The Role of Natural Killer Cells in Atherosclerosis Disease: Immunotargets and Therapy

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Abstract:

Atherosclerosis is a chronic inflammatory disease causing a wide range of cardiovascular diseases through lipid accumulation, infiltration by immune cells, and formation of plaques. Among different immune cells contributing to atherosclerosis, Natural Killer (NK) cells have gained considerable attention as potential contributors to both progressive and limiting phases of atherosclerosis. Natural killer (NK) cells constitute a component of the innate immune response, exhibiting cytotoxic capabilities and a unique capacity to identify and eliminate infected or distressed endothelium cells. The impact of their goods on the advancement of atherosclerosis is varied. Both can contribute to plaque development and induce rupture by cytotoxicity or cytokine activity. NK cell-cytotoxic activity breaks plaques but their cytokines could modulate inflammation which might alter plaque stability and disease advancement. Recent studies focused on clarification of the interaction with endothelial cells, smooth muscle cells, and macrophages, including those within atherosclerotic lesions, which would elucidate their dual role as either proatherogenic or antiatherogenic effectors. NK cell modulation

therapeutic strategies will be affected by the involvement of NKG2D and NFp30 receptors, among others. Nevertheless, their preclinical research results were not enough to advance their clinical investigation due to the presence of self-centered functions, inhibitory effects, and strict regulatory constraints. The examination examines the multiple functions of NK cells in atherosclerosis, their immunotargets, and current therapeutic approaches that may offer insights into potential NIH cell-based therapies for treating atherosclerotic cardiovascular diseases.

Key words: NK cells, atherosclerosis, immunomodulation, NK cell-based therapies, immune checkpoint therapies.

1.INTRODUCTION

Cardiovascular diseases related to atherosclerosis are termed chronic inflammatory diseases of the artery wall consisting of lipid, fibrotic, and cellular elements. This slowly results in the remodeling of the arteries by calcification and deposition of atheromatous plaques, and may rarely cause acute myocardial infarction and stroke [1].Mononuclear leukocytes are involved in the formation of atherosclerosis and are involved in sustaining a low grade inflammation in arterioles[2].In the context of the immune cells participating in atherosclerosis, NK cells are emerging as significant effector cells in protective as well as detrimental processes.These cells represent components of innate immunity capable of identifying and destroying PC+ cells in the absence of prior sensitization. Their function involves killing target cells through the action of cytotoxic granules and cytokines, including IFN-γ, which in turn regulate the immune response [3].Their role in atherosclerosis cannot be clearly classified. Recently, studies by EUR indicated that NK cells considerably influence the formation and stability of atherosclerotic plaques through cytotoxic effects exerted on target vascular cells and through immunomodulatory activities of other cells involved in plaque biosynthesis. In addition, NK cells have the potential to regulate vascular inflammation and can act directly or indirectly on many molecular targets, such as TLRs and their ligands, which are abundantly present in the atherosclerotic plaques within the surfaces of stressed or necrotic cells [4]. The scope of the target should aim at comprehensive research on NK cells in the development process of atherosclerosis to identify immunotargets and current therapeutic developments targeted

towards regulating NK cell activity in this disease. NK cells are part of the biological immune system; these can recognize and destroy virus-infected or transformed tumor cells without prior exposure to antigens. They use cytotoxic functions, such as perforin-mediated cytolysis, that require secondary activating and inactivating signals.

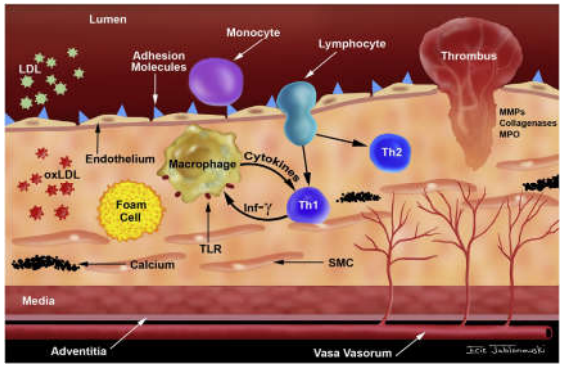

Figure 1. A schematic and simplified depiction of the several stages involved in the creation and disruption of an atherosclerotic plaque [75] .

Their functions in immunosurveillance also go beyond mere cytotoxic activity: they are cytokine producers and interactors with other immune cells, thus complementing immune surveillance and fortifying the defense mechanisms of the organism. The primary characteristic of NK cells is their receptors. It comprises inhibitory receptors for MHC class I molecules and activating receptors for stress ligands on target cells. The activation of these receptors will dictate the activation of NK cells, whereas cytokines, particularly interferon-gamma, will enhance the interaction of NL cells. These pathways are cardinal to preventing infections and regulate immune responses during pregnancy, cancer therapy, and viral infections. For example, NK cells have shown to be characterized by a modulatory effect in their interaction with trophoblasts within the context of pregnancy and in cancer immunotherapy by mechanisms of cytotoxicity and receptor-ligand binding [5]. The strength of case studies points toward an improvement of the efficacy of anti-tumorous receptors of NK cells and pertains to their potential usages of CAR treatments [6].More research would be required in order to reveal other regulatory factors for NK cells that may give boost to immunity and the NK cell-based treatments and cure methods.

