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Organ-specific phenotypic and functional features of NK cells in humans

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Abstract Natural killer (NK) cells kill virus-infected and tumor target cells without prior sensitization. Each NK cell expresses a multitude of activating and inhibitory receptors, and the interplay of signals determines the outcome of NK cell activity. NK cell-mediated cytolysis of target cell involves polarized degranulation at effector–target interface. Peripheral blood NK cell constitutes about 10 % of lymphocytes, and approximately 90 % of peripheral blood NK cells are $CD56^{dim}CD16^{+}$; however, there is a distinct subset of NK cells, $CD56^{bright}CD16^{-}$, expressed by certain lymphoid organs which are able to produce large amounts of cytokines including interferon-γ, tumor necrosis factor, and granulocyte–macrophage colony-stimulating factor, but the cytotoxicity is attained only on their prolonged activation. In this review, we discuss the accumulated data on distinct phenotypes of NK cells in human uterus, liver, intestine, skin, and lung and also attempt to correlate their phenotype with corresponding activity and functions, with significant stress on the role of NK cells in pathology in the specific organs. Our detailed understanding of altered NK cell activity in different organs and their inherent cytotoxic activity against tumor target cells will help us design better immunotherapeutic strategies in NK cell-mediated cancer therapies.

Keywords HCC · Inflammatory bowel disease · Melanoma · NK cells · NSCLC · Pre-eclampsia · Psoriasis

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Introduction

Natural killer (NK) cells are large granular lymphocytes that kill virus-infected and tumor cells without prior sensitization. Each NK cell expresses a multitude of activating and inhibitory receptors, and the cytotoxicity of these cells is determined by a fine balance between activation and inhibition signals [1]. These receptors may belong to either type I Ig-superfamily receptor or C-type lectin family of type II membrane proteins [2]. The activating receptors possess a short cytoplasmic tail and an adaptor molecule like DAP-12 that contain ITAMs (immune receptor tyrosine-based activation motifs, $Yxxl/Ix_{6-8}$, YxxL/I, x is any amino acid residue), leading to NK cell activation and cytokine production. Additionally, there are other cell surface receptors like NKG2D that are not directly coupled to ITAMs. They are non-covalently associated with DAP-10, which contains YxxM motif (x is any amino acid residue). These adaptor molecules, DAP-10 and DAP-12, contain negatively charged aspartic acid residues in the transmembrane domain that are involved in association with killer-activating receptors or NKG2D receptors. Inhibitory NK cell receptors recognize major histocompatibility (MHC) class I molecules and are characterized by immunoreceptor tyrosine-based inhibitory motifs in their long cytoplasmic tail, which recruit intracellular phosphatases, such as SHP1, SHP2, and SHIP that block the cascade initiated by activation receptor, thus causing inhibition of cytotoxicity [3].

Cytolysis of target cell may be achieved by a variety of effector mechanisms that include release of granules containing perforin and granzyme as well as TNF superfamily members (FasL/TNF) and their corresponding ligands (Fas/TNFR). FAS-independent NK cell cytotoxicity has been studied extensively and is mediated by cytolytic granule

polarization and degranulation. Das and Long (2010) established that granule polarization is the preferred target for inhibitory signal thus preventing NK cell cytotoxicity [4].

