoration of local blood perfusion into the ischemic regions is thought to be an efficient therapeutic strategy in inhibiting the expansion of abnormal cardiac tissue remodeling and reduction of cardiomyocyte death while accelerating the healing process.[11] Preclinical data suggest that NK cells may influence endothelial-cell behavior and vascular remodeling after myocardial injury.[12] Commensurate with these descriptions, NK cells can act as a double-edged sword in the control of the healing process/fibrotic changes in ischemic myocardium. It should be noted that the reported effects for NK cells may vary depending on the stage of infarction, NK cell subset, activation mode, tissue compartment, species, and testing strategy. This review examines mechanisms through which NK cells may lessen or aggravate ischemic myocardial injury.

2. Search strategy

A comprehensive search of published scientific literature on the role of NK cells, MI, ischemic cardiac injury, immune regulation, inflammation, cardiac remodeling, fibrosis, and tissue regeneration was conducted in various scientific sources including PubMed, Scopus, and Web of Science were systematically searched up to March 2026. Only articles published in English were included in the current review article. In the first step, the titles and abstracts of the articles were screened for relevance, and then eligible studies were evaluated in full text. Articles were selected based on scientific relevance, methodological soundness, novelty, and their contribution to understanding the role of NK cells in myocardial injury, tissue regeneration, and repair mechanisms.

3. NK cell features and function

Several studies have revealed that NK cells are a specialized subpopulation of innate lymphoid cells (ILCs) and constitute about 5–15% of circulating peripheral blood mononuclear cells (PBMCs) in humans.[13] In general, the characterization of NK cells is based on the expression of a membrane-bound marker, namely CD56, and the lack of CD3. It is suggested that NK cells can exert a pivotal role in immune surveillance, particularly in host defense against viral infections and tumor cells.[14,15] It is estimated that bone marrow is the main and primary

site for the NK-cell development and maturation into the circulation system. Along with this fact, different developmental stages, either naïve progenitor or functional mature NK cells, are present in the human bone marrow niche.[16] Within the bone marrow microenvironment, $CD34^{+}$ stem cells and progenitor cells exhibit lineage potential by expressing various cell markers and receptors.[17] In general, NK cells are classified into three stages as follows: commitment to a lymphoid lineage, NK/ILC lineage, and finally, conventional NK cell lineage.[18] Mature human NK cells are generally classified into two major subsets, including $CD56^{bright}$ and $CD56^{dim}$ cells, in which $CD56^{bright}$ NK cells with less cytotoxicity can release high amounts of cytokines associated with immune system function.[19] In contrast, $CD56^{dim}$ NK cells display greater cytotoxic potential, constitute the highest number of circulating NK cells.[20] However, several genomic and proteomic analyses revealed distinct NK cell subsets, NK1, 2, and 3 cells, with complexity in these cells' function and phenotype.[21,22] It seems that the existence of such heterogeneity is thought to facilitate the adaptation of NK cells to different tissue niches and pathologies.[23] In contrast to adaptive immune cells, the activity of NK cells does not rely solely on antigen-specific receptors, and the function of these cells is tuned via the regulation of stimulatory and inhibitory receptors, including killer immunoglobulin-like receptors (KIRs), CD16 (FcγRIIIA), and natural cytotoxicity receptors.[24] Due to these features, NK cells can recognize infected or malignant cells and mediate cytotoxic responses (**Figure 1**).[25]

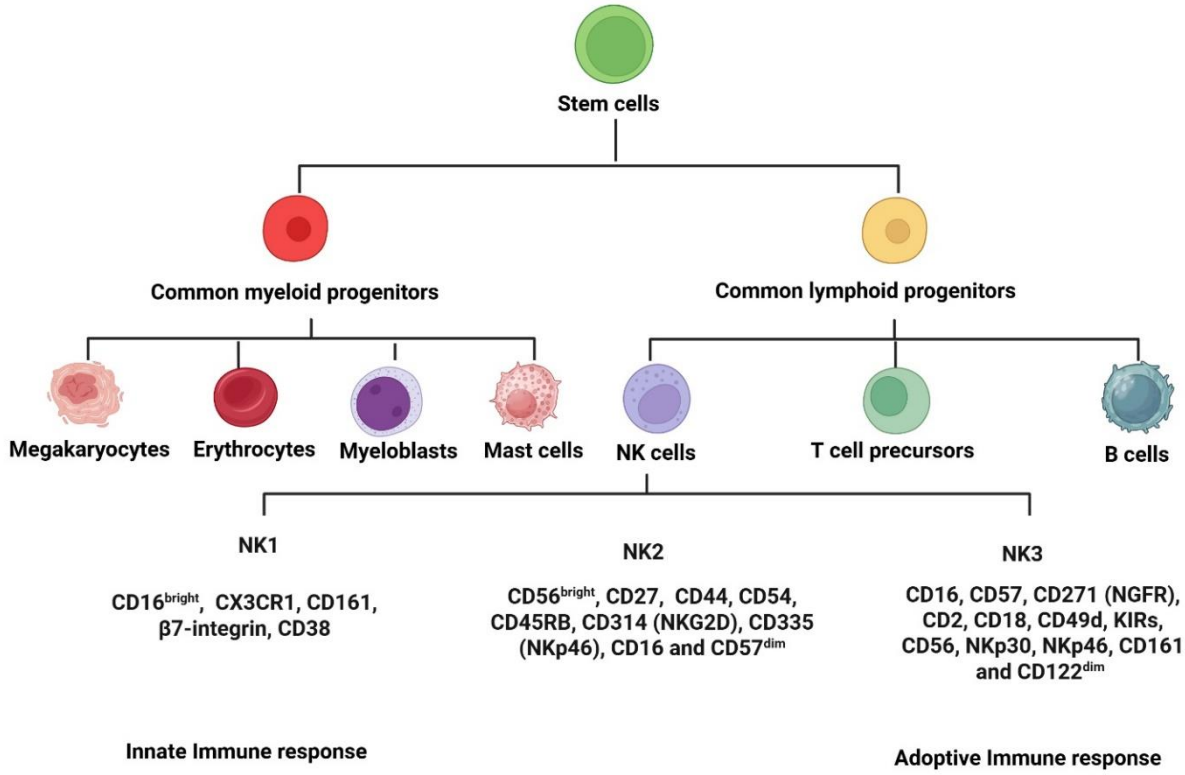


Figure 1. NK cell development, and type in humans. Created by BioRender's web-based software.

During their development, NK cells interact with major histocompatibility complex (MHC) class I molecules through KIRs.[26] The recognition of MHC class I molecules is thought to be an inhibitory mechanism in NK cell function.[27] The direct interaction of NK cell KIRs with target cell MHC I induces inhibitory signals that suppress NK cell activity and cytotoxicity (**Figure 2**).[28] By the application of such a function, NK cells can eliminate infected or tumor cells with reduced expression of MHC I.[29] The NK cell CD16 (FcγRIIIA) is actively involved in antibody-dependent cell-mediated cytotoxicity (ADCC) via direct attachment to the Fc region of

antibodies on the surface of target cells.[30,31] Several natural cytotoxicity receptors (NCRs), such as NKp46, NKp30, and NKp44 which belong to Ig-like transmembrane proteins, are identified on the surface of NK cell lineage. Notably, NKp46 and NKp30 are abundant on the surface of resting NK cells and activate the downstream signals with CD3-ζ and/or FcεRI-γ.[32] While NKp44 is expressed upon NK-cell activation via the promotion of KARAP/DAP12 adaptor molecule and orchestrates the tumoricidal properties and cytotoxicity and effector functions.[32]