2. ATHEROSCLEROSIS PATHOPHYSIOLOGY

2.1 Development of Atherosclerosis: Atherosclerosis is an ongoing inflammatory process resulting from endothelial abnormality, lipid infiltration, and plaque formation in arterial walls. Figure 2. depicting the progression of atherosclerosis, emphasizing the critical stages:

endothelial dysfunction, lipid accumulation, foam cell formation, plaque advancement, and potential rupture, resulting in cardiovascular complications.

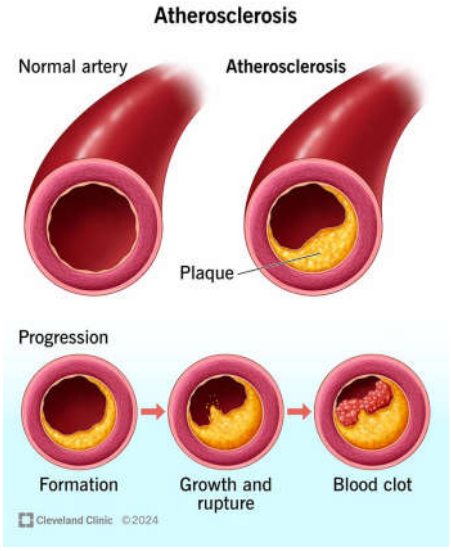

Figure 2. Development of Atherosclerosis

Endothelial Dysfunction: Oxidative stress and inflammatory mediators produce dysfunction in the case of endothelial cells, which line blood vessels. This dysfunction unleashes a cascade that enhances leukocyte adhesion and lipid infiltration [7].

Lipid Accumulation: LDL penetrates the subendothelial space and becomes oxidized. Subsequent to oxidation LDL stimulates an immune response which recruits more immune cells like macrophages and natural killer (NK) cells [8].

Plaque Formation: Cholesterol metabolism to lipids of tissue are accumulated in degenerating macrophage to form foam cells, T cells aggregate over time, plaques can develop calcium and cause blood flow blockage.

NK cells also promote instability in plaques through necrosis caused by the cytotoxic mechanisms of granzyme B and perforin production [9].

Function of Chronic Inflammation: Persistent inflammatory processes, engaging both innate and adaptive immune responses. Immunomodulators such NK cells exacerbate pathological processes in endothelial dysfunction, lipid peroxidation, and plaque formation.

rupture [10].

2.2 Function of Immune Cells in Atherosclerosis Advancement

NK cells are one of the important innate immune cells that have gained much attention in terms of their dual role in the process of atherosclerosis. The section has addressed this by focusing on cytotoxic mechanisms, the production of cytokines, and their interaction with other cell types of the immune system.

Pro-Atherogenic Role of NK Cells: A potential role of NK cells in lesion development was initially suggested due to cytotoxic activities involving perforin and granzyme B, and using genetic approaches in mice has shown that loss-function analysis resulted in reduced lesion size and gain-of-function analysis corroborated with the assertion that NK cells can aggravate atherosclerosis. They enhance necrotic core enlargement, which is important in the formation of vulnerable plaques hence increasing cardiovascular risk.

Other Immune Cells Communications: Both cytokine-activated and IL-18-dependent pathways seem to reveal that NK cells associate with macrophages and dendritic cells in atherosclerotic plaques, enhancing the inflammatory signal. This underscores their ability to maintain inflammatory responses that are otherwise chronic during atherogenesis. Data obtained in this study indicate that NK cell function correlates with lipid-APC interactions and has tremendous implications for the development of immunotherapies.

Ambiguity in Protective Versus Atherogenic Role: This includes works that support the promoted pro-atherogenic effects, and those according to which, under certain conditions, NK cells can behave protectingly. For example, the activation of NK cells using lipid antigens that associated with CD1d led to the decrease in lesion size in experimentally induced models [11].

Immunotherapy Targeting NK Cells: Some experimental therapeutic approaches, for example, the use of lipid antagonists to block the activation of NK cells, have found that the size of the plaque and the stabilization of the lesions is possible. This points to the possibility of establishing specific form of NK cell-based immunotherapies [12].

2.3. Inflammation and anti-inflammation Axis

Despite the full understanding of the disease pathophysiology, atherosclerosis is a chronic inflammation process with various efflux of proteins ranging from inflammatory and anti-inflammatory. The process in this condition occurs through cytokine synthesis for instance from macrophages, T cells and natural killer (NK} cells that contribute to plaque formation and its progression.