Human NK cells can be categorized into two subsets on the basis of intensity of CD56 and CD16 surface expression. Systemic NK cells display two types of subsets, $CD56^{dim}CD16^{+}$ and $CD56^{bright}CD16^{-}$. Approximately 90 % of peripheral blood NK cells (pNK) are $CD56^{dim}CD16^{+}$, which produce cytokines and lyse the target cells. By contrast, $CD56^{bright}CD16^{-}$ NK cell subsets preferentially expressed in certain lymphoid organs are able to produce large amounts of cytokines, including interferon-γ (INF-γ), tumor necrosis factor (TNF), and granulocyte–macrophage colony-stimulating factor, but cytotoxicity is attained only on their prolonged activation [5]. Vossen et al. [6] reported majority of circulating NK cell population, which are $CD56^{dim}$ and also $CD27^{-}$, release high levels of perforin and granzyme B and had strong cytotoxic activity. On the other hand, NK cells that were $CD27^{+}$ and $CD56^{bright}$ had markedly low levels of perforin and granzyme B and hence low cytotoxic potential. Also, recruitment of NK cells to different inflamed tissues is controlled via different chemokine receptors repertoire, and there exists a unique representation of NK cell subset in different tissues/organs [7]. These phenotypically different NK cell subsets showing disparate functions might be involved during different stages of infection and other pathological conditions. In this review, we have summarized the data on the distinct phenotype of NK cells in uterus, liver, intestine, skin, and lung and attempted to relate with their corresponding activity and functions in these different organs.

NK cells in uterus

Human deciduas possess almost 70 % of NK cells among total lymphocytes during pregnancy [8]. The main NK cell subset found in human uterine mucosa is $CD56^{bright}$ $CD16^{-}$, and the level of expression of CD56 on these NK cells is even higher than that of pNK cells [9]. Vacca et al. [10] analyzed hematopoietic precursors in deciduas and showed that CD34 cells differentiated into $CD56^{bright}$ $CD16^{-}$ NK cells on interaction with the components of the deciduas. On successful implantation, there was dramatic recruitment of immature NK cells that attained maturity in uterine microenvironment [11]. Manaster et al. [12] suggested that the higher percentage of NK cells during pregnancy play crucial role in implantation and vascular modification in the decidua, hence are vital for normal pregnancy. Recently, it has been reported that decidual NK cells express CMKLR1 (for a chemoattractant, chemerin); CMKLR1/chemerin interaction leads to NK cells recruitment to deciduas from periphery and formation of capillary-like tube, therefore mediating vascular remodeling during early pregnancy [13]. Though the role of chemerin in successful pregnancy has been established, its physiological role in disease outcome like pre-eclampsia is not yet clear.

Natural killer cells in the uterus remain non-toxic to the fetal-derived trophoblasts at the fetal–maternal interface. Extravillous trophoblast (EVT) cells lack HLA-A/B (human leukocyte antigen) expression and express an unusual combination of classical MHC class I molecule HLA-C as well as non-classical class I molecules HLA-G, which may protect fetal tissues from maternal immune system [14]. Vacca et al. [15] observed that dNK cells did not lyse trophoblast cell lines JAR and JEG3, while pNK cells could easily kill them. Interaction between the non-classical class I MHC molecule HLA-G and KIR2DL4 initiates the production of proinflammatory cytokines and proangiogenic factors (Ang1, Ang2, VEGF-A, VEGF-C, IFN-γ, and TGFβ1) that promote vascular remodeling as well as induce surface co-expression of HLA-E on trophoblast cells and thus lead to a strong inhibitory signals in dNK cells through CD94/NKG2A [16–18]. Moreover, uNK cells, but not pNK cells, secreted VEGF-C that activated TAP-1 expression on trophoblast cells and thus impart protection from uNK cell-mediated cytotoxicity [19]. Fu et al. [20] analyzed that $CD56^{bright}$ $CD27^{+}$ dNK cells maintain fetal–maternal tolerance by suppressing T_H17-mediated inflammatory response, and loss of this regulatory response leads to recurrent spontaneous abortion. Recently, it has been observed that combined factors like TGF-β, hypoxia, and demethylating agent are responsible for VEGF-A secretion, reduced cytotoxicity, and invasion of trophoblast cells by dNK cells [21]. In line with these studies, Yoksta et al. [22] established that NKp46 expression on uNK cells up-regulates the production of cytokines that facilitate normal pregnancy.

Impaired combination of maternal KIR receptors on dNK cells and fetal HLA on EVT cells could increase the risk of pregnancy-associated disorders [23]. Faridi et al. [24] analyzed KIR genotypes in women experiencing recurrent miscarriages and concluded that over activation of activating receptors may contribute to loss of pregnancy.

