Natural Killer Cell

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NK cells are a group of innate immune cells that show spontaneous cytolytic activity against cells under stress, such as virus-infected cells and tumor cells. They belong to the innate lymphoid cells (ILCs) family, a recently discovered group of lymphocytes, and represent about 5–15% of human peripheral blood mononuclear cells (PBMCs). Except for directly killing target cell through the release of perforin- and granzyme-containing cytotoxic granules, NK cells can also secrete interferon (IFN-γ), tumor necrosis factor (TNF), the granulocyte–macrophage colony-stimulating factor (GM-CSF), and a panel of various immunoregulatory cytokines (IL-5, IL-10, IL-13) and chemokines (CCL-3, CCL-4, CCL-5, CXCL), by which they act as modulators of the inflammatory response. NK cells have recently been recognized for their ability to kill malignant or infected cells and maintain immune homeostasis by killing certain healthy immune cells [6]. Likewise, there is accumulating evidence that NK cells possess memory ability. This finding is in contrast to the classical definition of NK cells, by which they belong only in innate immunity cells due to their lack of RAG (Recombination-activating gene) recombinase-dependent clonal antigen receptors. New data suggest that two types of immune memory patterns can be found in NK cells. The first pattern, similarly to B and T cells, is achieved by exerting immunological memory after an encounter with various antigens and the consequent creation of generations of antigen-specific memory NK cells. Secondly, NK cells can remember inflammatory cytokines milieus that imprint long-lasting non-antigen-specific NK cell effector function. These findings of NK cells' memory could open new horizons in their manipulation and provide us with new therapeutic targets, for example in ischemic heart disease, world's most notorious killer.

Keywords: NK cells ; Acute coronary syndrome ; Cardiac remodelling ; inflammation

1. Introduction

NK cells have been identified within atherosclerotic plaques in humans at an average of 1–2 cells per plaque lesion section [1]. Yet, it is important to acknowledge that understanding the role of NK cells in atherosclerosis is rather challenging because of the lack of representative mouse models of NK cell deficiency. As discussed by Winkels et al., commonly used NK cell deficiency models are all flawed[2]. Beige mutant mice, granzyme A-Ly49A transgenic mice, and ($Apoe^{-/-}$) mice treated with anti-asialo GM serum models, all of which should represent NK cell deficiency, at first lead to the interpretation that NK cells may be proatherogenic. However, beige mice (that carry Lyst gene mutation) seem to have impaired lysosomal storage, which could alter immune cell response. Granzyme A is not exclusive to NK cells as it is expressed by proatherogenic NKT cells and CD8 T cells, whereas asialo GM-1 can also be found on myeloid cells, T cells, and epithelial cells. Using these models, NK cells' role in atherosclerosis could not be delineated until recently. Nour-Eldine et al. used a precise genetic model of $Ncr1^{iCre}R26R^{lsl\text{-}DTA}$ mice (NK cells' deficiency model) and Noe mice (NK cells' hyper-reactivity model)[1]. Authors determined that neither NK cell deficiency nor hyper-reactivity affects the course of atherosclerosis except under conditions of modeled chronic viral infection (poly(I:C) injections), in which NK cell deficiency was shown to protect against atherosclerosis, implicating the proatherogenic role of NK cells under those terms. The latter could be important for the pathogenesis of coronary artery disease (CAD) in patients suffering from chronic infections. Several human trials have already been conducted on this topic. Hak et al. showed impaired NK cell activity in CAD and a reduction in the $CD3^-CD56^{bright}$ cell number[3]. Impairment of NK cell function can lead to increased susceptibility to atherogenic pathogens and promote CAD; however, it can also result in infection by those same pathogens. Increased vulnerability to infections is especially important in elderly people, where NK cells constitute the main mechanism of antiviral defense[4]. Ogata et al. demonstrated that NK cytotoxic activity in the elderly correlates with a history of severe infections or death due to infection [5][51]. In line with this, an expansion of NKG2C+ NK cells in patients with CAD seems to be associated with the loss of plaque stability in some patients with chronic CMV (Cytomegalovirus) infection[6]. On the other hand, there are several mechanisms by which CAD-associated pathogens interfere with the NK cell compartment. Both CMV and *C. pneumoniae* can lead to the production of IL-10, which quenches cytotoxic NK cell activity by counteracting IL-2 secretion[7][8]. Persistent CMV infection leads to an increase in the CD8+CD28-CD57+ T cell number, a T cell subset which suppresses NK cell function by secreting a non-antigen-specific soluble factor[9]. On the other hand, a reduction in the $CD3^-CD56^{bright}$ cell number in peripheral blood, as Hak et al. argue, is due to their migration