Pro-inflammatory mechanisms: The incident mediators of inflammation, specifically, IFN-γ, TNF-α, and cytotoxic granules from the NK cells increases lesion formation through endothelial damage and inflammation. To achieve these aims, the study recognises that NK cells become implicated in NEC enlargement through the release of perforin and granzyme B, thus enhancing plaque instability.

Anti-inflammatory mechanisms: Instead, the anti-inflammatory pathways attempt to modulate the plaque formation, promote healing and reduce the production of inflammation. For example, expression of Tim-3 on NK cells may suppress their pro-inflammatory activities and is correlated with decreased NK cell abundance in patients with advanced atherosclerosis.

Immune balance: Probably for protection against infections but also against oxidized LDL, immune cells including; NK cells are double-edged within atherosclerotic plaques a reason to investigate their regulation. The interaction between NK cell and macrophages/dendritic cells the other factor that significantly contributes to the lesion progression through communication and cytokine production [13].

3. NATURAL KILLER (NK) CELLS

Section	Details
Definition and Primary Functions of NK Cells	Natural killer (NK) cells are an essential component of the innate immune system.
	Key roles include:
	Identifying and eradicating infected or altered cells without prior sensitization.
	Contributing to immune surveillance and tumor defense [14].
Subtypes and Phenotypes of Natural Killer Cells	Natural killer (NK) cells are categorized into two categories according to CD56 expression:
	CD56bright natural killer cells:

	Mainly immunoregulatory.
	Elevated cytokine secretion.
	Minimal cytotoxic action.
	CD56dim natural killer cells:
	Essential cytotoxic agents.
	Equipped with perforin and granzyme for target cell lysis .
Mechanisms of Natural Killer Cell Activation	Activation transpires via:
	Identification of stressed cells that express ligands such as MICA/B.
	Engagement with antibody-coated cells through Fc receptors (ADCC mechanism).
	Absence of inhibitory signals from standard MHC-I molecules.
Mechanisms of Natural Killer Cell Cytotoxicity	Cytotoxicity is facilitated by:
	Perforin and granzyme B trigger apoptosis in target cells.

	Pathways of death receptors involving FasL or TRAIL [15].

Table no.1. Summary of Natural Killer (NK) Cells: Definition, Subtypes, Activation Mechanisms, and Cytotoxic Pathways.

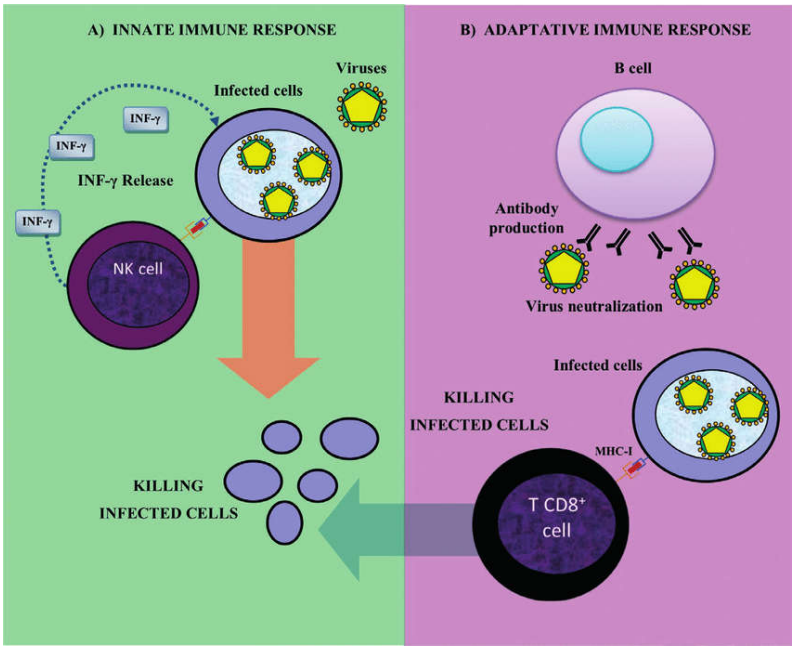

Figure 3. Role of Natural Killer (NK) Cells in Immune System

In Figure 3. which showing the distinctive function of natural killer (NK) cells within the immune system, emphasizing their capacity to directly identify and eliminate abnormal cells, such as virus-infected and malignant cells, without prior sensitization.

4. ACTIVITIES OF NK CELLS IN ATHEROSCLEROSIS

As cells of the innate immune system, natural killer (NK) cells participate in the development of atherosclerosis which is a chronic inflammation. Endothelial and smooth muscle cell cross talks are essential for dissection of their roles in the development of atherosclerosis. NK cells are present in atherosclerotic lesions and play roles in plaque progression as effector cells and cytokine producers.

