Review

Tissue-Resident NK Cells: Development, Maturation, and Clinical Relevance

Elaheh Hashemi,1,2 and Subramaniam Malarkannan1,2,3,4,*

1 Laboratory of Molecular Immunology and Immunotherapy, Blood Research Institute, Versiti, Milwaukee, WI 53226, USA; ehashemi@versiti.org
2 Department of Microbiology and Immunology, Medical College of Wisconsin, Milwaukee, WI 53226, USA
3 Department of Medicine, Medical College of Wisconsin, Milwaukee, WI 53226, USA
4 Department of Pediatrics, Medical College of Wisconsin, Milwaukee, WI 53226, USA
* Correspondence: smalarkannan@versiti.org

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Abstract: Natural killer (NK) cells belong to type 1 innate lymphoid cells (ILC1) and are essential in killing infected or transformed cells. NK cells mediate their effector functions using non-clonotypic germ-line-encoded activation receptors. The utilization of non-polymorphic and conserved activating receptors promoted the conceptual dogma that NK cells are homogeneous with limited but focused immune functions. However, emerging studies reveal that NK cells are highly heterogeneous with divergent immune functions. A distinct combination of several activation and inhibitory receptors form a diverse array of NK cell subsets in both humans and mice. Importantly, one of the central factors that determine NK cell heterogeneity and their divergent functions is their tissue residency. Decades of studies provided strong support that NK cells develop in the bone marrow. However, evolving evidence supports the notion that NK cells also develop and differentiate in tissues. Here, we summarize the molecular basis, phenotypic signatures, and functions of tissue-resident NK cells and compare them with conventional NK cells.

Keywords: NK cells; tissue-resident; anti-cancer responses

1. Introduction

Immune cells primarily reside in the lymphoid organs and traffic to the sites of infection or tumor transformation [1–4]. At the site of pathology, the migrated lymphocytes initiate responses to eliminate the threat. In contrast to this dogma, recent studies reveal the localized development and functions of tissue-resident immune cells [5–10]. Natural killer (NK) cells are the major innate lymphocytes [11–14]. NK cells mediate cytotoxicity [15–19] and produce significant quantities of inflammatory cytokines, including interferon-γ (IFN-γ) [20–24] and tumor necrosis factor-alpha (TNF-α) [25–28]. Our knowledge about the molecular basis of the development and functions of NK cells is progressing rapidly. Earlier studies have established that human NK cells consist of two major subsets (CD56bright and CD56dim) [29–32]. Recently, we and others, using single-cell RNA-based transcriptomic analyses, have shown that human NK cells are highly heterogeneous with diverse functions [8,33]. Most of our knowledge about NK cells are obtained using mouse spleen or bone marrow (BM), and human peripheral blood mononuclear cells (PBMC). These cells are referred to as conventional NK cells (cNK). Recent studies have started shedding insights into less-studied tissue-resident NK cells (trNK) [8,34,35]. The dichotomy between the cNK and trNK is the focus of this review.

NK cells lack clonotypic receptors and mediate their effector functions without prior sensitization [36]. They exert their function with germline coding activating and inhibitory receptors [37]. Activating receptors
such as NKG2D and NCRs are expressed in both cNK and trNK, and recognize induced self-ligands or antigens from pathogens [38–46]. Induced self-ligands include non-classical major histocompatibility complex class I [46] such as human MIC-A, MIC-B [39,47–51], and murine H60 [45,52,53], Rae (α–ε) [54], and Mult-1 [55,56]. Multiple viral proteins, including hemagglutinin (HA), are recognized by NCRs [1,2]. It is important to note that the expression of ligands for both NKG2D or NCR1 is predominantly occurs on epithelial cells, endothelial cells, and monocytes that are infected or stressed [3,4]. These observations provide a conceptual framework of how both cNK and trNK cells can be activated by similar mechanisms. Based on the expression of CD16 (FCyRIII), human cNK cells can be further divided into two subsets, CD56brightCD16− and CD56dimCD16+ [57–59]. The distribution of these subsets among the cNK and trNK differs significantly. Inhibitory receptors such as human killer immunoglobulin-like inhibitory receptors (KIR) [60] and murine Ly49s [61] primarily recognize classical Major Histocompatibility Complex Class I (MHC-I) and form the basis for ‘licensing’ that allows NK cells to differentiate between ‘self’ and ‘non-self’ [5–9]. Notably, cNK and trNK cells express differing levels or types of KIRs, emphasizing the potential divergent effector functions of these subsets.

cNK cells kill infected or transformed cells that have null or low expression levels of MHC-I molecules [62,63]. Individuals lacking NK cells are prone to viral infections [64–67]. cNK cells recruit innate cells, such as dendritic cells (DCs) [68], neutrophils, and macrophages, to initiate and augment immune responses [69,70]. During this interaction, naïve cNK cells are primed to augment their proliferative and functional capabilities. DCs produce a vast array of cytokines, including IL-15, IL-12, IL-23, IL-27, and IL-18, that have a direct role in the development and functions of cNK cells [71]. Interactions between DCs and cNK cells are essential for this priming [72] and to regulate adaptive immune responses [73,74]. Activation of DCs with Type-1 IFN-α/IFN-β by cNK cells results in the production and trans-presentation of IL-15/IL-15Rx complexes on the cell surface of plasmacytoid DCs [72]. The stimulation of DCs with Type-1 IFN-α/IFN-β by cNK cells, resulting in the trans-presentation of IL-15/IL-15Rx from DCs to the IL-15Rx/IL-2Rβ/IL-2Rγ complex on cNK cells, represents one of the necessary transition steps from innate to adaptive immune responses [75,76]. IL-12 produced by DCs prime cNK cells to produced Type 1 interferons, which in turn help to mature DCs and help in CD4+ T helper-1 (Th1) T cell priming in lymph nodes (LNs) [77]. Thus, the interplay between cNK cells and DCs form an essential link for both cNK and T-cell mediated immune responses [78]. Apart from the DCs, several other tissue-resident myeloid and stromal cells produce IL-7, IL-15, and IL-21. The contributions of these cells towards the development, tissue-retention, and functions of trNK cells are not fully understood. cNK and trNK are two developmentally and functionally divergent subgroups of NK cells. Here, we discuss the ontology, phenotypic and functional characteristics of the trNK cells.

2. cNK Versus trNK Cells

cNK cells develop in the BM [79]. Hematopoietic stem cells (HSCs) in the BM commit to early lymphoid progenitors (ELP) that express high levels of cKit, Sca1, and Flt3 [80,81]. ELPs develop into common lymphoid progenitors (CLPs) that possess a decreased expression of Sca1 and a high level of interleukin (IL)-7 receptor [82,83]. Multiple cytokines play essential roles during the development of cNK cells [79,84]. IL-15 is one of these which uses the common receptor gamma chain (γc) [85,86]. The expression of IL-2β receptor (CD22) results in an irreversible lineage commitment to cNK cells [83,84,87]. Immature cNK cells express CD117 and integrin α2 (DX5) [88]. In the following stages, these cells go through CD27+CD11b− to CD27+CD11b+ to CD27−CD11b+ [89]. Most of the cNK cells trafficked from the BM into the periphery predominantly are CD27−CD11b+ [79,84].

In contrast to the cNK cells, the developmental stages of trNK cells are poorly defined. Whether there are distinct precursors for trNK cells is yet to be elucidated. At what stage the commitment to trNK cells happens, is unknown. Moreover, whether specific cytokines drive NK cell progenitors (NKPs) toward tissue residency is an open question (Figure 1). Cytokine-mediated metabolic reprogramming plays an essential role in the developmental progression of cNK cells. In this context, the qualitative roles of cytokines on cNK cells are yet to be established. Cytokines like IL-12 and IL-15 induce
different levels of the expression of nutrient transporters in cNK cells [90]. It is important to note that the CD56bright CXCR6+ trNK cells express lower levels of Glut1, but higher levels of the amino acid transporter CD98 compared to CD56bright NK cells from peripheral blood following stimulation [90]. The functional relevance of such differences requires further investigation.