Pre-eclampsia is characterized by a poor placental perfusion due to failure of transformation of the maternal spiral arteries, leading to hypertension and proteinuria. Goldman-wohl et al. [25] described that reduced expression of HLA-G on EVT cells rendered trophoblasts susceptible to lysis by dNK cells, which in turn resulted in impaired trophoblast invasion and constriction of placental spiral arteries, resulting in restricted blood supply to the placenta. Furthermore, there was increased level of VEGF

soluble receptors, soluble fms-like tyrosine kinase, that act as anti-angiogenic factors, which in turn promotes maternal syndrome. The process of spiral artery remodeling involves apoptosis of vascular smooth muscle cells (VSMCs) and temporary loss of endothelial layer; these events were controlled by cells at maternal–fetal interface. Recently, Doppler ultrasound method was used to categorize NK cells into normal Resistance Index (RI) group and high RI group. dNK cells with normal-RI had shown more extensive vessel remodeling and activated pro-apoptotic factor, FasL, that induced vascular cell apoptosis, whereas dNK cells isolated from pregnancies with high RI failed to induce VSMCs apoptosis and led to impaired trophoblast invasion and impaired artery remodeling and therefore promoted pregnancy complications like pre-eclampsia [26].

Hence, during pregnancy there is increased migration of immature NK cells from periphery which undergo significant change in their receptor profile upon interaction with decidual components. Thus, NK cells play crucial role in spiral artery remodeling in fetal trophoblast and loss of dNK cells leads to pathological conditions like pre-eclampsia and recurrent spontaneous abortion [27].

NK cells in liver

Human liver contains distinct populations of NK cells, T cells, and NKT cells, defined by their expression of $CD3^{-}$ $CD56^{+}$, $CD3^{+}$ $CD56^{-}$, and $CD3^{+}$ $CD56^{+}$, respectively [28]. Majority of liver NK cells are $CD56^{bright}$ $CD16^{-}$ that showed a higher expression of NKG2A/CD94 and lower expression of KIRs resembling $CD56^{bright}$ pNK cells. This subset expresses the activation marker CD69 and showed elevated levels of adhesion molecule CD11a compared to $CD56^{bright}$ NK cells in blood [29]. Interestingly, the cytotoxic potential of $CD56^{bright}$ $CD16^{-}$ NK cells in liver is debatable. Burt et al. showed that liver NK cells were less cytotoxic than pNK cells in hepatic malignancy. They reported that $CD16^{-}$ NK cell subset expressed high level of NKp44, HLA-DR, and CD69 but had poor ability to kill K562- and MHC-I-deficient LCL721.221 targets. Further they showed that the small proportion of $CD56^{dim}$ $CD16^{+}$ subset in liver had lower perforin expression compared to their blood counterparts. Moreover, they observed lower expression of self-$KIR^{+}NKG2A^{-}$ and self-$KIR^{+}NKG2A^{+}$ by $CD16^{+}$ subset in liver as compared to pNK. The self-KIR expression levels on $CD16^{-}$ population in liver and peripheral blood were comparable. Hence, the $CD16^{+}$ population in liver, which contributed more significantly to liver NK cell-mediated cytotoxicity, comprised of a high percentage of unlicensed NK cells [30]. Thus, $CD56^{bright}$ subsets in liver were phenotypically and functionally distinct from same subset in periphery. In direct contrast to the above findings, Moroso et al. reported that $CD56^{bright}$ $CD16^{-}$ $CD\ 69^{+}$ population showed a higher proportion of perforin, granzyme A and B and exert twofold higher cytotoxicity by hepatic NK cells against K562 target cells without 1L-2 stimulation as compared to the same subset in blood. This unique subset of NK cells is transferred from donor to recipient after liver transplantation [29].