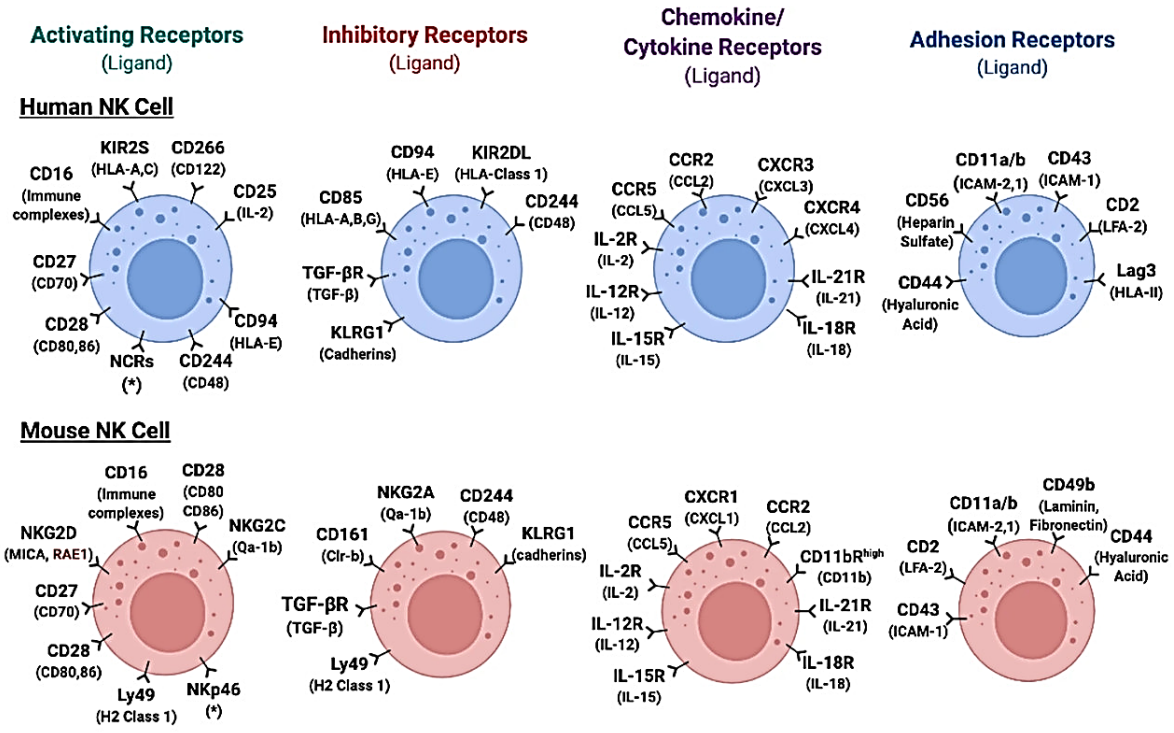


Figure 2. The function of different receptors in human and mouse NK cells. Several inhibitory and stimulatory signals can influence the function of NK cells. The combination of ITAMs and ITIMs, along with other stimulatory receptors and adhesion factors, can orchestrate the NK cell activity. ITAMs: immunoreceptor tyrosine-based activation motifs; ITIMs: immunoreceptor tyrosine-based inhibitory motifs. Asterisks (*) show multiple ligands, such as viral and tumor-associated ligands. Reproduced with permission.[33] Experimental & Molecular Medicine. 2020.

Target-cell elimination by NK cells occurs through two major mechanisms.[34] The primary mechanism of NK cell cytotoxicity is related to formation of immunological synapses and transfer of cytotoxic granules containing perforin and granzymes to the target cells.[35] Perforin facilitates the formation of pores on the juxtaposed cell membrane, resulting in the release of granzymes, which are serine proteases to induce apoptosis in a caspase-dependent manner.[35,36] Some studies reported that the expression of lysosomal-associated membrane proteins (LAMP-1/CD107a and LAMP-2/CD107b) has been reported during degranulation of NK cells and is associated with the cytotoxic activity of these cells.[37] Fas ligand (FasL) and TRAIL (TNF-related apoptosis-inducing ligand) are other death-receptor ligands with the potential to activate the apoptotic changes in the target cells.[36] Besides cytotoxic behavior, NK cells are an important cell source for the production and release of IFN-γ, TNF-α, and GM-CSF, interleukins (i.e., IL-5, IL-10, IL-13), and chemokines (e.g., CCL3, CCL4, CCL5, CXCL8), making these cells key regulators in immune response, inflammation, cell recruitment, and the healing process.[17,27] Despite the crucial role of NK cells in the regulation of tumoricidal and anti-viral mechanisms, the dysregulated NK-cell activity can contribute to the development or progression of various pathological conditions such as autoimmune disorders, chronic viral infections, and cardiovascular diseases such as CAD and AMI.[38-40]

4. Role of NK cells in the pathogenesis of MI

Following the initiation of AMI, vascular ECs undergo significant phenotypic and functional alterations, leading to the loss of vascular homeostasis.[41] The exposure of ECs to mild to moderate ischemia-reperfusion injury, like oxidative stress, TNF-α**,** IL-1β, or proinflammatory stimuli, activates these cells.[42] The phenotypic change of ECs coincides with the production and release of various cytokines (IL-6, IL-8, MCP-1, GM-CSF) and other factors such as membrane-bound adhesion molecules (ICAM-1, VCAM-1, E-selectin) on the luminal surface.[42] The local increase of inflammatory cytokines leads to the recruitment of different immune cell types, such as monocytes, T lymphocytes, neutrophils, mast cells, and NK cells to the site of injury, especially atherosclerotic plaques.[43] Emerging data have proved the direct involvement of NK cells in the progression of AMI-related pathologies.[7,12,44] Under hypoxic conditions in testicular tissue, activation of the KLF4–ALDH1L1–ICAM-1 axis promotes the recruitment and activation of NK cells. It was suggested that the increase of ICAM-1 is promoted via the intracellular KLF-4 following the recruitment of histone methyltransferase ASL1L to the ICAM-1 promoter.[45] NK cell-derived IFN-γ, TNF-α, IL-13, and type I interferons promote an inflammatory response and immune cell homing, resulting in cardiac tissue remodeling.[46] For instance, NK cell IFN-γ can destabilize the atherosclerotic plaques via the inhibition of collagen synthesis in vascular smooth muscle cells (VSMCs). These features result in the loss of fibrous caps and the possibility of rupture.[47] By the release of various tissue factors and extracellular matrix (ECM) components, the coagulation cascade is activated, leading to platelet activity, platelet aggregation, and thrombus formation, occlusion or narrowing of the supporting vessels to the myocardium, and AMI.[48] Regardless of its cellular source, local increase of TNF-α is directly associated with impaired cardiac tissue function, dilation, and hypertrophy.[49] Likewise, the intracardiac IL-1β is the main proinflammatory factor in chronic hypoxia following MI can dysregulate calcium homeostasis.[50] Along with these changes, the increase of IL-6 under advanced heart failure can also prohibit the number of recruited NK cells, compromising the cardiac tissue recovery.[51] The accumulation of NK cells for a prolonged time may contribute to cardiomyocyte injury via the release of perforin and IFN-γ.[5,52] Of course, it should not be forgotten that the factors can orchestrate both pro- and anti-inflammatory responses in a context-dependent manner.[53] Under such conditions, the activity of the NK cell ERG gene in MI individuals and mice stimulates HLX, contributing to proteasomal degradation, and STAT4 coincides with the reduction of perforin expression. These features can blunt the potential protective roles of NK cells after MI and advance the MI-related pathologies.[54] Calling attention, NK cells are effector cells in dynamic crosstalk with other immune cell types, such as monocytes and macrophages.[55] Due to the key role of monocytes and macrophages in the pathophysiology and vascular inflammation in infarcted myocardium and production of cytokines, chemokines, adhesion molecules, and reactive oxygen species (ROS) via NADPH oxidase, the close interaction between NK cells and monocyte/macrophages is inevitable.[56] Gunasena and co-workers revealed that NK cells interact with monocyte-derived macrophages following MI in COVID-19 patients. In response to COVID-19, all NK cell subsets are prone to express tissue specific marker namely CD69 coincided with the increase of proinflammatory intermediate monocytes and reduction of nonclassical monocytes. The exposure of macrophages to oxidized-low-density lipoprotein (Ox-LDL), the release of certain cytokines such as (TNF-α, IL-6), adhesion molecules, and ROS via NADPH oxidase along with activated NK cells can increase the probability of CVD in COVID-19 individuals (**Figure 3**).[56]