Figure 1. Phenotypic delineation of tissue-resident natural killer (trNK) cell subsets. Both human and mouse NK cells are shown. The surface markers of cNK cells from human blood or mice spleen are compared to the trNK cells from indicated tissues. (A) Conventional NK cells (cNK) are compared to lymph node (LN) and thymic NK cells. (B) Phenotypic markers of tissue-resident NK cells from the liver, lung, and uterus in humans and mice. CD56 is depicted in either bright green or light green to indicate the predominant presence of CD56bright or CD56dim subsets in the circulating conventional (cNK cells) or individual organs.
Cytokine profiles of trNK cells are different compared to that of cNK cells. Effector functions of cNK cells include mediating natural cytotoxicity and producing inflammatory cytokines such as TNF-α, IFN-γ, GM-CSF, IL-5, IL-8, IL-10, and IL-13 [91–94]. cNK cells also produce multiple chemokines, including XCL1, XCL2, CCL1, CCL3, CCL4, CCL5, CCL22, and CXCL8 [33,95–97], which help to generate and sustain the inflammatory environment [98,99]. Compared to cNK cells, the liver trNK cells have a higher expression of TNF-α and GM-CSF [8]. Moreover, a significant proportion of liver-resident NK cells are double-positive for IFN-α and TNF-α [8]. TrNK cells are lineage distinct from cNK cells with different requirements of transcription factors (Figure 2). For example, cNK cells were absent in Nfil3 (nuclear factor IL-3-regulated protein)-deficient mice, while these mice possess trNK cells in the liver, skin, and uterus [8,100]. Moreover, NK cells in mouse salivary glands develop in the absence of Nfil3 [101]. cNK cell development is independent of thymic influence, but the thymic-reliant NK cells are absent in nude and GATA3-deficient mice [102]. NK cells are also found in mucosal tissue, including the small intestine. Intestinal Lin−NKp46+NK1.1+ cells consist of Eomes+RORγt-fate map− cNK cells, which express CD27 and lack IL-7Rx, along with a smaller fraction of Eomes−RORγt-fate map+ NK cells [103] that is similar to liver-resident NK cells [104]. Thus, cNK and trNK cells significantly differ in their requirement of the developmental niche and transcriptional networks [105,106]. The topological organization of trNK cells within the microenvironment in organs such as lung or uterus holds clues about their functions, interacting partners, and cellular signals [107–110].

![Figure 2](image_url)

**Figure 2.** Unique transcription factor requirements and functions of trNK cells. Major common gamma chain receptor involved in the development of tissue-specific NK cells are indicated. Essential transcription factors that have been demonstrated are shown. A few of the defined functions of the trNK cells are listed under each subset.

Human cNK cells consist of two major subsets, CD56bright and CD56dim. Functionally, CD56bright NK cells have an increased capacity of cytokine production compared to CD56dim NK cells, which are cytotoxic [111,112]. In peripheral blood, the majority of cNK cells are CD56dim, while CD56bright is abundant in lymphoid tissues and outnumber in LNs, endometrium, and decidua [34,113–116]. Although cNK and trNK cells share common effector functions, recent studies indicate that the tissue site can dictate the potential functions of trNK subsets (Figure 1). Recent studies demonstrate that the trNK cells in the thymus, liver, lymph nodes, and uterus follow developmentally distinct pathways. For example, Dogra P et al. examined the expression of GzmB in CD56dimCD16+ compared to
CD56<sup>bright</sup>CD16<sup>−</sup> NK cells across blood and lymphoid tissues [117]. They found that the frequency of GzmB<sup>+</sup> in CD56<sup>dim</sup>CD16<sup>+</sup> NK cells is significantly higher in the lung compared to LNs and gut [117]. They also found that the expression of FcγRIIa depends on tissue type. Tonsils, gut, and LN CD56<sup>dim</sup>CD16<sup>+</sup> NK cells express substantially higher levels of FcγRIγ compared to CD56<sup>dim</sup>CD16<sup>+</sup> NK cells in the blood, BM, spleen, and lungs [117]. Moreover, trNK cells have specific functions that are exclusively related to organ-specific niches. For instance, trNK cells in the uterus have a role in placental vascular remodeling [118,119], fetal growth [120], and memory of pregnancy [121]. Irrespective of these advances, the developmental origin, subset heterogeneity, functional uniqueness of the trNK cells are yet to be fully defined. In the following sections, we focus on the specific features of trNK cells in lymphoid and non-lymphoid organs.

3. Thymic NK Cells

The presence of NK cells in the thymus has been known for a long time [122], and this subset is distinct from the cNK cells [102]. In mice, thymic NK cells are defined by CD127<sup>+</sup>Ly49<sup>low</sup>CD11b<sup>low</sup>, which represents an immature phenotype [8,102]. CLPs that migrated from the BM into the thymus can commit to becoming T/NK progenitors, and most of them develop into CD4<sup>+</sup>CD8<sup>+</sup> double negative (DN) precursors [123–127]. These CD4<sup>+</sup>CD8<sup>−</sup> thymocytes contain a limited number of precursors with the potential to commit to NK lineage [128]. This highly heterogeneous DN1 (c-Kit<sup>high</sup>CD44<sup>+</sup>CD25<sup>−</sup>CD122<sup>−</sup>NK1.1<sup>−</sup>) thymocytes that are yet to initiate the T cell receptor (TCR)-beta chain rearrangement were able to develop into NK1.1<sup>+</sup> NK cells following in vitro culture with IL-15, IL-7, Flt3L, and stem cell factor (SCF) [128]. These cells show immature BM-derived NK features and expressed CD127 [102]. In addition to DN1, another transitional subset of DN2 (DN2a/DN2b; CD44<sup>+</sup>CD25<sup>+</sup>) also has the potential to commit to NK lineage [129].

The thymic NK cells also traffic to other tissues. Among total NK cells, CD127<sup>+</sup> thymus-derived NK cells are present in around 5% in the BM, liver, and spleen; however, they are enriched (15–30%) in the mesenteric lymph nodes (LNs). These cells are phenotypically similar to thymic CD127<sup>+</sup> NK cells [88]. Like thymus-resident NK cells, they express lower levels of Ly49A, C/I, and G2 and lack the expression of Ly49D [102]. However, this notion of thymic-origin trNK cells present in the LN is complicated by the fact that there are early progenitors present within the LN. Thus, whether the thymic precursor migrates to LN to further develop or mature in the thymus and traffic to LNs is not known. Functions of thymic NK cells are largely not known. Unlike immature NK cells, thymic NK cells are functionally active, and they can produce cytokines, including IFN-γ [102]. The predicted functions include the formation and maintenance of thymic architecture, regulation of thymopoiesis, elimination of transformed thymocytes, and maintenance of T cell clonal diversity. Thymic NK cells may influence the T cell ontogeny through diverse mechanisms, including the elimination of negatively selected thymocytes using perforin/granzyme, Fas/FasL/TNF-related apoptosis-inducing ligand (TRAIL), or through the production of cytokines and chemokines. Similar to cNKs, thymic NK cells require Nfil3, which regulates the transcription of Id2 [130]. However, in contrast to cNK, thymic NK cells develop optimally with minimal phenotypic changes in the absence of Id2 [131]. Upstream E-box transcription factor, Ets1 regulates Id2; and Ets1 is required for thymic NK cell development [132]. This could be due to the reduced reliance of thymic NK cells on IL-15, which turns on Id2-dependent developmental progression [100,133]. Since thymic NK cells primarily depend on IL-7 and not IL-15 in the niche within the corticomedullary junction (ETP/DN1) or cortex (DN2a/DN2b) of the thymus, it is plausible that they utilize an alternative transcriptional program. The thymic NK cells require GATA3 for their development [102,128]. Since GATA3 regulates IL-7Rα receptor expression in a Notch-dependent manner, the absence of this transcription factor results in the lack of thymic NK cells [134,135]. This is further supported by the fact that both GATA3-deficient and athymic nude (Foxn1<sup>−/−</sup>) mice lack the thymic NK cells [102]. Most of the characterizations of thymic NK cells are based on murine models. One potential human subset that may represent the murine thymic counterpart is human LN-resident
CD34\textsuperscript{dim}CD56\textsuperscript{bright}CD16\textsuperscript{−}CD127\textsuperscript{+}c-Kit\textsuperscript{high} NK cells. Detailed future studies are required to fully appreciate the phenotypic and functional uniqueness of human thymic NK cells.