Ishiyama et al. [31] observed that upon IL-2 stimulation, the expression of TNF-related apoptosis-inducing ligand (TRAIL) significantly increased and up-regulated killing capacity of NK cells against HepG2, a hepatocellular carcinoma (HCC) cell line compared to pNK cells of the same donor.

Chuang et al. [32] reported that abundant NK cells occupied small bile ducts of liver in patients with primary biliary cirrhosis (PBC) and they recruited from periphery to liver during PBC and exerted higher cytotoxic effect, resulting in aggravated hepatic damage. Upon ligation of TLR4 in the presence of IFN-α, there is activation of NK cells and TRAIL expression in PBC patients [33]. Recently, it has been seen that $CD\ 16^{-}$ NK cell subsets accumulate in liver and contribute to chronic liver disease severity [34].

It has been reported that low density of NK cells in intratumoral cells of HCC patients promoted tumor survival [35]. Lin et al. [36] suggested that reduced NK cell population in HCC tumor is because of poor expression of chemerin protein. Also, lower expression of activating receptors NKG2D, NKP30, and NKP44 and increased expression of inhibitory receptors were observed in advanced cancer stage of HCC patients [37]. Li et al. [38] demonstrated that HCC-derived fibroblast factors induced impaired cytokine production and decreased cytotoxicity of NK cells.

Although studies have been carried out on the involvement of pNK cells in PBC [39] and especially in animal models [40], role of liver-specific NK cells in pathogenesis needs further exploration. Also, hepatic NK cells have been demonstrated to be hypoactive in cytotoxic potential due to weaker expression of activating receptors and poor chemerin expression preventing pNK recruitment to HCC, thus favoring tumor survival. In HCC, reduced NK cell population and hypoactivity of the hepatic NK cells favor tumor growth. Hence, immunotherapeutics using NK cells in HCC will require further understanding of HCC-mediated NK cell receptor modulation.

NK cells in intestine

Natural killer cells can be found throughout the human digestive tract and constitute a diverse phenotype. Most of

the NK cells and NK-like cell population among intraepithelial lymphocytes (IELs) had been shown to express CD56, CD161, CD122, CD69 and minor fraction expressed CD16 but lacked CD57 expression [41]. Leon et al. [42] identified a unique subset of NK-like cells among small intestinal IELs that were $CD3^-$ $CD16^-$ $CD7^+$ and resembled NK cells in other mucoid tissues. They showed a strong lytic activity with increased perforin content on stimulation with IL-2 as compared to pNK cells.

Lindgren et al. [43] demonstrated that $CD8^-CD16^-$ $CD56^{bright}$ NK cell subsets predominate gastrointestinal mucosa. Stimulation of mucosal NK cells with the combination of *Helicobacter pylori* antigen and IL-12 leads to NK cell activation and production of IFN-γ, thus playing important role in bacterial control. Lindgren et al. [44] proposed that TLR2 involved in recognition of *H. pylori* by NK cells in the gastrointestinal mucosa was capable of combating *H. pylori* infection by production of IFN-γ.

Zhang et al. [45] observed increased expression of HLA-Cw*07 gene in patients with ulcerative colitis (UC) and HLA-Cw*12 gene phenotype in Crohn's disease (CD) patients. This HLA overexpression reduced the activity of NK cells toward such target and thus increased IBD susceptibility. Also, IL-23 expression in inflamed mucosa of IBD promoted activation of NK cells and induced pro-inflammatory cytokine secretion such as IFN-γ and TNF that lead to the severity of IBD [46]. However, precise role of IL-23 in NK cell activation in mucosal inflammation needs further investigation.

The frequency of NK cells expressing CD16 increased in lamina propria of patients with CD or UC compared to healthy controls [47]. Takamaya et al. showed two distinct populations of NK cells in intestinal mucosa, $NKp44^-$ $NKp46^+$ $CD122^+$ $CD127^-$ and $NKp44^+$ $NKp46^-$ $CD122^-$ $CD127^+$. $NKp44^-$ $NKp46^+$ NK cells produced large amount of IFN-γ and their population was significantly raised in the intestinal mucosa of individuals with CD. On the other hand, $NKp44^+$ $NKp46^-$ cells were scarce in individuals with CD. Thus, altered balance between $NKp44^+$ $NKp46^-$ and $NKp44^-$ $NKp46^+$ cells may be involved in the pathogenesis of IBD [48].