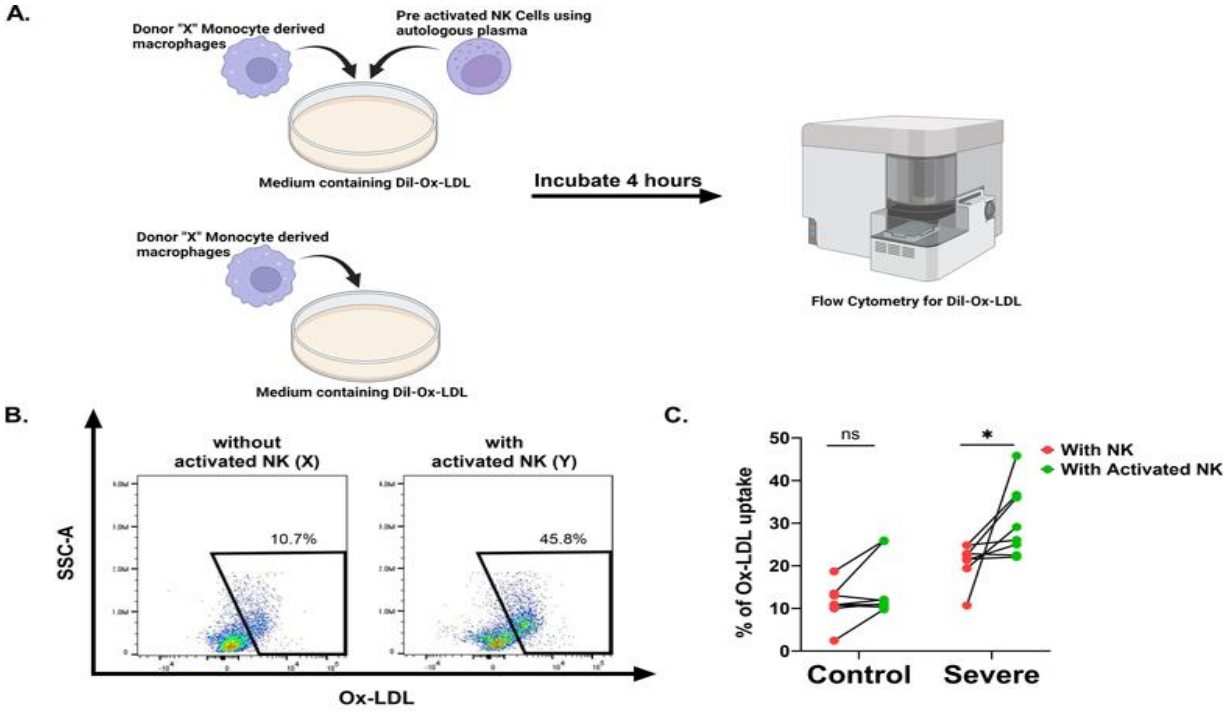


Figure 3. The stimulatory role of NK cells on the uptake of Ox-LDL by macrophages in in vitro conditions (A-C). The experimental procedure associated with the uptake of Dil-Ox-LDL by macrophages when exposed to activated NK cells in the presence of autologous plasma (A). Flow cytometry analysis of Ox-LDL uptake by macrophages exposed to activated NK cells compared to *the* NK cell-free group (B). The percentage of Dil-Ox-LDL$^+$ cells (n = 6). Wilcoxon signed-*rank* test. *p<0.05. Abbreviations: SSC: side scatter. Reproduced with permission.[56] Arteriosclerosis, Thrombosis, and Vascular Biology. 2024.

Several signaling pathways, such as the T-bet/IFN-γ/IL-12 axis, are provoked in this regard, leading to the recruitment of other and additional inflammatory cells to the infarcted myocardium.[8] Also, the IL-12/IL-18 axis enhances the release of IFN-γ by NK cells, making it a link between the innate and adaptive immune system. The uncontrolled and abnormal contents of these cytokines initiate the inflammatory responses, abnormal myocardial remodeling, and chronic heart failure (CHF).[8] Macrophages can stimulate the NK cells via the release of IL-12 and IL-18 in a paracrine manner or direct physical contact.[55] On the other hand, NK cell IFN-γ is the main cytokine for the recruitment and activity of monocytes/macrophages during AMI.[57] Additionally, in the presence of NK cell IFN-γ, the differentiation of monocyte-to-macrophages or dendritic cells is promoted, thereby the local levels of ILs such as IL-12, -15, -18 are heightened.[58] Interestingly, IL-12 and IL-18 can trigger the production of IFN-γ in NK cells. Therefore, this interaction is thought to be a positive feedback loop and cellular mechanism during few hours after initiation of innate inflammatory response.[58]

The NK cell homing in AMI and CAD patients can lead to a reduction of circulating NK cells with a high rate of spontaneous apoptosis and impaired receptor function.[12,44] Studies of YAN have shown that in patients with acute myocardial infarction, NK cell activity is reduced and the expression of inhibitory receptors on these cells is downregulated (NKG2D, NKp30, NKp46). These changes can lead to reduced protection of normal cells and increased damage to cardiac tissues.[44] Data have confirmed the significant reduction of $CD3^-/CD56^{bright}$ and $CD3^-/CD56^{dim}$ NK cell subsets, reduced cytotoxic properties, and IFN-γ production capacity.[7] It seems that chronic and low-grade inflammation in MI patients suffering myocarditis, ischemic disease, and even in individuals with transplant rejection is the main reason for the reduction of NK cell function.[5,8] The simultaneous down-regulation of NK cell receptors and increase of the LILRB1$^+$ NK cell population are common findings in MI individuals.[7,44] The LILRB1 receptor (also known as LIR-1 or ILT2) is an inhibitory receptor that interacts

with HLA class I molecules and can regulate the activity of NK cells. These LILRB1+ cells typically have high cytotoxicity and represent a dynamic adaptive immune response following ischemic heart injury.[59-62] Besides, a transient increase in granulysin-expressing NK cells has been indicated in MI patients during 7 days, and these features can last for 28 days, showing the dynamic activity of these cells following ischemic myocardial injuries.[39]

5. Protective of NK cells in MI

Despite their early pro-inflammatory activity, emerging evidence indicates that NK cells play crucial regenerative and remodeling roles during the later stages of MI. NK cells support immune regulation in the post-cardiac injury period by controlling inflammation, preventing excessive accumulation of immune cells in cardiac tissue, and thereby maintaining stable cardiac function.[5,6] Studies have shown that these cells play an important role in preventing cardiac fibrosis by directly limiting collagen production in cardiac fibroblasts and inhibiting the accumulation of specific inflammatory populations and fibrotic precursor cell types, such as eosinophils (**Figure 4**).[63]