4. Liver-Resident NK Cells

NK cells were first described as ‘pit cells’ in the rat liver in the 1970s [136]. NK cells in the human liver represent up to 30–50% of all hepatic lymphocytes in contrast to 5–16% in PBMC [137]. Given the fact that the liver represents the largest internal organ by mass, the number of trNK cells is significant, and thereby their functions [138]. The link between the liver and the NK cells starts in the fetal liver, where the earliest hematopoiesis occurs [139]. The adult BM is the major generative organ in later life [140,141]. Moreover, the hepatic vascular system has unique characteristics relative to other organs [138]. Two afferent vessels come into the liver, hepatic artery, and portal vein [138]. Terminal branches of the hepatic portal vein and artery mix as they enter the sinusoids [138]. In parabiotic mice, the host liver contains CD49a\textsuperscript{+}DX5\textsuperscript{−}NK cells of host origin and circulating CD49a\textsuperscript{−}DX5\textsuperscript{+} NK cells derived from both host and the other parabiont, indicating that the CD49a\textsuperscript{+}DX5\textsuperscript{+} cells are trNK cells [8,145]. In contrast, the CD49a\textsuperscript{−}DX5\textsuperscript{+} NK cells are cNK cells [8]. The trNK cells are similar to immature cNK cells because they express the conventional markers NK1.1 and Nkp46; but, low levels of CD11b and lack CD49b [8]. CD49a\textsuperscript{−}DX5\textsuperscript{+} liver subset displays high levels of TRAIL [8,146]. Sojka et al. show that liver trNK cells develop independently of the thymus or GATA3, which is the required transcription factor for thymic NK cells [8]. Moreover, in Nfil3-deficient mice, a normal number of liver trNK cells were present, while these mice had no cNK cells in the spleen [8,100]. These data suggest CD49a\textsuperscript{+}DX5\textsuperscript{−} trNK cells in the liver are of residents and a distinct lineage from CD127\textsuperscript{+} thymic NK and cNK cells [8].

In humans, intrahepatic resident NK cells (ihNK) are imprinted in a liver-specific signature with high cellular heterogeneity [138]. ihNK contained a higher proportion of CD56\textsuperscript{bright} NK cells compared to PBMC. First, CD56\textsuperscript{bright}CXCR6\textsuperscript{+} were defined as markers for liver tissue residency, but later among CD56\textsuperscript{bright}CXCR6\textsuperscript{+} population, a subset, which are Eomes\textsuperscript{hi}Tbet\textsuperscript{lo} are considered as trNK cells that are absent in the blood [147]. CD56\textsuperscript{bright}CXCR6\textsuperscript{+} trNK population is characterized by high expression of CD69 and CXCR6 and low expression of DNAM, perforin, and granzyme B, which attributes a non-cytotoxic function for this trNK subset [34,148]. These cells are located primarily in the sinusoids where they express a unique repertoire of chemokine receptors, including CCR5 and CXCR6, and retained in the microenvironment through the interaction of these receptors and their ligands expressed on sinusoidal endothelial cells [34]. Liver-resident NK cells are also characterized by specific transcription factors. One of them, Hobit, is highly expressed in CD56\textsuperscript{bright} trNK cells, along with chemokine receptors, CXCR6, adhesion molecules CD69, and CD49a that is associated with liver residency [149]. Hobit\textsuperscript{pos}CD56\textsuperscript{bright} trNK cells in the liver also possessed a higher level of T-bet and Blimp-1 when compared to Hobit\textsuperscript{neg}CD56\textsuperscript{bright} trNK cells [149,150]. The effector functions of liver-resident NK cells may be non-cytotoxic, but produce a higher level of inflammatory cytokines (Figures 2 and 3). In patients with cirrhosis, CD49a\textsuperscript{+} NK cells include subsets of CD34\textsuperscript{+}CD25\textsuperscript{+} cells that proliferate in response to low doses of IL-2 [151]. This suggests that human liver-resident NK cells have distinct functional characteristics and may contribute to liver inflammation and fibrosis.
Figure 3. Inflammatory cytokine production from trNK cells. Cytokines produced from each type of trNK cells are shown along with the major cytokine and chemokine receptors.

5. Lung-Resident NK Cells

When the lung alveolar surfaces are exposed to pathogens and harmful materials, the innate immune system, including NK cells, provides initial protection [152–156]. In humans, NK cells accounting for about 10–20% of the lymphocytes in the lungs [107]. In mice, 10% of lymphocytes consist of NK cells [107,157]. The majority of NK cells in the human lung are circulating CD56dimCD16+, and the frequency of mature CD57+ NKG2D− cells is higher in the lung compared to peripheral blood [7]. These cells express higher levels of KIR2DL1, KIR2DL2/S2, KIR2DL3, and KIR3DL1. In human lung, approximately 10% of CD56dimCD16+ and 75% of CD56brightCD16+ NK cells, which also express CD69. CD69 is a hallmark for tissue residency [158–160]. Michaelsson et al. first demonstrated the presence of lung trNK cells [161]. They report three distinct lung trNK cell subsets, CD16+CD69+CD49a+CD103+, CD16−CD69+CD49a+CD103−, and CD69−CD16− [161]. The first two subsets express a higher level of ITGA1 (CD49a), ZNF683 (Hobit), RGS1, and RGS2, and lower levels of SELL (CD62L), S1PR5, and KLF3 transcripts compared to the CD69− subset [161]. These have been previously reported as the hallmark genes of CD8+ tissue-resident memory T cells (T_{RM}) [162,163]. CD69+CD16− subset expresses tissue residency markers to a lesser extent; therefore, this subset is considered similar to cNK cells [161]. Comparison of lung trNK to cNK cells or CD8+ T_{RM} cells indicates that these are similar to BM NK cells and CD8+ T_{RM} cells rather than splenic naïve CD8+ T cells [161]. Lung trNK cells play an important role in respiratory diseases, including infectious diseases, allergy, and cancer [107,164].

Circulating cNK cells from the periphery are recruited to the lung during infections. For example, during the early stages of Mycobacterium tuberculosis (MTb) infection, NK cells with upregulated CD69, IFN-γ, and perforin accumulate in the lungs [165]. Moreover, NK subsets representing CD94^{high}KIR^{low} were recruited from the blood into the lungs during respiratory tract inflammation [166]. In mice, CD11b^{high}CD2^{low} cells are the predominant lung-resident NK subset [167] and shown to have a role in the control of pulmonary tumor growth [164]. NK cells in tumor tissues of patients with non-small-cell lung cancer (NSCLC) show distinct receptor expression patterns with lower expression of NKp30, NKp80, KIR2DL1, and KIR2DL2 and higher expression of NKp44, NG2/2A, CD69, and HLA-DR [107]. These studies characterize lung trNK cells and their functions, but detailed studies are needed to uncover the developmental progression, transcription factor profiles, and functions of the NK cell subsets in the lung.
6. Lymph Node-Resident NK Cells

LN s provide niches with diverse and concerted interactions of immune cells, which facilitate robust responses [114,168−171]. The human body has 500 to 600 LNs that are distributed to provide region-specific immune responses [172]. The LN is divided into three central regions, cortex, paracortex, and medulla. The cortex is the outer region of LN that contains B cell follicles and interfollicular zone (IFZ) [173−175]. In LNs, NK cells, which constitute 2−5% of lymphocytes [35,113,116,176], are localized in IFZ along with γδ T cells, natural killer T (NKT) cells, and innate-like CD8+ T cells [177]. NK cells in the LN consist of multiple subsets, and they are cNK, NK cells that possess the thymic origin, and a unique lymphoid tissue-resident NK (Ltr-NK) that are shown to develop within this organ. Most of these NK cells are located adjacent to lymphatic sinus-lining sentinel macrophages [178]. Stromal cells regulate the movement of lymphocytes, including cNK cells within the LN by secreting chemokines such as CCL21, CCL19, and CXCL13 [179].