Reduced NK cell infiltration colorectal carcinoma (CRC) tissue has been reported [49]. NK cell and CRC interaction induced alteration of phenotype on NK cells. The tumor cell-associated NK cells down-regulated the expression of activating receptors NKG2D, NKp44, DNAM-1 and had reduced capacity to produce IFN-γ [50]. Likewise, NK cells derived from colon carcinoma showed low expression of DNAM-1 and NKG2D [51]. Furthermore, NK cells in gastric cancer tissue expressed low levels of NKG2D that might be responsible for impaired NK cell function and cancer growth [52]. Combined blocking of NCRs (NKp30, NKp44, and NKp46) leads to the inhibition of NK cell cytotoxicity against H7 29, SW 480 colon cancer cell line [53]. Thus, modulation of NK cell receptors and function involved in disease progression has been consistently observed but the mechanism for receptors modulation on intestinal NK cells is still unclear.

NK cells in skin

$CD56^{bright}$ $CD16^-$ NK cells predominate in skin, express chemokine receptor CCR8, and lack CCR7 expression in contrast to pNK cells [54].

Skin-derived NK cells have potential to lyse melanoma cells. $CD56^+$ $CD3^-$ NK cells exerted cytotoxicity against SK-Mel2 melanoma cell line and produced perforin [55]. Carrega et al. [55] compared NK cell-mediated lysis of 10 different autologous melanoma cell lines and suggested that either deletion or low expression level of HLA class I allele specific for KIR was responsible for NK cell-mediated autologous melanoma cell lysis.

NK cells are actively engaged in psoriasis, a chronic inflammatory condition of skin, characterized by red, raised, scaly plaques typically on elbows, knees, and scalp. $CD56^{bright}$ $CD3^-$ NK cell population has been shown to infiltrate psoriatic skin in response to CXCL10 and CCL5 ligands for chemokine receptors (CXCR3 and CCR5 resp.) expressed on skin NK cells. This NK cell subset also expressed activation marker CD69 and produces high levels of IFN-γ in vitro on IL-2 stimulation [56]. Batista et al. [57] isolated NK cells from psoriatic and healthy skin and observed significant increase in percentage of $CD57^-$ $CD56^+$ $CD16^+$ population with increased expression of NKG2A on NK cells in lesional skin. However, this $CD57^-$ $CD56^+$ $CD16^+$ population showed higher IFN-γ production on IL-2 stimulation. Thus, it can be concluded that psoriatic skin harbors less differentiated phenotype, and future studies are needed to determine the significance of this phenotype on cytolytic activity of NK cells in psoriasis.

Carbone et al. [58] identified a distinct population of NK cells that are $CD56^{bright}$ $CD16^-$ $CD62L^-$ in skin during allergic contact dermatitis. They expressed chemokine receptor CXCR3, CCR6, CCR5, C-type lectin NKG2A, NKp44, NKp46, NKG2D, and perforin that contributed to the activation of IFN-γ and TNF-α, thus associated with allergic responses.

Balsamo et al. [59] demonstrated that melanoma cell lines displayed increased expression of classical and non-classical HLA-I molecules upon co-culture. They also demonstrated that NK–melanoma interaction resulted in the release of IFN-γ and down-regulation of activating receptors NKG2D, NKp44, and DNAM-1, which render

the melanoma cells resistant to NK cell-mediated lysis. Moreover, NK–melanoma interaction also resulted in lower expression of G-protein-coupled receptor, GPR 56, which was involved in tumor progression and metastasis [60].