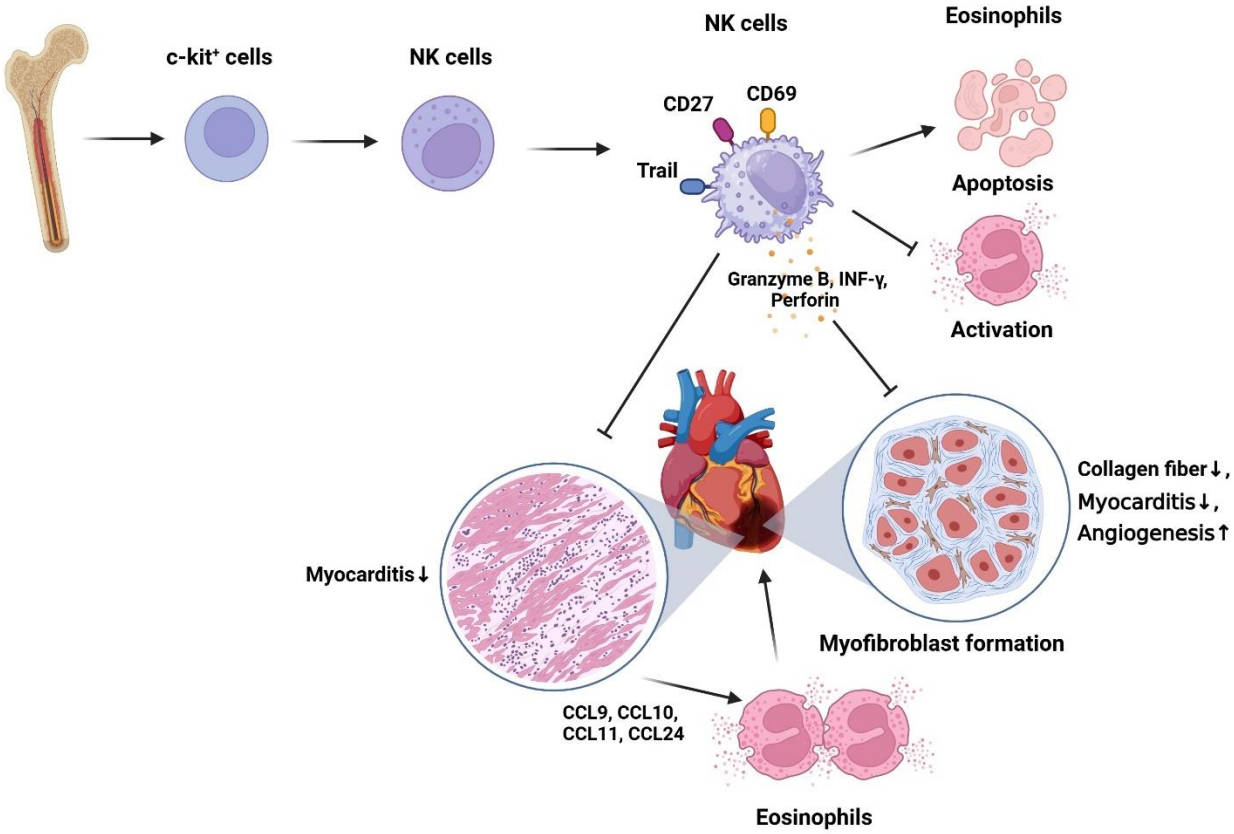


Figure 4. The role of NK cells in cardiac tissue fibrosis. Along with the progression of ischemic changes within the myocardium, the number of activated NK cells is increased, followed by the release of granzyme-B and IFN-γ. It was suggested that activated NK cells can express markers such as CD69, TRAIL, and CD27. This hyperactivity can result in reduced fibrotic tissue formation via the inhibition of eosinophil recruitment and apoptosis. During the MI, the differentiation of NK cells from bone marrow c-Kit$^+$ bone marrow cells was indicated. These features can lead to the reduction of cardiac cell apoptosis, collagen fiber deposition, and fibrosis with promoted angiogenesis response. Created by BioRender's web-based software.

In addition, NK cells interact with cardiac ECs (CECs) after MI to promote vascular remodeling and angiogenesis. NK cells activated by IL-2 infusion promote blood vessel remodeling through α4β7 integrin and the lectin-like receptor KLRG1, without directly participating in initial vessel formation.[5,8] In this process, NK cells first bind to cardiac endothelial cells via α4β7 and VCAM-1 and then disrupt N-cadherin binding via KLRG1. This disruption causes β-catenin to translocate from the cytoplasm to the nucleus, thereby eliminating the inhibitory effect of cell-cell contact on endothelial proliferation. Following this event, the Wnt/β-catenin pathway

is activated, leading to increased endothelial cell proliferation and vascular remodeling.[6,64-66] As mentioned above, a transient reduction of circulating NK cells is a common finding in the first few hours and early hours post-MI (**Figure 5**).[67] Data showed that NK cell counts were reduced in patients with ST-segment elevation MI (STEMI) compared to healthy controls. This decrease was mainly attributed to compositional alterations within the $CD56^{dim}$ NK cell subset. Moreover, throughout the disease course (from t_0 to 24 hours), a further decline and redistribution of NK cell populations were observed (**Figure 6**).[68]

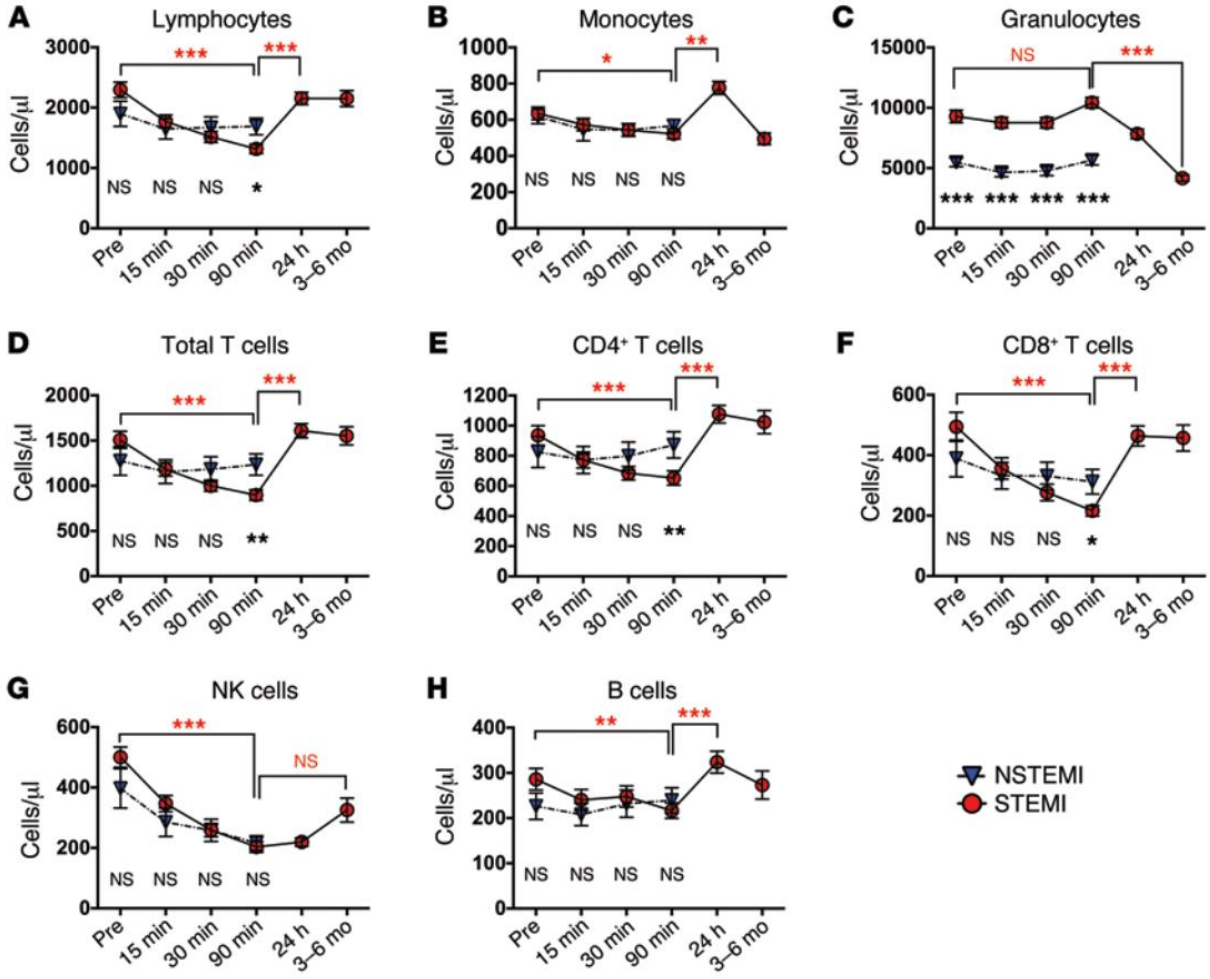


Figure 5. Changes in levels of immune cells at different time points (**A**-**H**). The number of lymphocytes (**A**), monocytes (**B**), and granulocytes (**C**) was changed over time in STEMI patients. Time points were measured from reperfusion in the STEMI group and from first culprit vessel instrumentation (or initial "Pre" blood sampling if no intervention occurred in the NSTEMI group. Total T lymphocytes (**D**), $CD4^+$ T lymphocytes (**E**), and $CD8^+$ lymphocytes (**F**). $CD3^-$ lymphocyte subset (**G** and **H**). NK cells (**G**), B cells (**H**). Red asterisks refer to the differences in values between two groups at different time points (Friedman test, with Dunn's multiple-comparisons test). Black asterisks refer to significant differences between STEMI and non-STEMI individuals (Mann-Whitney U test). STEMI: n = 59; NSTEMI: n = 15. *p<0.05, **p<0.01, ***p<0.001. Reproduced with permission.[67] Journal of Clinical Investigation. 2015