A recent study using single-cell RNA sequencing suggests that the organization of the LN into distinct functional compartments is due to the specific type of stromal cell subsets present in the cortex, paracortex, and medulla of the LN [179]. T cell-zone reticular cells (TRCs) that express CXCL9 and CXCL10 are also located in IFZ and play an essential role in positioning dendritic cells (DCs) and T cells within the IFZ. However, neither the interaction of LN-NK subsets with other immune cells within IFZ nor the presence of an exclusive LN-NK niche has been explored. In human, more than 75% of all NK cells in LNs are CD56bright [35,116,180]. Circulating CD56bright NK cells enter the LNs via high endothelial venules (HEV) and afferent lymph vessels [31,181], which express CCR7 and CD62L [182,183]. They can be recruited by the CCL19 and CCL21 chemokines, which are highly expressed in LNs [113]. Ltr-NK subset in the LNs consists of 60% of total NK cells and covers the majority of the CD56bright compartment. These Ltr-NK cells were identified based on the co-expression of CD69 and CXCR6 [35]. Ltr-NK cells also express NKp46, and most of them are CD16−CD49a+CD27bright [35].

Ltr-NK cells do not express DNAX accessory molecule 1 (DNAM1), an activating receptor that is uniformly expressed on circulating CD56bright NK cells [35]. Functionally, Ltr-NK cells produce less IFN-γ and reduced capacity to lyse K562 cells compared to the circulating CD56bright NK cells [35]. Specifically, CD56dimCD16+ Ltr-NK cells express substantially higher levels of FcRly compared to CD56dimCD16+ cNK cells in the blood, BM, spleen, and lungs. Freud et al. identified a new CD34+CD56+CD127+ immature NK subset in the LN, which may develop into Ltr-NK [184]. Recently, Ferber et al. showed that LNs contain CD56brightCD127+CD161+ cells that represent less differentiated precursor NK cells compared to other peripheral sites [117]. Mice lacking Eomes and T-bet failed to develop cNK cells with a modest reduction in Ltr-NK cells [185]. Moreover, it was reported that the Klf4-deficient mice contain lower numbers of cNK cells in the blood and the spleen but normal numbers of trNK cells in other organs such as the liver and LNs [186]. Tox−/− mice have a similar phenotype to Id2−/− mice and lack mature cNK cells in the periphery as well as LNs [186,187]. Further studies are needed to investigate the possibility of LN as another primary site for the development of a unique Ltr-NK subset. The transcriptional requirement for the development of Ltr-NK cells needs to be determined.

7. Uterine NK Cells

Potentially, the most relevant immune cells during pregnancy are NK cells. In mice, during the non-menstrual period, NK cells make up 30% of endometrial lymphocytes, and this number increases significantly (70% of lymphocytes) during pregnancy and decidualization [188,189]. Almost all the NK cells in the non-pregnant uterus (endometrium) and pregnant uterus (decidua) are CD56bright [31,190]. Uterine CD56bright NK cells (uNK) express CD94, NKG2A, and lack of expression of CD16 (Figures 1 and 2) [190]. These uNK cells are distinct from peripheral blood in multiple aspects. Most of the uNK cells express CD49a and CD103 [191]. Moreover, KIR receptors on uNK cells are distinct from cNK cells [192,193]. Decidua NK cells are educated by maternal HLA-C molecules, which influences the expression of KIR receptors [192]. Due to this unique ‘licensing’ program, the expression levels of KIR2DL1+ and KIR2DL3/L2/S2+ on decidua NK cells are increased compared to cNK cells [192].
uNK cells are transcriptionally distinct from cNK cells, and microRNA profiles of these cells are also different [194]. Specific miRNA, miR-362-5p, is highly upregulated in decidua NK cells, which targets CYLD, a negative regulator of the NF-κB signaling pathway [194].

uNK cell frequency may change through the menstrual cycle or during pregnancy. Sojka et al. used Ncr1-iCre-Rosa<sup>tm1Zag</sup> mice containing membrane-bound Td-tomato to track NK cells during pregnancy [188,195–197]. In this mouse, when Cre is expressed, the floxed Td-tomato cassette and the stop codon are removed, and expression of membrane-bound GFP occurs, facilitating the tracking of uNK cells. Using this method, Sojka et al. show that on the gestational day 6.5, the decidua basalis contained proliferating GFP<sup>+</sup> uNK cells, before the development of mesometrial lymphoid aggregate of pregnancy (MLAp), challenging the idea of considering MLAp as a source of immature uNK cells [198]. At gestational day 10.5 (mid-gestation), they found GFP<sup>+</sup> uNK cells within the prominent MLAp structure. Shortly after midgestation, the number of GFP<sup>+</sup> uNK cells began to decline at the implantation site [198]. Remarkably, at 2.5 days post-partum, the number of GFP<sup>+</sup> uNK cells start to resemble those in the non-pregnant uterus.

Although the transcription factor Nfil3 is essential for normal placental and embryonic development, it is not required for uNK cell development [199]. Moreover, assessing the gestational day 10 implantation sites showed that the deletion of T-bet did not modify the differentiation or function of uNK cells, while Eomes may regulate activation and IFN-γ production in uNK cells [200]. uNK cells may also play an essential role in the fetomaternal interface [201–204]. Vento et al. analyzed the transcriptome of about 70,000 single-cells from human first-trimester placentas, and they found three subsets decidual NK cells (dNK1, dNK2, and dNK3) [205]. These subsets co-express the tissue-resident markers CD49a (ITGA1) and CD9. dNK1 cells express CD39 (ENTPD1), CYP26A1, and B4GALNT1, whereas the defining markers of dNK2 cells are ANXA1 and ITGB2; dNK3 cells express CD160, KLRB1, and CD103 (ITGAE), but not the innate lymphocyte cell marker CD127 [205].

8. Clinical Relevance of trNK Cells

The role of cNK cells in tumor clearance is well established [64,206–208]. However, the anti-tumor functions of trNK cells are far from defined. Impairment in overall NK cell functions leads to an increased risk of cancer [209]. Tumor-infiltrating NK cells (TINKs) or tumor-associated NK cells (TANKs) [210] are involved in both clearances of malignancies and immunosuppression, depending on the tumor microenvironment (TMEs). However, the identities of the TINKs and TANKs within the TME are yet to be established. NK cells are involved in the clearance of hepatocellular carcinomas [211,212], colorectal carcinoma [213], gastric carcinoma [214], and squamous cell lung cancer [215]. Therapies formulated with haploidentical or autologous cNK cells hold promise to treat hematological malignancies, including acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) [216–218]. Moreover, allogeneic cNK cell-based therapies pose no or less risk of graft-versus-host disease (GvHD) [219]. Based on these observations, multiple Food and Drug Administration (FDA)-approved clinical trials using donor-derived cNK cells are being formulated and employed, including the ones expressing CAR [212,220–224]. Irrespective of these impressive advancements, the functional characterization, and utilization of cNK cells from human PBMCs, we are only beginning to understand the clinical relevance of trNK cells.