into the atherosclerotic arterial wall[3]. This is supported by Dalbeth et al., who suggested that CD3-CD56^{bright} cells are capable of migrating to the sites of local inflammation, where they enhance inflammation by stimulating TNF-α production by monocytes[10]. In a recent study, Bonaccorsi et al. observed that atherosclerotic plaques were enriched in CD56^{bright} NK cells compared with autologous peripheral blood[11]. Interestingly, the CD56^{bright} NK cell subset was even more abundant in symptomatic patients, highlighting the possible importance of CD56^{bright} NK cells in plaque instability. In agreement with the latter finding, authors have also observed a higher production of IFN-γ by plaque-resident NK cells. In summary, we argue that the results provided by Bonaccorsi et al., which envisage CD56^{bright} NK cells' role in the pathophysiology of plaque instability, could only be extrapolated to patients with chronic viral infections. Szymanowski et al. showed that apoptosis of NK cells is increased in patients with CAD, as reflected in the finding that the plasma Fas ligand (FasL), as a measurable marker of cellular apoptosis, significantly correlated with NK cell apoptosis ex vivo in CAD patients. On the other hand, cytokine-induced apoptosis of NK cells resulted in the marked release of FasL, showing that NK cells can be a potential source of soluble FasL. At the same time, FasL seems to regulate the apoptotic susceptibility of NK cells and their levels in CAD[12].

The interaction between activated macrophages and NK cells has been known to trigger an immune response[13]. Cell-to-cell contact and secreted mediators contribute to this crosstalk. When cocultured with macrophages previously exposed to poly I:C, CpG DNA, LPS, or Lacto-N-fucopentaose III, NK cells produce more IFN-γ and upregulate the CD69 marker on their surface[14]. This is achieved through multiple direct cell-to-cell contacts. Firstly, NK cells increase IFN-γ production by LPS-activated macrophages via CD40–CD40L interaction in mice[15]. Although both LPS-activated and inactivated macrophages stimulate NKG2D expression on NK cells, activated macrophages seem to induce NK cells more, highlighting the importance of the NKG2D–NKG2D ligand (RAI-1, MHC class I related chain A (MICA) and UL16-binding protein S) axis in the inflammatory response[14]. Finally, the induction of IFN-γ secretion by NK cells can also be achieved via the interaction between CD2B4 on NK cells and CD48 on LPS-activated macrophages. Based on the exposure dose of LPS, macrophages can elicit different effects on NK cells[14][16]. When exposed to low doses of LPS, macrophages stimulate NK cell proliferation, CD2B4 upregulation, and, finally, their release of IFN-γ. Conversely, when exposed to high doses of LPS, activated macrophages stimulate NK cytotoxicity. In an ex vivo experiment by Dong et al., NK cells produced more IFN-γ when cocultured with dendritic cells previously exposed to oxidized LDL via the CD48–CD2B4 pathway[17]. Unfortunately, except for the latter experiment, these cell-to-cell interactions have not yet been investigated in the setting of vascular inflammation; however, based on the ubiquity of inflammation and available knowledge on atherogenic pathogens, we can hypothesize that it is possible to extrapolate these findings to atherosclerosis. We must be cautious in our predictions, as NK cell activation in humans is in many aspects different from that in mice[18]. Unlike direct cell-to-cell contact, secreted mediators that contribute to the macrophage–NK crosstalk have been, at least to some extent, investigated in vascular dysfunction. Another equally important facet of the crosstalk is the influence of activated NK cells on macrophages, as their mutual relationship creates a positive feedback loop that represents an important augmentation mechanism in the early innate inflammatory response[19]. NK-cell-derived interferon-γ (IFN-γ) stimulated mice to differentiate monocytes to macrophages and inflammatory dendritic cells (DCs). Additionally, IFN-γ caused the replacement of resident mononuclear phagocytes with circulating monocytes that further differentiated into either inflammatory DCs or macrophages. Importantly, these cells further serve as a major source of IL-12, an effect abolished in NK cell depletion[19]. Hence, IFN-γ helps in initiating and augmenting the inflammatory response by driving the local differentiation of monocytes and regulating immune cell dynamics at the inflammation site.