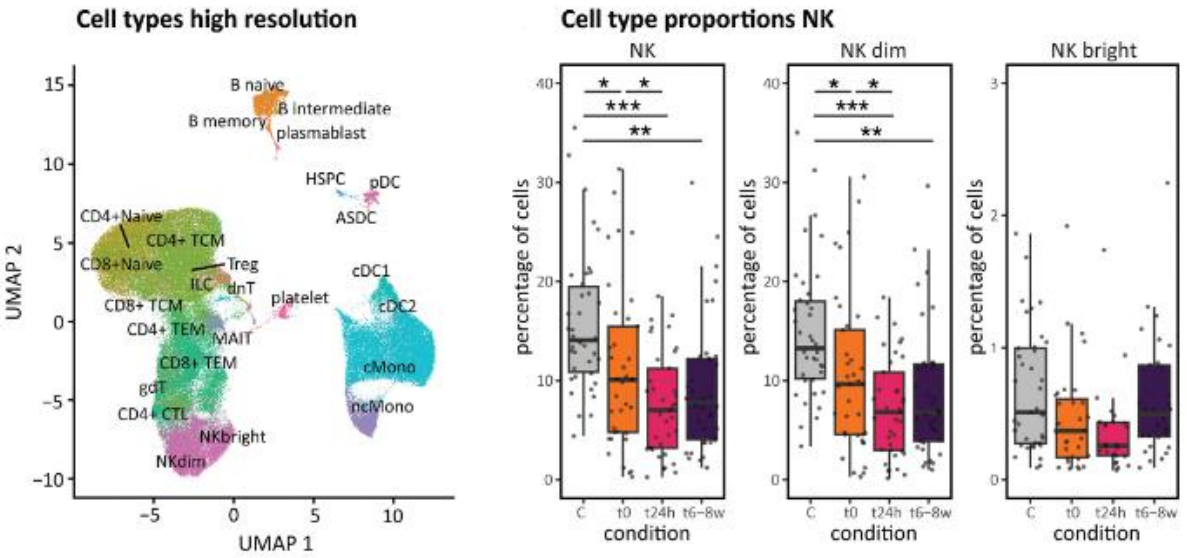


Figure 6. The type of blood mononuclear cells was analyzed at t0, t24h, and t6–8w in the STEMI and control groups in uniform manifold approximation and projections (UMAPs). Data revealed at least 29 minor cell types (**left panel**). Major class and 2 subtypes of NK cells were monitored in controls and post-STEMI (**Right panels**). Abbreviations: ASDC indicates AXL SIGLEC6 dendritic cell; C, control; cMono, classical monocytes; CTL, cytotoxic T cell; cDC, conventional dendritic cell; HSPC, hematopoietic stem and progenitor cell; ILC, innate lymphoid cell; MAIT, mucosal-associated invariant T cell; ncMono, nonclassical monocytes; pDC, plasmacytoid dendritic cell; TCM, T-central memory; and TEM, T-effector memory. Significant Holm's adjusted P value *P<0.05, **P<0.01, ***P<0.001. Reproduced with permission.[68] Circulation: Genomic and Precision Medicine. 2024.

Regarding the existence of limited and contradictory data, the precise and correct role of NK cells in AMI patients and post-MI repair has not been fully addressed.[7,9,12] Therefore, frequency and phenotype of NK cells are changed post-MI, highlighting the modulatory activity of these cells during regeneration and remodeling of infarcted myocardium.[7] Following the MI, immune system components undergo three phases, including inflammation, proliferation, and maturation. It is thought that the time and intensity of each phase can pre-determine the regenerative and remodeling outcome. Based on data, NK cells can control the inflammation within the infarcted myocardium through IFN-γ, perforin, and anti-inflammatory cytokines.[69] However, the precise role and activity of these cells following MI is intricate because of both pro- and anti-inflammatory properties. As a common belief, the infiltration of NK cells reaches peak levels about the first week after vascular occlusion, leading to the possibility of proliferation of NK cells.[70] Within the infarcted myocardium, damage-associated molecular patterns (DAMPs) are released from dead cardiac cells, leading to the recruitment of immune cells and initiation of an acute inflammatory response.[71] Cardiac tissue macrophages are also present in the affected regions to scavenge dead cells while releasing pro-angiogenesis (VEGF, FGF-2) to stimulate new blood vessel formation and proliferation of local progenitor cells.[72] Therefore, these data have shown that NK cells, along with macrophages or other immune cells, regulate the reparative mechanisms and tissue homeostasis post-MI injuries.[73] On one hand, the recruited NK cells accelerate the maturation of monocytes and elimination of eosinophils via apoptosis. In the hand, NK cells can control excessive immune response by regulating T cells, type 2 innate lymphoid cell (ILC2)-derived cytokines (IL-5, IL-13), and heart fibroblast activity, controlling excessive inflammation.[8,12] It is thought that the release of perforin and IFN-γ is largely determinant in the alleviation of MI-related pathologies.[74] The production and release of anti-chemokines, perforin, and IFN-γ by NK cells can also regulate the recruitment of NK cells [7]. In the presence of these factors, the production and accumulation of collagen and myofibroblast generation are controlled, while the number of apoptotic cardiomyocytes is also

diminished.[5,70,75] The reduction of local eosinophils is also related to the reduction of collagen production and scar formation post-MI.[5,8] Despite the high prevalence of MI, current conventional therapies target primarily symptoms rather than the underlying immune mechanisms. Therefore, the application of immunomodulatory treatments can, in part, prevent the progression of adverse MI pathologies and help to improve the cardiac tissue outcome.[76] In some experiments, the activity of NK cells and cognate receptors was inhibited, leading to the attenuation of inflammation and adverse myocardial remodeling.[7] Therefore, it is thought that by inhibiting NK cell function, maturation and recruitment of inflammatory cells, and production and release of numerous cytokines(IFN-γ, TNF-α, IL-13) will be reshaped, resulting in the induction of hemopoietic cell apoptosis.[77] Of note, NK cell stimulation can lead these cells to acquire homeostatic levels, and the possibility of excessive inflammation and aberrant tissue remodeling is reduced under MI conditions.[9] In recent years, the advent of stem cell-based therapies has revolutionized human medicine for cardiac repair.[78] For example, transplantation of allogenic stem cells can yield suitable regenerative outcomes and immunomodulatory properties.[79] One critical point is that the possible interaction of transplanted cells with resident or recruited immune cells, especially NK cells, can pre-determine the fate of stem cell therapies, especially in MI individuals.[12] Under non-inflammatory conditions, transplanted stem cells are relatively resistant to NK cell cytotoxicity.[80] Of course, active NK cells can, in part, damage the stem cells via the promotion of cytotoxic pathways.[81] Interestingly, in inflamed niches such as infarcted myocardium, the NK cell-mediated cytotoxicity of stem cells is reduced.[82] Both inflammatory conditions and the regulatory role of stem cells on NK cells are essential factors to reduce transplanted cell toxicity.[81,83] In this regard, allogenic stem cells can suppress the cytotoxicity of NK cells, consistent with the switch to cytokine production and anti-inflammatory status.[84] Therefore, the reciprocal interaction with NK cells can help to increase the viability of transplanted cells via activation of immunomodulatory mechanisms.[85,86]