Thymic NK cells are predicted to possess intrathymic functions and other functions in the secondary lymphoid organs or tissues when seeded extrathymically [102]. In mice, the Gata-3/IL-7-dependent thymic NK cells express a lesser level of inhibitory Ly49 receptors. Similar observations in humans are yet to be made. However, thymic NK cells are predicted to provide a regulatory function during the T cell ontogeny in the thymus, quite possibly in the elimination of negatively selected T cells. The CD127<sup>+</sup> thymus-derived NK cells in mice (and CD56<sup>bright</sup>CD16<sup>+</sup> in humans) in the LN produce a higher amount of inflammatory cytokines such as IFN-γ; however, they are also known to mediate a sub-optimal level of cytotoxicity compared to that of bone marrow-derived splenic NK cells [102]. Thus, the thymic NK cells have the potentials in regulating the expression levels of MHC class I on stromal cells. The clinical relevance of these
findings is manifold. If the mechanism of how NK cells influence the T cell selection, it can be employed in methodologies where a T cell-based cellular therapy is being developed. It is not known whether at least some of the T cell-based autoimmune diseases are due to a defect in thymic NK cells.

Hepatic NK cells contain both the cNK and trNK cells. The number of these two subsets constitutes 50% of total hepatic lymphocytes [138]. Liver-specific CD56bright/CD16−/CD69+ trNK cells represent half of all NK cells in this organ, which are retained by the expression of homing chemokine receptors CXCR3, CXCR6, and CCR5 [34]. Given that the major function of the liver is detoxification, the trNK cells are of high clinical relevance. One of the major functions of trNK cells is the maintenance of hepatic tolerance and homeostasis. Interaction of trNK cells with hepatocytes via CD94/NKG2A-MHC non-classical class I-HLA-E results in the production of immunosuppressive factor TGF-β, which along with IL-6 from myeloid cells such as DCs, expand CD4+ regulatory T cells. Hepatocellular carcinoma is the leading liver-related malignancy, primarily caused by Hepatitis B or Hepatitis C viral infections. Acute hepatitis infection in humans leads to an altered trNK cell phenotype in the liver. Viral infections augment the expression of NCR1 (Nkp46) with an increased cytotoxic degranulation and inflammatory cytokine production [225]. Hepatic carcinomas and metastatic colorectal cancer in the liver contain a high number of intra-tumoral NCR1+ NK cells [226]. These observations emphasize the need to characterize and identify methods to augment the effector functions of tumor-infiltrating NK cells in the liver.

More than 80% of the lung NK cells are terminally-differentiated CD56dimCD16+ cells. The remaining 20% of the NK cells are composed of immature CD56brightCD16− and less-differentiated CD56dimCD16− cells. Lung-resident NK cells primarily identified using CD49a, CD69, and CD103 [227]. The upper respiratory system is the primary site of many viral infections, including influenza and Sars-Cov-2. The lung-resident CD56brightCD49a+ NK cells play an essential role in clearing influenza-infected epithelial cells and produce IFN-γ to facilitate the generation of CD8+ T-cell-based Tc1 or CD4+ T-cell-based Th1 responses. Moreover, the regeneration of tracheal epithelial cells depends on IL-22 produced by a subset of innate-like NK cells present in the lung [228,229]. In mice, clearance of pulmonary pseudometastases following the challenge with B16F10 melanoma strictly depends on the optimal functions of NK cells [230–232]. In patients with non-small-cell lung carcinoma (NSCLC), the number of tumor-infiltrating NK cells were significantly increased, which correlated with the overall survival rate [215]. Irrespective of these findings, the independent clinical relevance of lung-resident versus circulating NK cells is yet to be determined.

LN NK cells are a mixed population of circulating and thymus-derived NK cells [89,102]. Apart from this, a unique LN-derived NK subset has been recently identified [184]. NK cells in LNs mediate the interaction between innate and adaptive immune cells. LN is the major draining site where tumor- or pathogen-derived antigens are encountered by immune cells. NK cells in the LN are known to interact with antigen-bearing DCs and drive the differentiation of CD4+ T cells to induce early resistance to *Leishmania major* and *Toxoplasma gondii* [233,234]. Circulating NK cells are recruited in a CXCR3-dependent manner to LNs. IFN-γ production by these NK cells has an essential role in T11 polarization [235]. A gradient of sphingosine-1 phosphate (S1P) in LNs position NK cells and regulate their IFN-γ responses [236]. Tumor-draining LNs are the first site of metastasis in most types of cancers and often used in staging cancer progression [237,238]. Using NK cells with TRAIL liposomes enhances their retention time within the tumor-draining LNs to induce apoptosis in cancer cells [237].

Uterine NK cells possess specific roles during pregnancy, including the formation of the fetal-maternal interface and placental vascular remodeling [239]. In humans, the dilatation of uterine spiral arteries is attributed to trophoblasts. However, in mice, losing smooth muscles and dilation of vessels considered to be the functions of uNK cells [239]. NK cell-deficient mice have a defect in spiral artery remodeling [239]. Another role of uNK cells during pregnancy is to promote fetal development [120]. CD49a+Eomes+ trNK cells in the uterus have been defined, which secretes growth-promoting factors (GPF), including pleiotrophin and osteoglycin [240]. These CD49a+Eomes+ uNK cells enhance fetal growth during the early stages [240]. Decrease in the GPF-secreting NK cell
subset impaired fetal development, resulting in fetal growth restriction [240]. Detailed studies are needed to further define uNK cell functions in the uterus to prevent the risk of pre-eclampsia.

9. Summary and Future Outlook

The ability of NK cells to utilize germline-encoded non-clonotypic receptors to recognize and clear malignant or infected cells provide clinical promise. However, this paradigm of simplicity is challenged by the fact that NK cells are highly heterogeneous. This is further complicated by the findings that there are subsets of NK cells that are tissue-resident. These trNK cells display unique tissue-specific markers and are developmentally less mature [104]. These differences likely due to their local microenvironment and tissue localization. Despite recent insights that have helped to characterize trNK cells, essential questions remain unanswered. The term ‘tissue-resident’ is not fully defined at the transcriptional or transcriptomic levels. The cell plasticity is being tested in multiple models to differentiate the circulating versus the permanently tissue-residing NK cells. Determining their unique functions will vastly help in the formulations of specific NK cell-based therapies. Significant work needs to be performed in order to characterize trNK cells fully.

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Abbreviation

| NK       | Natural killer |
|---------|---------------|
| ILC1    | Innate lymphoid cells |
| Tr      | Tissue-resident |
| Prf1    | Perforin |
| IFN-γ   | Interferon-γ |
| TNF-α   | Tumor necrosis factor alpha |
| BM      | Bone marrow |
| cNK cells | Convectional NK cells |
| PBMC    | Peripheral blood mononuclear cells |
| HSCs    | Hematopoietic stem cells |
| ELP     | Early lymphoid progenitors |
| CLP     | Common lymphoid progenitors |
| IL      | Interleukin |
| KIR     | Immunoglobulin-like inhibitory receptors |
| MHC-1   | MHC Class I |
| GM-CSF  | Granulocyte–monocyte colony-stimulating factor |
| NFIL3   | Nuclear factor IL-3-regulated protein |
| DN      | CD4⁺CD8⁻ double negative |
| SCF     | Stem cell factor |
| ETPs    | Early thymic precursors |
| LNs     | Lymph nodes |
| TRAIL   | TNF-related apoptosis-inducing ligand |
| ihNK    | Intrahepatic resident NK cells |
| TrRM    | Tissue-resident memory T cells |
| NSCLC   | Non-small-cell lung cancer |
| IFZ     | Interfollicular zone |
| NKT     | Natural killer T cells |
| TRCs    | T-zone reticular cells |
| HEV     | High endothelial venules |
| Ltr     | Lymphoid-tissue resident |
| DNAM1   | DNA_accessory molecule 1 |
| S1P     | Sphingosine-1 phosphate |
| Endometrium | Non-pregnant uterus |
| Decidua | Pregnant uterus |
| gd      | gestational day |
| MLAp    | Mesometrial lymphoid aggregate of pregnancy |
References

1. Griffith, J.W.; Sokol, C.L.; Luster, A.D. Chemokines and chemokine receptors: Positioning cells for host defense and immunity. *Annu. Rev. Immunol.* **2014**, *32*, 659–702. [CrossRef]