2. NK Cells in Acute Coronary Syndrome (ACS)

There is a large discrepancy in scientific data concerning the peripheral blood NK cell number in ACS. Certain authors demonstrated a decline in the peripheral blood NK cell number[16][17][18][19][20][21][22][23], while others demonstrated an elevated number of NK cells in ACS patients compared to healthy controls[24][25]. In studies that compared NK cell levels in ACS and stable angina (SA), most authors found no difference between the two, except for Backtemann et al., who demonstrated a difference at first but failed to repeat it in further studies[20][21]. Backtemann et al. found that in most of the patients, the number of NK cells is restored after one year in both NSTEMI and SA[21]. The recovery in NSTEMI indicates that the NK cell number could reflect disease activity, whereas SA observation could be explained by clinical improvement. In certain patients, the NK cell number failed to reconstitute to that of controls after a one-year follow-up. These patients had a larger waist circumference, triglyceride levels, and remnant cholesterol levels, all indicative of metabolic syndrome. Lynch et al. found that obese patients with metabolic syndrome had lower levels of NK cells compared to obese patients without metabolic syndrome[26]. Increased levels of IL-6 were also observed in patients who failed to restore NK cell levels, which may point towards a lower NK cell proliferation rate[27]. In summary, it seems that the NK cell compartment failed to reconstitute in these patients due to persistent low-grade inflammation, i.e., metabolic syndrome.

Unlike the NK cell number, the data seem to be consistent regarding NK cell function impairment in terms of ACS. Yan et al. measured mRNA expression in both activating and inhibitory receptors on NK cells and found that the expression of both types of receptors was markedly reduced in patients with MI compared to SA and healthy controls[23]. In addition, patients with SA had a lower number of NK cells, similar to those with MI, but with no observed functional impairment. Likewise, several authors demonstrated NK cell function impairment by culturing NK cells extracted from patients with ACS. Reduced NK cell activity against K522 target cells, K562 target cells, and K562 target cells loaded with CFSE was observed, respectively [28][29]. It is important to highlight that these observations cannot be completely equated with the NK cytotoxic reactions against autologous cells in vivo. Another important finding by Ortega et al. is the higher percentage of IL-10+ NK cells found in AMI patients. Interestingly, their research showed a negative correlation between IL-10 levels and the severity of the infarction, the TIMI risk score in particular. Additionally, patients with better recovery displayed a reduction in the percentage of IL-10 production. Based on this observation, authors have addressed the importance of IL-10 in regulating NK cell function and the healing of an infarcted heart[28].