NK Cell Interactions with Endothelial Cells: The NK cells have been detected in the atherosclerotic plaques, and they indirectly influence endothelial cells hence could alter the function of the endothelial cells by the secretion of cytokines such as IFN-γ this cytokine is considered to have a pro-inflammatory effect and may hinder the recovery of endothelial deterioration[16,17]. Presence of NK cells in vascular endothelium is linked with larger lesion size, greater necrotic core expansion, and therefore they may play a direct role in endothelial damage and progression of atherosclerosis. The NK cells also interact with the endothelial cells through their recognition of the stress-induced ligands, and result in cytotoxic effects that may favor the endothelial damage and instability of the plaque[18].

NK Cell Interactions with Smooth Muscle Cells: Increased attention has been drawn toward the proliferation and migration of SMCs; in rabbit model of SMCs, natural killer (NK) cell activation has been noted to propel the accumulation of atherosclerotic plaques[19]. Natural killer (NK) cells may influence smooth muscle cells (SMCs) through the production of cytokines and growth factors, which foster inflammation and likely contribute to plaque formation. The release of perforin and granzyme B from NK cells causes the apoptosis of SMCs, which destabilizes plaques and contributes to atherogenesis. Although the NK cells have been implicated in the progression of atherosclerosis through interaction with endothelial and smooth muscle cells, this relationship is complex, and thus further research into it might reveal new therapeutic approaches that interfere with NK cells to reduce atherosclerosis. However, to selectively use NK cells to monitor disease development while refraining from causing tissue destruction has been a problem in formulating drugs to target this process without compromising the immune response [20].

4.1 Role of NK Cells in Early Atherogenesis

Natural Killer (NK) cells are attributed prominent roles concerning the atherosclerotic process, with remarkable participation during the initial stages of atherogenesis. Asthma,migraine and myocardial infarction are examples of elements of the innate immune response that are part of the inflammatory processes that are also seen in atherosclerosis.NK cells are involved in the release of inflammatory cytokines and have cytotoxic properties that can worsen an inflammatory environment within the plaque of atherosclerosis. This response is especially important at the onset of atherosclerosis when it contributes to exacerbation and fibrous cap formation in the plaque.

Inflammatory Cytokine Release: As for the special role of NK cells in the environment of inflammation in atherosclerosis, they release such pro-inflammatory cytokines as TNF-α and IFN-γ. These cytokines can help summon and activate other immune cells which can escalate the inflammation going on at the arterial wall [21].

Cytotoxic Activity: All NK cells belong to the group of cytotoxic lymphocytes cells. Therefore, they can be implicated in the direct account of the death of endothelial as well as other cell in the plaque. It may also cause plaques to become unstable and if so, such structural failure may represent a critical step in the formation of atherosclerosis and acute cardiovascular events [22].

Interaction with Other Immune Cells: They engage with various immune cells among them the macrophages and T cells in the atherosclerotic plaque. Such interactions may also serve to amplify or suppress immune responses because the inflammatory and the anti-inflammatory mechanisms are both engaged in atherosclerosis [23]. While previous studies have shown that inflammatory and cytotoxic effects of NK cells are in some ways affecting pathogenesis of atherosclerosis, attempts are being made to develop strategies that target NK cells for therapeutic purposes as well. Modulation of NK cell activity can be a new avenue for controlling inflammation and stabilizing the atherosclerotic plaques, which should give better cardiovascular outcome. Nevertheless, the double role of NK cells, that is both pro-inflammatory but also potential regulatory, requires a much more subtle strategy for therapeutic targeting [24].

More attention has been drawn to the involvement of natural killer cells in atherosclerosis, particularly to their role in plaque development and in the regulation of macrophages and foam cells. Despite their relatively low number in the atherosclerotic plaques, NK cells may play an important role in the inflammatory environment and, through various mechanisms, be highly responsible for the disease's progression.

Cytotoxic Activity: NK cells may be cytotoxic to macrophages and can modulate foam cell generation, a critical process for plaque growth [25].

Cytokine Production: It synthesises pro-inflammatory cytokines that could be pro-atherogenic, therefore affecting the other immune cells that are involved in plaque formation [26].

Regulatory Function: NK cells might also be involved in the immune regulation, shifting the pro-inflammatory/anti-inflammatory cytokines in the plaque environment [27].

Interactions with Macrophages and Foam Cells: Activated NK cells can also stimulate macrophages to take up lipids, the formation of foam cells necessary for the maturation and continued growth of the plaque. This interaction may enhance or suppress foamy cell formation in dependence on cytokine expression patterns. Although there is growing insight into NK cells in atherosclerosis, their function is complex and still unknown at various stages of the disease and in the local microenvironment. More studies should be performed to explain these interactions and their consequences for practical treatments [28]. Current knowledge of Natural Killer (NK) cells in atherosclerosis is limited, but especially in their function as effector cells in the context of matrix degradation and apoptosis in relation to plaque stability is still unknown. Knowledge of these mechanisms is important in the design of therapies that will most likely enhance the NK cell function as an approach of enhancing CV health.