6. Role of NKs in the promotion/inhibition of angiogenesis after MI

The establishment of blood perfusion into the infarct region is thought to be a key element in proper cardiac tissue remodeling via rescuing the vulnerable cardiac cells.[87] Neutrophils are the first to invade the infarcted myocardium, followed by monocytes, macrophages, and NK cells, each contributing to distinct phases of inflammation and repair.[88,89] Following MI, a strong angiogenic response that starts in the infarct border zone and spreads into the necrotic infarct core is necessary for tissue healing. New mechanistic insights into postinfarction angiogenesis and how to target it to enhance cardiac function following MI have been made possible by technological advancements in several fields. Emerging data have indicated NK cells' stimulatory/inhibitory role in angiogenesis potential during several physiological and pathological conditions.[90] Data have shown that hypoxic conditions can influence the function of various immune system cells (NK cells, γδT lymphocytes, and adaptive T lymphocytes).[90] It seems that the effect of hypoxia on NK cells is controversial. In this regard, the direct exposure of NK cells to hypoxia can deteriorate the function and biological activity via the downregulation of receptors. These features coincide with the loss of granzyme B granules, autophagic death, and reduction of cytokine production.[91] While hypoxia can also regulate the function of NK cells via the stimulation of angiogenesis, inhibition of apoptosis, and suppression of immune cell activity. To be specific, hypoxic conditions blunt the cytotoxic changes in NK cells via the reduction of lytic substances and receptor-ligand interaction.[90] These discrepancies would be possibly related to the intensity of hypoxia and extent of ischemic area, and differences in model systems applied.[92] In support of this notion, hypoxia can impair the NK cell functionality via the perturbation of metabolism and fragmentation of mitochondria and a deficit in the CD122/IL-2Rβ axis.[92] Of note, pre-activation with certain cytokines, such as IL-21 and 4-1BBL and IL-15, can restore the function of

hypoxic NK cells.[92] IL-15 is a potent factor to restore the NK cell function via the activation of mTORC1, leading to the production of IFN-γ in stressful conditions [93]

The hypoxic area, which extends to the subendocardial region and infarct border zone, causes many initially surviving cardiomyocytes to die by apoptosis within 12 hours.[94] In hypoxic conditions, the expression of HIF-1α in NK cells results in the down-regulation of NKp46, NKp30, NKp44, and NKG2D, making these cells insensitive to stimulatory cytokines such as IL-2.[91] The inhibition of ERK/STAT3 is integral to reducing these receptors. Besides, the reduction of CD107a contributes to the loss of cytokine production (granzyme B and IFN-γ) capacity in NK cells.[95] The manipulation of NK cells to down-regulate the HIF-1α restored their function via expression of effectors, receptors, and activation of the NF-κB pathway.[96]

It has been indicated that the activation/inhibition of distinct signaling pathways, i.e., mTOR/c-Myc pathways, can help maintain the pro-angiogenic function of NK cells under hypoxic conditions.[97] Calling attention, mTORC1 has a superior role in the regulation of NK cell metabolism via the glycolytic pathway and mitochondrial activity, thereby controlling the proliferation and differentiation.[98] Of course, it should not be forgotten that the existence of hypoxic conditions and promotion of glycolysis inside the NK cells result in the regulation of angiogenesis. Yan et al. found that the inhibition of glycolysis in NK cells increases the production of VEGF. The inhibition of mTORC1 predisposes these cells to reduced glycolytic activity and oxidative phosphorylation, diminishing IFN-γ and TNF-α levels and CD107a-dependent degranulation.[99] Upon the activation of autophagy under stressful conditions such as hypoxia, the mTORC1 is inhibited, leading to the release of injured organelles and misfolded proteins.[100] To the best of our knowledge, the close relationship between the autophagic response and angiogenesis potential has not been indicated in NK cells under hypoxic/ischemic conditions. The culture of NK cells under hypoxic conditions can stimulate all NK cell subsets to produce and release VEGF (VEGF-A_{165}↑ and VEGF-A_{121}↑), independent of TGF-β activity and acquisition of ILC1-like phenotype.[101] Therefore, one can hypothesize that low oxygen levels, even the reduction of NK cell recruitment and cytotoxicity in the presence of TGF-β within the hypoxic myocardium, can switch local NK cells to a proangiogenic phenotype. Upon the promotion of ischemic changes in myocardium, several factors, such as TGF-β, soluble HLA-G, prostaglandin E2, adenosine, extracellular vesicles, and miRNAs, are produced with the potential to decrease NK cell activity and induce angiogenesis by releasing VEGF, PlGF, CXCL8, and IL-10 to support the growth and enhance EC proliferation, migration, and tube formation.[102] It seems that there is a close relationship between the existence of NK cells and angiogenesis potential in the target tissues. In this regard, it was suggested that IFN-γ-releasing NK cells can recall macrophages into the cornea and choroid in the laser-induced choroidal neovascularization mouse model to increase the local levels of VEGF-A, VEGF-C, and VEGFR3. The inhibition of NK cells using an anti-NK1.1 antibody blunts these effects after 7 days.[103] Based on different studies, it is logical that a wide range of cytokines and factors can influence the angiogenesis properties of NK cells under ischemic conditions. For example, the injection of IL-2 after induction of ligation of left anterior descending coronary artery (LAD) in immune competent (C57Bl6) mice led to improved cardiac function (fractional shortening↑) without effects on immune-deficient (NOD-SCID IL2Rγ^{null}) mice.[104] Data showed enhanced microvascular density (CD31↑, Ki67↑, and CD144↑) with the increase of recruited NK cells into the ischemic site. However, no effects were achieved in the number of cardiac $CD4^+$ and $CD8^+$ cells (**Figure 7**).[104]