2. Kim, C.H. Chemokine-chemokine receptor network in immune cell trafficking. *Curr. Drug Targets Immune Endocr. Metabol. Disord.* **2004**, *4*, 343–361. [CrossRef]

3. Schulz, O.; Hammerschmidt, S.I.; Moschovakis, G.L.; Förster, R.J. Chemokines and chemokine receptors in lymphoid tissue dynamics. *Annu. Rev. Immunol.* **2016**, *34*, 203–242. [CrossRef]

4. Sokol, C.L.; Luster, A.D. The chemokine system in innate immunity. *Cold Spring Harb. Perspect. Biol.* **2015**, *7*, a016303. [CrossRef]

5. Fernandez-Ruiz, D.; Ng, W.Y.; Holz, L.E.; Ma, J.Z.; Zaid, A.; Wong, Y.C.; Lau, L.S.; Mollard, V.; Cozijnsen, A.; Collins, N.J. Liver-resident memory CD8+ T cells form a front-line defense against malaria liver-stage infection. *Immunity* **2016**, *45*, 889–902. [CrossRef] [PubMed]

6. Krueger, P.D.; Kim, T.S.; Sung, S.-J.; Braciale, T.J.; Hahn, Y.S. Liver-resident CD103+ dendritic cells prime antiviral CD8+ T cells in situ. *J. Immunol.* **2015**, *194*, 3213–3222. [CrossRef] [PubMed]

7. Marquardt, N.; Kekäläinen, E.; Chen, P.; Kvedaraite, E.; Wilson, J.N.; Ivarsson, M.A.; Mjöberg, J.; Berglin, L.; Säfholm, J.; Manson, M.I.J.; et al. Human lung natural killer cells are predominantly comprised of highly differentiated hypofunctional CD69− CD56dim cells. *J. Allergy Clin. Immunol.* **2017**, *139*, 1321–1330.e4. [CrossRef] [PubMed]

8. Sojka, D.K.; Plougastel-Douglas, B.; Yang, L.; Pak-Wittel, M.A.; Arytymow, M.N.; Ivanova, Y.; Zhong, C.; Chase, J.M.; Rothman, P.B.; Yu, J.J. Tissue-resident natural killer (NK) cells are cell lineages distinct from thymic and conventional splenic NK cells. *elife* **2014**, *3*, e01659. [CrossRef] [PubMed]

9. Victorino, F.; Sojka, D.K.; Brodsky, K.S.; McMamme, E.N.; Masterson, J.C.; Homann, D.; Yokoyama, W.M.; Eltzschig, H.K.; Clambey, E.T. Tissue-resident NK cells mediate ischemic kidney injury and are not depleted by Anti–Asialo-GM1 antibody. *J. Immunol.* **2015**, *195*, 4973–4985. [CrossRef] [PubMed]

10. Zhou, J.; Peng, H.; Li, K.; Qu, K.; Wang, B.; Wu, Y.; Ye, L.; Dong, Z.; Wei, H.; Sun, R.J.I. Liver-resident NK cells control antiviral activity of hepatic T cells via the PD-1-PD-L1 axis. *Immunity* **2019**, *50*, 403–417.e4. [CrossRef] [PubMed]

11. Gwalani, L.A.; Orange, J.S. Single degranulations in NK cells can mediate target cell killing. *J. Immunol.* **2018**, *200*, 3231–3243. [CrossRef] [PubMed]

12. Garrido, C.; Abad-Fernandez, M.; Tuyishime, M.; Pollara, J.J.; Ferrari, G.; Soriano-Sarabia, N.; Margolis, D.M. Interleukin-15-stimulated natural killer cells clear HIV-1-infected cells following latency reversal ex vivo. *J. Virol.* **2018**, *92*, e00235-18. [CrossRef] [PubMed]

13. Mandelboim, O.; Lieberman, N.; Lev, M.; Paul, L.; Arnon, T.I.; Bushkin, Y.; Davis, D.M.; Strominger, J.L.; Yewdell, J.W.; Porgador, A. Recognition of haemagglutinins on virus-infected cells by NKp46 activates lysis by human NK cells. *Nature* **2001**, *409*, 1055–1060. [CrossRef]

14. Lodovien, M.B.; Lanier, L.L. Viral modulation of NK cell immunity. *Nat. Rev. Microbiol.* **2005**, *3*, 59–69. [CrossRef] [PubMed]

15. Fehninger, T.A.; Cai, S.F.; Cao, X.; Bredemeyer, A.J.; Presti, R.M.; French, A.R.; Ley, T.J. Acquisition of murine NK cell cytotoxicity requires the translation of a pre-existing pool of granzyme B and perforin mRNAs. *Immunity* **2007**, *26*, 798–811. [CrossRef]

16. Salcedo, T.; Azzoni, L.; Wolf, S.F.; Perussia, B. Modulation of perforin and granzyme messenger RNA expression in human natural killer cells. *J. Immunol.* **1993**, *151*, 2511–2520.

17. Shresta, S.; Maclvor, D.M.; Heusel, J.W.; Russell, J.H.; Ley, T.J. Natural killer and lymphokine-activated killer cells require granzyme B for the rapid induction of apoptosis in susceptible target cells. *Proc. Natl. Acad. Sci. USA* **1995**, *92*, 5679–5683. [CrossRef]

18. King, A.; Wooding, P.; Gardner, L.; Loke, Y.W. Immunology: Expression of perforin, granzyme A and TIA-1 by human uterine CD56+ NK cells implies they are activated and capable of effector functions. *Hum. Reprod.* **1993**, *8*, 2061–2067. [CrossRef]

19. Vermijlen, D.; Luo, D.; Robaye, B.; Seynaeve, C.; Baekeland, M.; Wisse, E. Pit cells (Hepatic natural killer cells) of the rat induce apoptosis in colon carcinoma cells by the perforin/granzyme pathway. *Hepatology* **1999**, *29*, 51–56. [CrossRef]
20. Arase, H.; Arase, N.; Saito, T. Interferon gamma production by natural killer (NK) cells and NK1. 1+ T cells upon NKR-P1 cross-linking. *J. Exp. Med.* 1996, 183, 2391–2396. [CrossRef] [PubMed]

21. Luepte-Eversloh, M.; Hammer, Q.; Durek, P.; Nordström, K.; Gasparoni, G.; Pink, M.; Hamann, A.; Walter, J.; Chang, H.-D.; Dong, J. Human cytomegalovirus drives epigenetic imprinting of the IFNG locus in NKG2Chi natural killer cells. *PLoS Pathog.* 2014, 10, e1004441. [CrossRef] [PubMed]

22. Lindgren, Å.; Pavlovic, V.; Flach, C.-F.; Sjöling, Å.; Lundin, S. Interferon-gamma secretion is induced in IL-12 stimulated human NK cells by Helicobacter pylori or TLR2 ligands. *Innate Immun.* 2011, 17, 191–203. [CrossRef] [PubMed]

23. Kokordelis, P.; Krämer, B.; Körner, C.; Boesecke, C.; Voigt, E.; Ingiliz, P.; Glässner, A.; Eisenhardt, M.; Wolter, F.; Kaczmarek, D. An effective interferon-gamma-mediated inhibition of hepatitis C virus replication by natural killer cells is associated with spontaneous clearance of acute hepatitis C in human immunodeficiency virus-positive patients. *Hepatology* 2014, 59, 814–827. [CrossRef] [PubMed]

24. Stein, N.; Berhani, O.; Schmiedel, D.; Duev-Cohen, A.; Seidel, E.; Kol, I.; Tsukerman, P.; Hecht, M.; Reches, A.; Gamliel, M. IFNG-ASI Enhances Interferon Gamma Production in Human Natural Killer Cells. *iScience* 2019, 11, 466–473. [CrossRef]

25. Makowska, A.; Franzen, S.; Braunschweig, T.; Denecke, B.; Shen, L.; Balovoč, V.; Busson, P.; Kontny, U. Interferon beta increases NK cell cytotoxicity against tumor cells in patients with nasopharyngeal carcinoma via tumor necrosis factor apoptosis-inducing ligand. *Cancer Immunol. Immunother.* 2019, 68, 1317–1329. [CrossRef]