Matrix Degradation: NK cells appear to be implicated in the digestion of the components of the extracellular matrix of the atherosclerotic plaque and ensuing weakening of the plaque dose to rupture[29].

Apoptosis Induction: NKG explained that NK cells were cytotoxic to many of the cell types present within the plaque such as the macrophages and the smooth muscle cells which alters plaque composition and stability.

Therapeutic Implications: Immunotherapy Potential-Targeting NK cell pathways could give rise to other treatment methods through which plaques are more stable and hence decrease the chances of cardiovascular events.This is based on the studies that re-polarizing immune responses have been shown to slow atherosclerosis progression [30].Clinical Trials is On-going research and clinical trials will be directed toward the capacity to modulate NK cell activity for the treatment of atherosclerosis, an area which exploits their use in the regulation of immune responses [31].

4.2. Evidence from Preclinical and Clinical Studies

It is believed that the involvement of Natural Killer (NK) cells is very important due to the fact that the more recent preclinical and clinical evidence indicates that the cells are likely to play a multi-faceted part in atherosclerosis. They are involved in immune action in the progress of atherosclerosis and it has impact on inflammation and vascular function.

Preclinical Findings: In mice the authors detected an absence of NK cells, which resulted in enhanced atherosclerotic lesion formation. This has defined the functionality of NK cells as protective cells.

Clinical Observations: Some previous studies pointed out that there have been changes in the number of NK cell in atherosclerosis patients and with the increasing of the disease severity the activity of NK cell will also be enhanced. However, the consequences of NK cells' presence ambivalent as they may promote both pro- and anti-atherogenic processes [32] indicate the need for further investigation of these cells and their therapeutic application in atherosclerosis [32].

5. IMMUNOTARGETS IN ATHEROSCLEROSIS: NATURAL KILLER CELLS

5.1. Therapeutic Targets for NK Cell-Mediated Aggression

Natural killer (NK) cell involvement in atherosclerosis has been discussed lately and its therapeutic relevance as immunotargets is being more explored. These functions are associated with the biosynthesis of endothelial lipid, growth factors, cytokines, and chemokines, matrix metalloproteinases, fibrin, tissue factors, plasminogen activators, and other components of the hematopoietic system based on the interaction of natural killer cells with other cells implicated in atherogenesis and in the regression of atherosclerosis.

NK Cell Activation in Atherosclerosis: Different actions and effects of NK cells are seen in atherosclerosis concerning the instability or progression of the plaque [33,34].Depression of activation of NK cells may be effective to decrease chronic inflammation that is related to atherosclerosis and to prevent acute cardiovascular events with stabilization of unstable plaque [35].

Therapeutic Strategies Targeting NK Cells: This is due to the development of experimental, unaltered immunomodulatory techniques aimed at rebalancing pro-atherogenic NK cell activity. The efficacy of reducing atherosclerotic burden will be assessed for drugs that selectively activate NK cells through clinical studies.Targeting NK cells may provide an exciting therapeutic pathway; however, it is worth mentioning that these cells play a bivalent role in immunity, and over-inhibition can be detrimental to the host's ability to respond to infections or malignancies. Hence, appropriate therapeutic strategies are warranted in this regard [36].

NK Cell-Driven Targets for Therapeutic Application: Involvement of Natural Killer (NK) cells in atherosclerosis is progressively acknowledged, specifically with their potential function as immunological targets for therapeutic approaches. The NK cells are heavily implicated in the inflammatory context typical of atherosclerosis, and change in their activities would find new directions for therapeutic applications.

Cytokine Modulation: NK cells exhibit immunological functions and they release a number of cytokines which can affect inflammation or/and immunity. Regulation of the cytokine production pathways of NK cells could play a potential role in the inhibition of progression and destabilization of atherosclerotic lesions and plaques.

Repolarization Strategies: A potential application of the observed capacity to alter the polarisation of NK cells toward an anti-inflammatory state is in the prevention of chronic inflammation elicited by atherosclerosis. Despite, this concept has been recently developed in cancer immunotherapy and it may be applicable to cardiovascular disease [37].

Interplay with Other Immune Cells: These cells including NK cells regulates the activity of macrophages and T cells and therefore the immune response during atherosclerosis. This has led to insights into such interactions that open up for targeted therapies, enhancing NK cell activity while suppressing pro-inflammatory responses. The complex nature of their role in atherosclerosis is exciting therapeutic potential but at the same time necessitates further study to understand better their mechanisms and optimize therapeutic strategies. Balancing NK cell activation and inhibition will be necessary to prevent exacerbating inflammation in atherosclerotic patients [38].