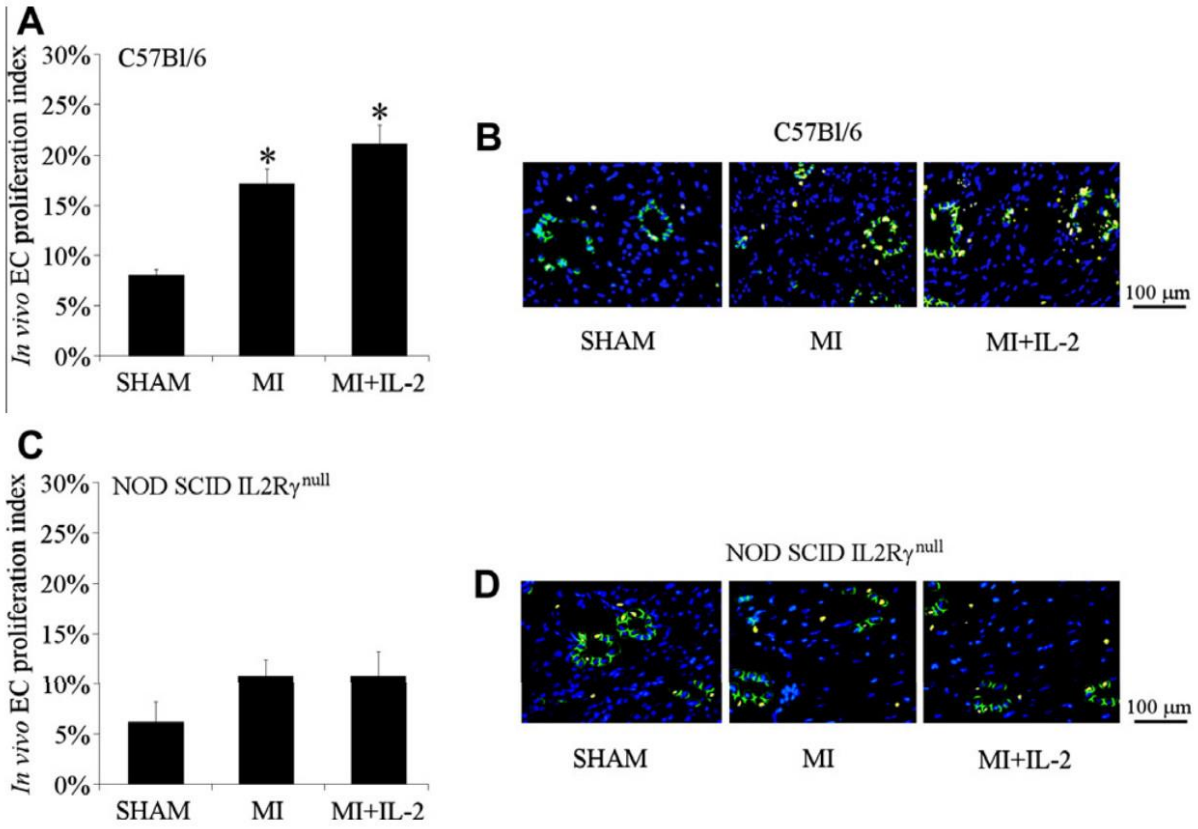


Figure 7. Monitoring EC proliferation in the infarcted myocardium in C57Bl/6 (**A-B**) and NODSCID IL2Rc^{null} (**C-D**) mice after rhIL-2 injection. Panels B and D include images of cardiac tissue stained for yellow-colored Ki67 and green-colored CD144. Nuclei were stained with blue-colored DAPI. Data are expressed as means ± SEM; *p<0.05. Reproduced with permission.[104] Cytokine. 2011.

In humans, IL-2-activated NK cells from MI patients have the potential to accelerate myocardial regeneration with reduced cytotoxic function.[7] In C57BL/6 mice, myelomonocytic inflammatory cells are recruited to the ischemic myocardium within 24 hours. On day 6, recruited lymphoid/NK cells produce notable levels of TNF-α, CCL2, and IL-2. In the NOD SCID mice with MI induced by LAD, IL-2-activated NK cells promote the healing of ischemic myocardium via stimulation of angiogenesis and direct attachment to the endothelial VCAM-1.[105], while the local increase of IL-12 can repress the angiogenesis potential by increasing IFN-γ and stimulating related downstream effectors. The inhibition of asialo GM1 or NK 1.1 can reverse the IL-12 inhibition of bFGF, thereby stimulating angiogenesis in athymic mice.[106] In a subcutaneously injected Matrigel plug, numerous ECs can be detected in the presence or absence of IL-12. However, the total number of recruited cells into the Matrigel plug in IL-12 + bFGF was less when compared to the mice that received bFGF only, indicating the inhibition of angiogenesis in the presence of IL-12. Besides, the number of esterase^{+} cells belonging to the monocyte/macrophage lineage was also diminished. Along with these data, it was shown that IL-12 can increase the number of activated B220-positive NK cells around the vascular units, resulting in the suppression of angiogenesis (**Figure 8**).[106]

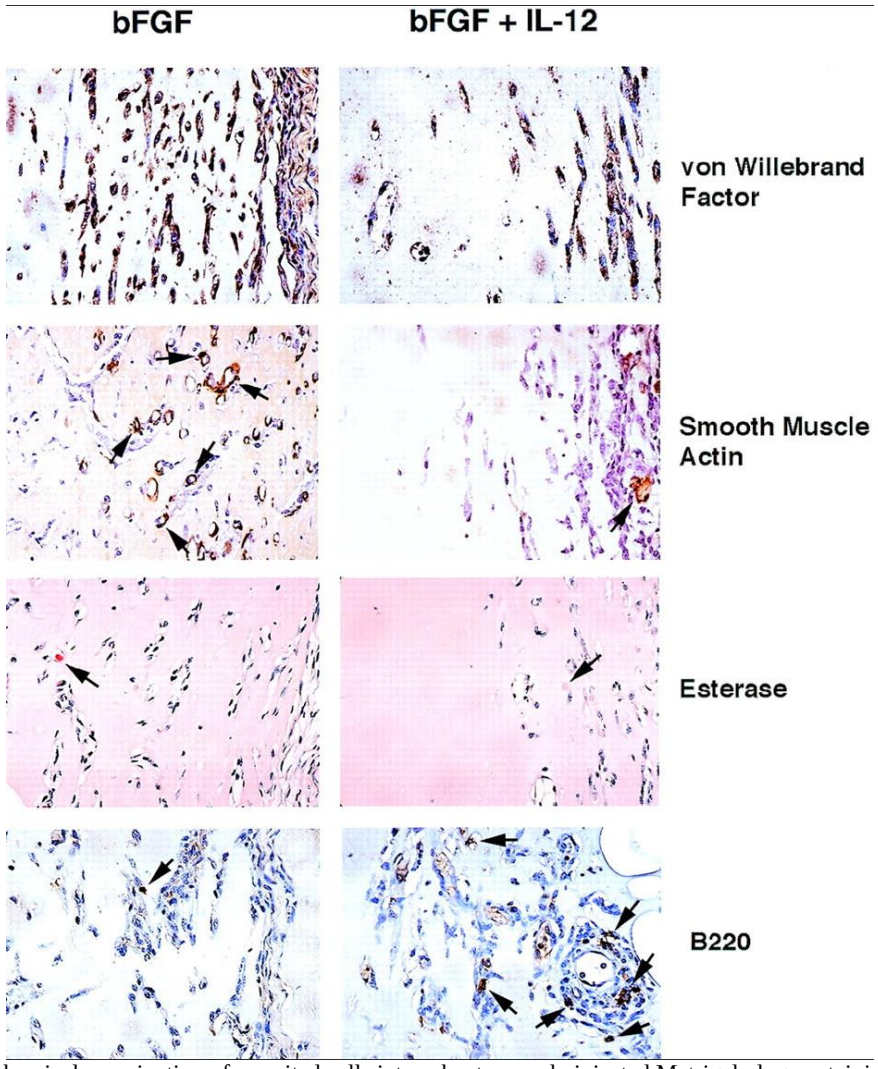


Figure 8. Histochemical examination of recruited cells into subcutaneously injected Matrigel plug containing IL-12, and IL-12 plus bFGF in mice. Microvascular intensity was assessed in terms of vWF and α-SMA-positive vessels. The presence of activated NK cells was monitored using an anti-B220 antibody. Hematoxylin was used for counterstaining. Esterase staining was done using the standard protocol. Magnification: 40X. adapted with permission.[106] Blood. 1999

Several studies have revealed that NK cells can make direct interactions with cardiac ECs following MI to stimulate angiogenesis.[104] Upon NK cell-EC interaction, pro-angiogenic mediators are released, leading to the activation of ECs and new blood formation. It has been shown that IFN-γ receptor 1 and IL-1 receptor type 1 are expressed in cardiac ECs about 1 to 7 days after AMI, which promotes ischemia-derived microvascular ECs.[107] Of note, IL-2-activated NK cells can stimulate angiogenesis via α4β7 integrin and KLRG1 without new blood vessel formation. The attachment is mediated via NK cell α4β7 with endothelial VCAM-1, resulting in the disruption of N-cadherin-mediated junctions by KLRG1 activity.[5] Wang et al found that *in vitro* culture of IL-2-activated NK cells can lead to the proliferation of cardiac ECs. Along with these changes, the direct injection of IL-2-activated NK cells in MI rats increased the up-regulation of MCP-1, TNF-α, CD31, and IL-2, and VEGF coincided with higher microvascular density and an improvement of heart ejection fraction.[108] These features indicate that NK cells can actively control the angiogenesis process within the ischemic regions, especially in the infarcted myocardium.