Morettas group demonstrated that NK–melanoma interaction on co-culture favored the release of indoleamine 2,3 dioxygenase (IDO) and prostaglandin E2 (PGE2), which trigger down-regulation of activating receptors NKp44, NKp30, and NKG2D. This resulted in restricted NK cell-mediated cytolytic activity against melanoma cell and thus aided in tumor progression [61].

NK cells in lung

The lungs and the upper respiratory tract are constantly prone to infection by various bacterial and viral infections, and innate immune system is known to play a crucial role in preventing disease progression.

The study of NK cell subsets in broncho-alveolar lavage fluid (BALF) as well as blood of healthy individuals and sarcoidosis patients revealed that frequencies of $CD56^{bright}$ (2.1 %) and $CD56^{dim}$ (98 %) NK cells in BALF were similar to $CD56^{bright}$ (2.9 %) and $CD56^{dim}$ (96.5 %) subset in peripheral blood NK cells. They also reported NK cells representing $CD94^{high}$ KIR^{low} subset which were recruited from periphery to lungs during respiratory tract inflammation [62]. Similarly, Pokkali et al. [63] reported that NK cells migrated to lungs during TB infection from peripheral blood in response to IL-8, IP-10, and MCP-1. These $CD56^{bright}$ NK cell subsets also showed up-regulated chemokine receptor expression (CCR1, CCR2, and CCR7), activation marker CD69, and TLRs.

Carrega et al. isolated NK cells from non-small-cell lung cancer (NSCLC) specimen; they displayed $CD56^{bright}$ $CD16^{-}$ subset with higher frequency. NSCLC associated NK cells showed higher expression of activation marker NKp44, HLA-DR, CD-69, failed to express CD107a and thus exerted lower cytotoxicity against NK cell susceptible K562 cell line but retained ability to produce cytokines comparable to pNK cells [64]. Likewise, Platonova et al. reported that NK cells infiltrated NSCLC and were restricted to tumor stroma. Intratumoral NK cells showed increased expression of activating receptors NKp44, CD69, and inhibitory receptors CD161, CD94, NKG2A and reduced expression of NKp30, NKp80, DNAM-1, and CD16. Moreover, NSCLC showed higher expression of non-classical HLA-E and HLA-G, protecting them from NK cell cytotoxicity [65]. In line with these studies, Cremer et al. also described tumor-induced modulation of NK cell receptors NKp30, NKp80, DNAM-1, and NKG2D expression and reduced activity of NK cells against NSCLC tumors [66]. It has been reported that $CD11b^{-}$ $CD27^{-}$ NK cell population infiltered NSCLC tumor tissue, and the frequency of this altered population increased as tumor progressed. Thus, $CD11b^{-}$ $CD27^{-}$ NK cells are associated with progression lung cancer [67]. Thus, NK cells have the capacity to migrate to inflammatory sites with varying expression levels of chemokine receptors, and these NK cell distinct subsets are either detrimental or productive for the defense against infection or anti-tumor response that might open prospective for manipulating NK cells during immunotherapeutics strategies.

Conclusion

Cytotoxicity by NK cells is based on interplay of activating and inhibitory receptors. Migration of NK cells from periphery to different organs and their receptors modulation may be regulated by cytokines and organ-specific microenvironment. Cytotoxic potential of infiltrating NK cells has been greatly exploited for elimination of tumor cells. Adoptive transfer of in vitro activated allogeneic and autologous NK cells has exhibited clinical efficacy toward control of NSCLC and HCC [68, 69]. However, poor clinical responses were observed with adoptively transferred NK cells in melanoma patients [70]. Thus, cytotoxic potential of NK cells against tumors localized in different organs against tumors needs to be explored further to establish promising and safe NK cell-based immunotherapy. Better understanding of the mechanisms behind receptor modulation, activity, and proliferation of organ-specific NK cell- and tumor-mediated modulation of NK cell activity will give insights into devising good manufacturing practice conditions for adoptive transfer of organ-specific NK cells against various tumors and to answer many of our unresolved lacunae in the development of NK cell-based cancer therapeutic strategies.

Conflict of interest None.

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