Modulating NK cell recruitment and adhesion: The role of Natural Killer (NK) cells in atherosclerosis is a phenomenon that is increasingly being recognized, mainly concerning their potential as targets for immunotherapy. Inflammation in atherosclerotic lesions includes NK cells. Their mechanism of recruitment and adhesion may be a way through which therapeutic strategies can be designed. Chemokines and adhesion molecules, upregulated in inflamed vascular tissues, recruit NK cells to atherosclerotic plaques [39]. Pro-inflammatory cytokines such as IL-12 and IL-18 stimulate NK cell activity and recruitment; hence, it has been proposed that targeting these pathways can modulate the presence of NK cells in plaques [40]. Adhesion molecules such as ICAM-1 and VCAM-1 on endothelial cells mediate the adhesion of NK cells to the vascular endothelium and thereby allow their infiltration into atherosclerotic lesions [41]. Hence, modulation of these adhesion molecules can represent a therapeutic avenue in

controlling the migration and activity of NK cells in atherosclerosis. On the other hand, whereas enhancing the activity of NK cells might offer some therapeutic benefits, overactivation of NK cells might cause increased inflammation and instability in plaques; thus, the approach has to be balanced in targeting these cells in atherosclerosis therapy [42].

NK cell checkpoint inhibitors: Interest in Natural Killer (NK) cell functions is increasing in connection with their potential as new immunotargets in therapy. NK cells take part in vascular homeostasis and may modulate the atherosclerosis development through several mechanisms, one of which is immune-checkpoint interaction. The insight into such interactions opens perspectives for new therapeutic approaches. NK cells have been reported to express several immune checkpoints, including PD-1 and CTLA-4, that can negatively regulate the activity of NK cells within atherosclerotic plaques. The blockade of these checkpoints could improve NK cell function and would thus be useful in preventing atherosclerosis progression and enhancing cardiovascular outcomes. The increased cardiovascular risks recently seen with immune checkpoint inhibitors in cancer patients suggest the need for caution in such assessments within the context of atherosclerosis. New studies suggest re-polarization of NK cells by pharmacological agents in the treatment of atherosclerosis. Even though the involvement of NK cells is the most promising target for therapeutic intervention in atherosclerosis, the complexity of immune interactions involving these cells merits further research to fully establish their roles and optimize treatments [43].

NK cell-derived extracellular vesicles play a role in transferring bioactive molecules, which may influence other immune cells and vascular endothelial cells, thus changing plaque stability [44]. These vesicles may harbor cytokines and other modulators of the inflammatory milieu within an atherosclerotic lesion. Targeting NK cells and their EVs provides a new approach for immunotherapy in atherosclerosis potentially to augment protective immune response while dampening inflammation[45]. Balancing the subpopulations of NK cells as well as their functional status may help in designing therapeutic strategy to restore immune homeostasis in atherosclerosis[46]. On the other hand, although their therapeutic potential, pro-inflammatory activities of NK cells may also play a role in destabilizing plaques, and their role in the pathogenesis of atherosclerosis is complex that needs to be interpreted with caution in therapeutic considerations [47].

6.THERAPEUTIC APPROACHES and CLINICAL STUDIES

6.1 Present day treatment techniques that target NK cells

Now recent studies have shown that the NK cells have a role in the pathogenesis of atherosclerosis; however, further research into possible therapeutic strategies that can modulate these immunocytes is being made. The recent interventions and freshly introduced strategies explicate the possibility of NK cells in the treatment of cardiovascular diseases such as atherosclerosis.

Immunotherapeutic Strategies: It has been shown in the present studies that regulating NK cell reactivity impacts atherosclerosis progression. Such includes, employing therapeutic intervention measures that increases NK activity therefore decreasing inflammation associated with atherosclerosis.

Clinical Studies: The two landmark studies have demonstrated how targeting innate immune pathways through NK cells can significantly decrease cardiovascular risk, thus possibly changing the clinical practice of treatment toward immunotherapy.

The research is ongoing with small molecule inhibitors targeting the signaling pathways of NK cells. Such drugs could potentially reprogram NK cells to play a more protective role in the context of atherosclerosis. Studies on specific inhibitors that modulate NK cell activity are important for new therapeutic approaches, as shown by the latest studies on their role in chronic inflammation and atherosclerosis. Although focusing on NK cells brings forth promising avenues for therapy, the complexity of interactions between immune cells in atherosclerosis should not be overlooked. Interactions of different cells within the immune system may complicate therapies targeted at NK cells, and thus, full appreciation of the immune landscape in cardiovascular diseases is required [48].

Monoclonal Antibodies: These drugs are being developed to target NK cells and other immune checkpoints specifically, with the intention of enhancing the anti-inflammatory response in atherosclerosis [49]. A combination of monoclonal antibodies with existing lipid-lowering therapies may offer synergistic effects, thereby enhancing patient outcomes in atherosclerotic cardiovascular disease. While the optimism around NK cells and the therapeutic avenues they afford, patient selection and the customization of treatments to optimize the benefits of immunotherapeutic strategies remain significant challenges inherent in these treatment regimens [50].