26. Small, H.Y.; Nosalski, R.; Morgan, H.; Beattie, E.; Guzik, T.; Graham, D.; Delles, C. The Role of Tumor Necrosis Factor α and Natural Killer Cells in Uterine Artery Function During Pregnancy in the Stroke Prone Spontaneously Hypertensive Rat. *Hypertension* 2016, 68, 1298–1307. [CrossRef] [PubMed]

27. Parr, E.L.; Chen, H.-L.; Parr, M.B.; Hunt, J.S. Synthesis and granular localization of tumor necrosis factor-alpha in activated NK cells in the pregnant mouse uterus. *J. Reprod. Immunol.* 1995, 28, 31–40. [CrossRef]

28. Takeda, K.; Hayakawa, Y.; Smyth, M.J.; Kayagaki, N.; Yamaguchi, N.; Kakuta, S.; Ikawa, Y.; Yagita, H.; Okumura, K. Involvement of tumor necrosis factor-related apoptosis-inducing ligand in surveillance of tumor metastasis by liver natural killer cells. *Nat. Med.* 2001, 7, 94–100. [CrossRef]

29. Chan, A.; Hong, D.-L.; Atzberger, A.; Kollnberger, S.; Filer, A.D.; Buckley, C.D.; McMichael, A.; Enver, T.; Bowness, P. CD56bright human NK cells differentiate into CD56dim cells: Role of contact with peripheral fibroblasts. *J. Immunol.* 2007, 179, 89–94. [CrossRef]

30. Romagnani, C.; Juelke, K.; Falco, M.; Morandi, B.; D’Agostino, A.; Costa, R.; Ratto, G.; Forte, G.; Carrega, P.; Lui, G. CD56brightCD16− killer Ig-like receptor—NK cells display longer telomeres and acquire features of CD56dim NK cells upon activation. *J. Immunol.* 2007, 178, 4947–4955. [CrossRef]

31. Melsen, J.E.; Lugthart, G.; Lankester, A.C.; Schilham, M.W. Human circulating and tissue-resident CD56bright natural killer cell populations. *Front. Immunol.* 2016, 7, 262. [CrossRef] [PubMed]

32. Takahashi, E.; Kuranaga, N.; Satoh, K.; Habu, Y.; Shinomiya, N.; Asano, T.; Seki, S.; Hayakawa, M. Induction of CD16+CD56bright NK cells with antitumour cytotoxicity not only from CD16−CD56bright NK Cells but also from CD16−CD56dim NK cells. *Scand. J. Immunol.* 2007, 65, 126–138. [CrossRef] [PubMed]

33. Yang, C.; Siebert, J.R.; Burns, R.; Gerbec, Z.J.; Bonacci, B.; Rymaszewski, A.; Rau, M.; Riese, M.J.; Rao, S.; Carlson, K.-S. Heterogeneity of human bone marrow and blood natural killer cells defined by single-cell transcriptome. *Nat. Commun.* 2019, 10, 1–16. [CrossRef] [PubMed]

34. Hudspeth, K.; Donadon, M.; Cimino, M.; Pontarini, E.; Tentorio, P.; Preti, M.; Hong, M.; Bertoletti, A.; Bicciato, S.; Invernizzi, P.; et al. Human liver-resident CD56(bright)/CD16(neg) NK cells are retained within hepatic sinusoids via the engagement of CCR5 and CXCR6 pathways. *J. Autoimmun.* 2016, 66, 40–50. [CrossRef]

35. Lugthart, G.; Melsen, J.E.; Vervat, C.; van Ostaijen-tan Den, M.M.; Corver, W.E.; Roelen, D.L.; van Bergen, J.; van Tol, M.J.; Lankester, A.C.; Schilham, M.W. Human lymphoid tissues harbor a distinct CD69+CXCR6+ NK cell population. *J. Autoimmun.* 2016, 69, 197–204. [CrossRef]

36. Rajasekaran, K.; Riese, M.J.; Rao, S.; Wang, L.; Thakar, M.S.; Sentman, C.L.; Malarkannan, S. Signaling in effector lymphocytes: Insights toward safer immunotherapy. *Front. Immunol.* 2016, 7, 176. [CrossRef]

37. Vivier, E.; Nunès, J.A.; Vély, F. Natural killer cell signaling pathways. *Science* 2004, 306, 1517–1519. [CrossRef]
38. Ho, E.L.; Heusel, J.W.; Brown, M.G.; Matsumoto, K.; Scalzo, A.A.; Yokoyama, W.M. Murine Nkg2d and Cd94 are clustered within the natural killer complex and are expressed independently in natural killer cells. *Proc. Natl. Acad. Sci. USA* 1998, 95, 6320–6325. [CrossRef]

39. Bauer, S.; Groh, V.; Wu, J.; Steinle, A.; Phillips, J.H.; Lanier, L.L.; Spies, T. Activation of NK cells and T cells by NKG2D, a receptor for stress-inducible MICA. *Science* 1999, 285, 727–729. [CrossRef]

40. Vitale, M.; Bottino, C.; Sivori, S.; Sanseverino, L.; Castriconi, R.; Marcenaro, E.; Augugliaro, R.; Moretta, L.; Moretta, A. Nkp44, a novel triggering surface molecule specifically expressed by activated natural killer cells, is involved in non-major histocompatibility complex-restricted tumor cell lysis. *J. Exp. Med.* 1998, 187, 2065–2072. [CrossRef]

41. Pende, D.; Parolini, S.; Pessino, A.; Sivori, S.; Augugliaro, R.; Morelli, L.; Marcenaro, E.; Accame, L.; Malaspina, A.; Biassoni, R.; et al. Identification and molecular characterization of Nkp30, a novel triggering receptor involved in natural cytotoxicity mediated by human natural killer cells. *J. Exp. Med.* 1999, 190, 1505–1516. [CrossRef] [PubMed]

42. Sivori, S.; Parolini, S.; Marcenaro, E.; Castriconi, R.; Pende, D.; Millo, R.; Moretta, A. Involvement of natural cytotoxicity receptors in human natural killer cell-mediated lysis of neuroblastoma and glioblastoma cell lines. *J. Neuroimmunol.* 2000, 107, 220–225. [CrossRef]

43. De Maria, A.; Biassoni, R.; Fogli, M.; Rizzi, M.; Cantoni, C.; Costa, P.; Conte, R.; Mavilio, D.; Ensoli, B.; Cafaro, A.; et al. Identification, molecular cloning and functional characterization of Nkp46 and Nkp30 natural cytotoxicity receptors in Macaca fascicularis NK cells. *Eur. J. Immunol.* 2001, 31, 3546–3556. [CrossRef]

44. Arnon, T.I.; Lev, M.; Katz, G.; Chernobrov, Y.; Porgador, A.; Mandelboim, O. Recognition of viral hemagglutinins by Nkp44 but not by Nkp30. *Eur. J. Immunol.* 2001, 31, 2680–2689. [CrossRef]

45. Diefenbach, A.; Jamieson, A.M.; Liu, S.D.; Shastri, N.; Raulet, D.H. Ligands for the murine NKG2D receptor: Expression by tumor cells and activation of NK cells and macrophages. *Nat. Immunol.* 2000, 1, 119–126. [CrossRef] [PubMed]

46. Samarakoon, A.; Chu, H.; Malarkannan, S. Murine NKG2D ligands: “Double, double toil and trouble”. *Mol. Immunol.* 2009, 46, 1011–1019. [CrossRef]

47. Steinle, A.; Li, P.; Morris, D.L.; Groh, V.; Lanier, L.L.; Strong, R.K.; Spies, T. Interactions of human NKG2D with its ligands MICA, MICB, and homologs of the mouse RAE-1 protein family. *Immunogenetics* 2001, 53, 279–287. [CrossRef]