NK cells seem to become more activated and susceptible to apoptosis in ACS. Since it has been established that the expression of IL-18R is associated with the upregulated expression of the IFN-γ, the increase of circulating type 1 NK cells (IL-18R+) in ACS compared to SA indicates a more activated state of NK cells in ACS[21][30][31]. NK cells in both non-STEMI and SA patients are more prone to activation by IL-2 compared with controls[28]. Although plasma levels of IL-15 do not differ between patients with ACS and controls, it is hypothesized that IL-15 is upregulated in ACS, indicating the activation of NK cells[21]. The latter is possible, since IL-15 is mostly receptor-bound and plasma levels do not necessarily reflect the true quantity of IL-15 in the organism. Li et al. demonstrated that the number of apoptotic NK cells in blood is higher than in controls, and the NK cells of patients with CAD were more sensitive to oxidized lipids ex vivo, especially 7β-hydroxycholesterol (7betaOH) [78]. Carotenoid levels, which have antioxidant properties and an immunoregulatory role, were generally lower in CAD patients and inversely correlated to spontaneous NK cell apoptosis[32]. Therefore, there are two plausible explanations of NK cell apoptosis, the first being oxidative stress, which failed to be demonstrated in vivo, and the second being increased apoptosis as a consequence of NK cell activation. The mechanism of ineffective degranulation might also explain the functional deficiency of NK cells in the ACS, as demonstrated by Hong et al. [33]. The authors found that NK cytotoxicity was significantly lower in ACS patients compared to healthy controls. This functional deficiency was attributed to an ineffective mechanism of degranulation of toxic granules within NK cells rather than to differences in the expression levels of intracellular cytotoxic granules.

As discussed by Knorr et al., there is an important crosstalk between NK cells and monocytes in ACS[18]. By secreting IL-12 or IL-18, or through direct cell-to-cell contact, macrophages can play a role in NK cell activation, whereas NK cells, by producing IFN-γ, stimulate monocytes on differentiation to macrophages and/or DCs. Macrophages and DCs further produce IL-12 and IL-18 that synergistically stimulate NK cells in the production of IFN-γ, creating a positive feedback loop as aforementioned[34][35]. This crosstalk seems to be steered by the RAAS axis and certain parts of this mutual activation have been disclosed in mice arterial hypertension models[36]. ATII and aldosterone play a regulatory role by stimulating or attenuating the production of chemokines and cytokines from monocytes and/or NK cells. Kossmann et al. demonstrated that IFN-$\gamma^{-/-}$ and Tbx21$^{-/-}$ mice (mice deficient in the gene encoding for T-bet) were partially protected from ATII-induced vascular endothelial and smooth muscle dysfunction, whereas the depletion of myelomonocytic cell in LysM^{iDTR} mice treated with the diphtheria toxin produced the same effect[37]. Hence, this indicates that ATII-induced vascular damage is both NK-cell- and monocyte-dependent and highlights the importance of the T-box/IFN-γ/IL-12 pathway in this manner.

Furthermore, multiple studies have led to an understanding of the interaction between NK cells and dendritic cells (DC), an interaction that could affect the course of post-MI remodeling. Ayach et al. demonstrated the c-kit-dependent effects of NK cells in cardiac remodeling, which they hypothesize is achieved through the crosstalk between NK cells and DC, leading to a protective paracrine effect[38]. This claim is supported by multiple pieces of evidence. Firstly, c-kit-deficient mice have a reduced NK cell number and cytotoxicity, an effect abrogated by bone marrow transplant (BMT)[38]. Likewise, c-kit-deficient mice have exhibited significantly impaired cardiac function compared to wild-type mice with MI, but this effect was significantly reduced in mice treated with BMT due to the amelioration of adverse heart remodeling. Finally, BMT showed no beneficial effect on the improvement of heart function in c-kit-deficient mice treated with an NK blocker, implying the contribution of NK cells in this process. Additionally, Borg et al. demonstrated that imatinib mesylate (c-kit inhibitor[39]) is able to promote NK cell activation via dendritic cells, but not directly[40].

The beneficial effects of NK cells on cardiac remodeling and heart failure in general were recently discussed by Strassheim et al.[41]. NK cells seem to act protectively against the development of cardiac fibrosis by preventing the accumulation of specific inflammatory populations in the heart and by directly limiting collagen formation in cardiac fibroblasts[42]. By using monocrotaline-induced pulmonary artery hypertension (PAH) rat models, Ormiston et al. and Tamosiuniene et al., respectively, demonstrated that NK cells prevent right ventricular hypertrophy and right ventricular

systolic pressure growth, thus indicating their preventive role in this manner[43][44]. According to Edwards et al., NK cell deficiency has been associated with an increased risk of death in PAH patients[45]. Finally, NK cells from PAH patients contribute to vascular remodeling and have higher levels of MMP-9[42].

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