Gene Editing: Various CRISPR approaches are currently being examined for their ability to modify NK cell activities, hence improving their efficacy in addressing atherosclerosis [51].

CAR-NK Therapies: CAR-NK cell therapies are now being developed to target cells within atherosclerotic plaques. The new approach in the treatment could be very promising, though there are still challenges for translating these findings into the clinical setting, and there is a need for more research to optimize NK cell-targeted therapies for atherosclerosis [52].

6.2 Challenges and limitations in NK Cell-Targeted Therapies: The engagement of Natural Killer (NK) cells in atherosclerosis therefore represents both potential therapeutic benefit and important challenges. The NK cells have been related to both inflammation modulation and plaque stability; however, their targeted therapies pose several limitations that must be addressed to make them clinically applicable.

Heterogeneity of Atherosclerosis: Atherosclerosis is a complex disease in which individuals exhibit distinct immune responses; therefore, developing universal therapies for NK cells may not be achievable [53].

Immune Evasion: The ability of an atherosclerotic plaque to assume tumor-like properties might contribute to evading NK cells' surveillance and potentially diminishing therapeutic approaches designed to enhance the function of NK cells.

Safety Concerns: The activation of NK cells could lead to increased inflammation or tissue damage, which may pose safety risks to patients with pre-existing cardiovascular diseases [54]. Limitations of Current Research

Insufficient Clinical Studies: There are few clinical studies that focus on NK cells in the context of atherosclerosis, which limits the understanding of their therapeutic potential.

Complex Interactions: The interaction between NK cells and other immune cells in the atherosclerotic environment is not well defined, and this may become a limitation in the designing of successful therapies. Yet, more research into the biology of NK cells and their role in atherosclerosis may open up novel therapeutic strategies that can promote cardiovascular health. A balanced approach, however, must be adopted to avoid possible risks of modulating NK cells [55].

7. FUTURE DIRECTIONS AND RESEARCH OPPORTUNITIES

7.1 Identifying biomarkers for NK cell activity in atherosclerosis: The study of Natural Killer (NK) cells in atherosclerosis opens vast future research opportunities, particularly in the identification of biomarkers for NK cell activity. Elucidation of these biomarkers may thus improve the diagnosis and treatment of atherosclerosis, which is a condition of chronic inflammation and immune dysregulation. NK cells are increasingly recognized for their role in vascular homeostasis and inflammation in atherosclerosis. Their activity will define the progression of atherosclerotic lesions and, thus, become a potential target for therapy. Biomarkers for NK-cell activity may provide insight into their functional status within the context of atherosclerosis, thus being useful for risk stratification and personalized treatment approaches. The research should be focused on specific NK cell surface markers and cytokine profiles that correlate with the severity and progression of disease. Targeting NK cell pathways may provide novel therapeutic strategies, similar to approaches seen in cancer immunotherapy. Understanding NK cell reprogramming could lead to innovative treatments that mitigate inflammation and promote plaque stability. This is interesting but important because there are other immune cells involved that play critical roles in the immune landscape of atherosclerosis, in disease progression and response to therapy [56].

7.2 Moving Toward Personalized Medicine Approaches

Customization of NK Cell-Based Immunotherapies: The role of natural killer (NK) cells in either enhancing or reducing atherosclerosis underscores the need for personalized immunotherapeutic strategies. NK cells have been implicated in the pathogenesis of atherosclerosis through cytotoxic mechanisms mediated by perforin and granzyme B pathways [57]. The therapies targeting these pathways can be customized for the treatment of patients with enhanced inflammatory responses.

Biomarkers for NK Cell Activity: Biomarkers of distinct NK cell functions, including cytokine release or granzyme, will assist in stratifying patients into tailored interventions. High levels of Tim-3 expression on NK cells have been associated with dysfunction in atherosclerosis and provide a targetable biomarker for disease progression and personalized therapy [58].

Therapeutic Modulation Using Lipid Antigen Presentation: The lipid antigens presented by CD1d molecules on NK cells might open the door for immunomodulation. Such pathways can be intervened by lipid antagonists, like DPPE-PEG350, in reducing the number of

atherosclerotic lesions and have created new avenues for personalized treatment that target antigen presentation [59].

Highly selective intervention within subgroups of overactivated NK cells: Genetic and functional alterations in NK cells may render individuals more predisposed to significant atherosclerotic progress. For instance, increased NK cell reactivity enhances core development of necrotic regions, which may be reduced by the use of carefully modulating therapeutic approaches to countermand distinctive immune profiles [60].