7. Methodological limitations and confounders in NK cells

Despite the growing number of studies investigating the role of NK cells in angiogenesis in cardiac and other tissues (Tables 1 and 2), several limitations restrict the direct translation of the available evidence into

clinical applications. Interpretation of studies on NK cells in MI is not straightforward and complex due to numerous methodological limitations and potential confounding factors. For example, anti-NK1.1 and anti-asialo-GM1 antibodies are not entirely specific for NK cells and may also affect other innate lymphoid cells or immune cell subsets, making it difficult to attribute the observed phenotypes to NK cells alone. Furthermore, IL-2-based protocols used to expand or activate NK cells are not limited to NK cells and may affect T cell populations and other effector cells, adding further uncertainty to the interpretation of inflammatory and vascular outcomes. An important determinant is the timing of NK cell manipulation relative to the onset of ischemia because the recruitment, activation, and effector functions of NK cells differ during the acute inflammatory, proliferative, and repair phases of MI, and thus studies performed at different time points may yield seemingly contradictory results. Substantial species differences exist between murine and human NK-cell biology, including differences in receptor expression, subset distribution, activation thresholds, and cytokine responsiveness. As a result, findings derived from rodent models cannot be directly extrapolated to patients with MI without independent validation in human systems. Likewise, local cytokine context, particularly the concentration and duration of IFN-γ signaling, may modulate whether NK-cell activity is predominantly reparative or injurious.

Table 1: Studies related to monitoring the role of NK cells in MI

Study design	Species/ patient cohort	MI model	Timing after infarction	NK cell phenotype	Experimental manipulation	Angiogenesis	Cardiac function endpoint	Ref.
Human observational	Patients with AMI and SA	Clinical AMI	Acute	NK cells (activity)	-	-	-	44
Prospective Clinical study	AMI patients	Clinical MI	72 h and 3 months	$CD56^{bright}$/$CD56^{dim}$ subsets	-	-	Clinical follow-up	7,8
Animal mechanistic	Mouse MI model	Experimental MI	Acute	NK cells	ERG/HLX/STAT4/ Perforin pathway	-	Myocardial injury	54
Animal mechanistic	Mouse MI model	Permanent left anterior descending (LAD) coronary artery ligation	Acute	$CD3^{-}NK1.1^{+}NKp46^{+}$ mature NK cells with increased granzyme B**,** GM-CSF**,** NKG2A, and NKG2D expression	Genetic NK cell deficiency (NKKO mice), anti-NK1.1-mediated depletion, anti-NKG2A activation, CCR2-deficient NK-cell adoptive transfer	-	Cardiac cell death	69
Animal	Mouse MI model	AMI (LAD)	Inflammatory cells: 24 h; NK-cell infiltration:	IL-2-activated NK cells	Adoptive transfer of IL-2-activated NK cells; RNA silencing;	Endothelial cell proliferation, neovasculariza	Myocardial collagen deposition	105

			Day 6 post-MI		neutralizing antibodies against α4β7 integrin and KLRG1	tion, infarct angiogenesis		
Animal	Mouse MI model	(LAD) coronary artery ligation	(rh)IL-2 administered 2 days after MI	IL-2-activated endogenous NK cells	Single intravenous injection of recombinant human IL-2 (rhIL-2); comparison between immunocompetent and immune-deficient mice	Capillary density (scar and border zone), endothelial cell proliferation, NK-cell infiltration into infarcted myocardium	Left ventricular fractional shortening (LVFS), myocardial collagen deposition	[104]

Table 2: Indirect evidence supporting the angiogenesis role of NK cells

Disease/Tissue	Species	Experimental model	NK phenotype	Experimental manipulation	Biological mechanism	Major finding	Potential implication for MI	Ref.
Cornea	Mouse	Basic fibroblast growth factor (bFGF) corneal micro-pellet model and laser-induced choroidal neovascularization (CNV)	NK1.1$^+$	NK-cell depletion using anti-NK1.1 monoclonal antibody; in vitro co-culture of NK cells, macrophages, and HUVECs	Angiogenesis, macrophage recruitment, VEGF signaling	NK cells promoted angiogenesis	Suggests NK-mediated vascular remodeling after MI	[103]
Human peripheral blood	Human	In vitro culture of circulating NK cells under chronic hypoxia and/or TGF-β stimulation	Circulating NK cells; ILC1-like (CD9$^+$/CD103$^+$) subset induced by TGF-β	Exposure to TGF-β, chronic hypoxia, or both	Hypoxia-induced angiogenic signaling, VEGF-A production, phenotypic plasticity	Hypoxic NK cells produced VEGF-A	Possible contribution to ischemic angiogenesis	[101]
Tumor	Human	In vitro hypoxia model	Human NK cells	Exposure to hypoxia (1%	NK-cell cytotoxicity,	Hypoxia significantly	Hypoxia can directly suppress	[95]

		(1% O_2) using NK cells co-cultured with K562 and MM.1S tumor cells	(IL-2-activated); expression of NKp30, NKp46, NKG2D, CD107a, granzyme B, and IFN-γ evaluated	O_2); SHP-1 knockdown (siRNA); SHP-1 inhibitor (TPI-1); ERK and STAT3 signaling analyses	hypoxia signaling, intracellular signaling (ERK/STAT3/SHP-1)	reduced NK-cell cytotoxicity by decreasing granzyme B, IFN-γ, CD107a, NKp30, NKp46, and NKG2D expression.	NK-cell effector function through SHP-1-dependent signaling.	
Tumor	Mouse	Mouse tumor models (RMA-S lymphoma, LLC), human peripheral blood NK cells, in vitro hypoxia	HIF-1α-deficient NK cells with enhanced IFN-γ production and NF-κB activation	NK-specific Hif-1α deletion, pharmacological HIF-1α inhibition (KC7F2), IL-18 neutralization, chronic hypoxia, adoptive NK-cell transfer	HIF-1α–IL-18–NF-κB–IFN-γ signaling	HIF-1α inhibition restored NK activity	suggests hypoxia-related regulation after MI	[96]
Infection	Mouse	Infection model (Cysts of the avirulent ME-49 strain of T. gondii were obtained from the brains)	Endogenous IFN-γ-producing NK cells	Infection model with analysis of NK cell-derived IFN-γ and mononuclear phagocyte dynamic	Immune regulation, monocyte differentiation, dendritic-cell maturation, IL-12 production, innate immune activation	NK cell-derived IFN-γ promoted the replacement of resident mononuclear phagocytes by recruited monocytes and drove their differentiation into inflammatory dendritic cells (moDCs) and macrophages.	NK cells can orchestrate monocyte differentiation and macrophage/DC polarization through IFN-γ signaling.	[58]

8. Conclusion

NK cells are capable of ischemic tissue healing via different mechanisms. Due to pleiotropic roles of NK cells under ischemic conditions, it seems that these cells can mediate both pro- and anti-angiogenic effects within the infarcted myocardium. Whether and how the balance between the pro- and anti-angiogenesis potential dominates remains to be determined through further experimental studies. By understanding the underlying mechanisms, it is possible to control the therapeutic capacity of NK cells, especially the angiogenesis potential in MI patients. However, available NK-cell depletion and activation strategies may lack subset specificity, making it difficult to precisely determine the roles of individual NK-cell populations following MI. For instance, the application of anti-NK1.1 in mice can influence other immune cell populations and exert confounding effects and the activation of NK cells using IL-2 can simultaneously activate T cell subsets and their angiogenesis properties. Therefore, it is suggested that these data should be interpreted with caution. The existence of biological differences between human and mouse NK cells can also affect the cytokine production capacity, and response to the proangiogenesis cytokines, limiting the direct translation of such findings from animal models to humans. It seems that future studies and employing more precise NK-cell isolation and lineage-tracing methods for monitoring NK cell subset activity and application of humanized models may provide more reliable insights about the role of NK cells in angiogenesis status following MI. Noteworthy, several biological parameters such as inflammation, vascular growth, fibrotic changes, and granulation tissue formation can also affect the effects of NK cells on cardiac repair. Therefore, it is mandatory future studies monitor the angiogenic behavior of NK cells at various time windows following the MI.

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Author Contributions

F.V.N., Z.M., P.M-J, and A.R. literature search, drafting of the manuscript. R.R. conceptualization; resources, funding acquisition, supervision. All authors have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate

No human and/or animal samples were used in the current manuscript. The study was registered as titled “The role of natural killer cells in the angiogenesis process following ischemic injury: review study” To the Research Ethics Committees of the Vice-Chancellor in Research Affairs, Tabriz University of Medical Sciences.

Consent for publication

Not applicable.

Conflict of interest disclosure

None declared.

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