This potential would therefore emerge through a combination of NK cell therapies and systemic inflammation management. Treatments that reduce overactivated NK cells may further alleviate systemic inflammation and increase susceptibility of atherosclerotic plaques to injury [61].

7.3 Synergistic Effects of NK Cell Modulation in Combination with Current Atherosclerosis Therapies

NK cells are the most crucial in managing the immune response, and the potential for their application as a therapy in addition to available therapies for atherosclerosis is quite promising. Studies in relevant disciplines reflect the promise of incorporating NK cell modulation with other treatment approaches:

Improved Therapeutic Efficacy through Combination Therapies: NK cells in combination with immune checkpoint inhibitors like anti-PD-1 antibodies showed enhanced efficacy in other diseases such as glioblastoma and cancers. This therapy can improve infiltration of cytotoxic lymphocytes and may also modify the immune environment [62].Radiotherapy in combination with CAR-NK cell therapy has shown improved benefits in overcoming solid tumor challenges by altering the tumor microenvironment [63].

Immunomodulation Potentiates NK Activity: Inhibitors such as pan-HDAC that can increase cell adhesion molecules enhance the interaction between NK cells and tumors, indicating that biochemical agents could be used in combination with NK therapy [64].Immunotherapies that include IL-12 and 4-1BB activation have been combined with synergistic effects through enhancing immune activation by NK cells, which may be extrapolated to atherosclerosis [65]. It has been demonstrated that selenium nanoparticles, in combination with small molecules like metformin, can enhance NK cell cytotoxicity and

receptor expression and, therefore, provide a basis for novel combinations in immunotherapy [66].

Challenges and Opportunities in Translation: These approaches, adapted to atherosclerosis, require deeper insight into the interaction of NK cells with the vascular immune microenvironment. Potential pathways of immunotargeting might be offered by oncolytic viral platforms, which are known to induce NK cell activation [67].

7.4. Main Challenges and Translational Differences

Despite intense research on the role of natural killer (NK) cells in atherosclerosis, translational gaps are still highly significant. Although preclinical models have been of utmost importance in the understanding of immunological mechanisms involved in NK cells, translation to the clinical management of atherosclerosis is challenged by a myriad of issues. This review tackles the translational gaps, relying on relevant researches.

Preclinical Limitations: Animal models rarely translate to the complexity of human atherosclerosis. For example, studies conducted on mice indicate that NK cells play a proatherogenic role, mainly by mechanisms involving the release of granzyme B and perforin [68]. Another limitation is the difference in experimental approaches, which could be diet-induced or genetic models, limiting translation to the clinical setting [69].

Human Significance: The difference between human NK cells and animal models in NK cell function is reflected in examples such as the differential cytokine profile and activation pathways [70]. Advanced atherosclerosis degrades NK cell functionality, rendering an immunosuppressive microenvironment that complicates their use therapeutically [71].

Therapeutic Translation: While NK cell modulation shows promise in preclinical studies, clinical trials face challenges such as variability in patient immune responses and the risk of unintended inflammatory effects [72].Novel strategies, including genetic engineering or immune checkpoint modulation, are promising but require validation in human trials to ensure efficacy and safety [73].

Recommendations for Future Research: Developing humanized mouse models or advanced organ-on-chip systems to better mimic human NK cell biology in atherosclerosis. Identifying NK cell-related biomarkers for monitoring disease progression and treatment response. Investigating combination therapies, such as NK cell modulators with lipid-lowering drugs, to

achieve synergistic effects. Designing trials to test NK cell-based immunotherapies in diverse patient populations, accounting for genetic and environmental factors [74].

8.CONCLUSION

Natural Killer (NK) cells play an important but intricate role in the pathogenesis of atherosclerosis. Because NK cells represent an integral component of the immune system, these cells simultaneously promote and stabilize atherosclerotic plaques through cytotoxicity and release of cytokines. Their modulatory role at the level of the immune response in atherosclerosis is complex: in particular, NK cells can play a role, through pro-inflammatory cytokine production and cytotoxic activity toward vascular cells, in destabilizing plaques and prone to rupture. Under different conditions, they may find protective roles due to the regulation of inflammation as well as promotion of stabilization of plaques themselves. The bivalent function of NK cells in atherogenesis introduces an enormous challenge in the understanding of their actual role and therapeutic possibilities. NK cells may worsen inflammation, while contributing to plaque development; however, their modulation might also be an opportunity for the limitation of plaque progression and favor stabilization of plaques. Therapeutic approaches against NK-cell activity, such as receptor modulation or therapies based on NK cells, may be of promise for future cardiovascular interventions. However, while developing effective therapeutic strategies, it is critical to carefully review the potential off-target effects, safety issues, and diversity within NK cell populations. Further studies are required to establish details regarding the manner in which NK cells participate in the regulation of atherosclerosis to formulate targeted interventions that can strategically exploit their protective roles while reducing their pro-atherogenic activities.

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