48. Li, P.; Willie, S.T.; Bauer, S.; Morris, D.L.; Spies, T.; Strong, R.K. Crystal structure of the MHC class I homolog MIC-A, a gammadelta T cell ligand. *Immunity* 1999, 10, 577–584. [CrossRef]

49. Holmes, M.A.; Li, P.; Petersdorf, E.W.; Strong, R.K. Structural studies of allelic diversity of the MHC class I homolog MIC-B, a stress-inducible ligand for the activating immunoreceptor NKG2D. *J. Immunol.* 2002, 169, 1395–1400. [CrossRef]

50. Groh, V.; Bahram, S.; Bauer, S.; Herman, A.; Beauchamp, M.; Spies, T. Cell stress-regulated human major histocompatibility complex class I gene expressed in gastrointestinal epithelium. *Proc. Natl. Acad. Sci. USA* 1996, 93, 12445–12450. [CrossRef] [PubMed]

51. Groh, V.; Steinle, A.; Bauer, S.; Spies, T. Recognition of stress-induced MHC molecules by intestinal epithelial gammadelta T cells. *Science* 1998, 279, 1737–1740. [CrossRef] [PubMed]

52. Malarkannan, S.; Shih, P.P.; Eden, P.A.; Horng, T.; Zuberi, A.R.; Christianson, G.; Roopenian, D.; Shastri, N. The molecular and functional characterization of a dominant minor H antigen, H60. *J. Immunol.* 1998, 161, 3501–3509. [PubMed]

53. Malarkannan, S.; Horng, T.; Eden, P.; Gonzalez, F.; Shih, P.; Brouwenstijn, N.; Klinge, H.; Christianson, G.; Roopenian, D.; Shastri, N. Differences that matter: Major cytotoxic T cell-stimulating minor histocompatibility antigens. *Immunity* 2000, 13, 333–344. [CrossRef]

54. Cervenka, A.; Bakker, A.B.; McClanahan, T.; Wagner, J.; Wu, J.; Phillips, J.H.; Lanier, L.L. Retinoic acid early inducible genes define a ligand family for the activating NKG2D receptor in mice. *Immunity* 2000, 12, 721–727. [CrossRef]

55. Carayannopoulos, L.N.; Naidenko, O.V.; Fremont, D.H.; Yokoyama, W.M. Cutting edge: Murine UL16-binding protein-like transcript 1: A newly described transcript encoding a high-affinity ligand for murine NKG2D. *J. Immunol.* 2002, 169, 4079–4083. [CrossRef]
56. Tokuyama, M.; Lorin, C.; Delebecque, F.; Jung, H.; Raulet, D.H.; Coscoy, L. Expression of the RAE-1 family of stimulatory NK-cell ligands requires activation of the PI3K pathway during viral infection and transformation. PLoS Pathog. 2011, 7, e1002265. [CrossRef]

57. Nagler, A.; Lanier, L.L.; Cwirla, S.; Phillips, J.H. Comparative studies of human FcRIII-positive and negative natural killer cells. J. Immunol. 1989, 143, 3183–3191.

58. Moretta, A.; Tambussi, G.; Bottino, C.; Tripodi, G.; Merli, A.; Ciccone, E.; Pantaleo, G.; Moretta, L. A novel surface antigen expressed by a subset of human CD3- CD16+ natural killer cells. Role in cell activation and regulation of cytolytic function. J. Exp. Med. 1990, 171, 695–714. [CrossRef]

59. Carson, W.; Caligiuri, M. Natural Killer Cell Subsets and Development. Methods 1996, 9, 327–343. [CrossRef]

60. Hobbs, J.A.; Cho, S.; Roberts, T.J.; Sriram, V.; Zhang, J.; Xu, M.; Brutkiewicz, R.R. Selective loss of natural killer cell helper function. J. Immunol. 2002, 168, 4539–4544. [PubMed]

61. Parikh, B.A.; Bern, M.D.; Piersma, S.J.; Yang, L.; Beckman, D.L.; Poursine-Laurent, J.; Douglas, B.P.; Lam, V.C.; Lanier, L.L. NK cells in host responses to viral infections. Proc. Natl. Acad. Sci. USA 2005, 102, 13224–13229. [CrossRef]

62. Herberman, R.B.; Nunn, M.E.; Lavrin, D.H. Natural cytotoxic reactivity of mouse lymphoid cells against syngeneic and allogeneic tumors. Int. J. Cancer 1975, 16, 216–229. [CrossRef]

63. Orange, J.S. Human natural killer cell deficiencies and susceptibility to infection. Microb. Infect. 2002, 4, 1545–1558. [CrossRef]

64. Bukowski, J.F.; Woda, B.A.; Habu, S.; Okumura, K.; Welsh, R.M. Natural killer cell depletion enhances virus synthesis and virus-induced hepatitis in vivo. J. Immunol. 1983, 131, 1531–1538.

65. Cooper, M.A.; Fehniger, T.A.; Fuchs, A.; Colonna, M.; Caligiuri, M.A. NK cell and DC interactions. Trends Immunol. 2004, 25, 47–52. [CrossRef]

66. Unanue, E.R. Inter-relationship among macrophages, natural killer cells and neutrophils in early stages of Listeria resistance. Curr. Opin. Immunol. 1997, 9, 35–43. [CrossRef]

67. Cook, K.D.; Whitmire, J.K. The depletion of NK cells prevents T cell exhaustion to efficiently control disseminating virus infection. J. Immunol. 2013, 190, 641–649. [CrossRef]

68. Seaman, W.; Sieisenger, M.; Eriksson, E.; Koo, G. Depletion of natural killer cells in mice by monoclonal antibody to NK-1.1. Reduction in host defense against malignancy without loss of cellular or humoral immunity. J. Immunol. 1987, 138, 4539–4544. [PubMed]

69. Obb, J.A.; Cho, S.; Roberts, T.J.; Sriram, V.; Zhang, J.; Xu, M.; Bruntkiewicz, R.R. Selective loss of natural killer T cells by apoptosis following infection with lymphocytic choriomeningitis virus. J. Virol. 2001, 75, 10746–10754. [CrossRef] [PubMed]

70. Cook, K.D.; Whitmire, J.K. The depletion of NK cells prevents T cell exhaustion to efficiently control disseminating virus infection. J. Immunol. 2013, 190, 641–649. [CrossRef]

71. Seaman, W.; Sieisenger, M.; Eriksson, E.; Koo, G. Depletion of natural killer cells in mice by monoclonal antibody to NK-1.1. Reduction in host defense against malignancy without loss of cellular or humoral immunity. J. Immunol. 1987, 138, 4539–4544. [PubMed]

72. Hobbs, J.A.; Cho, S.; Roberts, T.J.; Sriram, V.; Zhang, J.; Xu, M.; Bruntkiewicz, R.R. Selective loss of natural killer T cells by apoptosis following infection with lymphocytic choriomeningitis virus. J. Virol. 2001, 75, 10746–10754. [CrossRef] [PubMed]

73. Cook, K.D.; Whitmire, J.K. The depletion of NK cells prevents T cell exhaustion to efficiently control disseminating virus infection. J. Immunol. 2013, 190, 641–649. [CrossRef]

74. Seaman, W.; Sieisenger, M.; Eriksson, E.; Koo, G. Depletion of natural killer cells in mice by monoclonal antibody to NK-1.1. Reduction in host defense against malignancy without loss of cellular or humoral immunity. J. Immunol. 1987, 138, 4539–4544. [PubMed]

75. Hobbs, J.A.; Cho, S.; Roberts, T.J.; Sriram, V.; Zhang, J.; Xu, M.; Bruntkiewicz, R.R. Selective loss of natural killer T cells by apoptosis following infection with lymphocytic choriomeningitis virus. J. Virol. 2001, 75, 10746–10754. [CrossRef] [PubMed]

76. Cook, K.D.; Whitmire, J.K. The depletion of NK cells prevents T cell exhaustion to efficiently control disseminating virus infection. J. Immunol. 2013, 190, 641–649. [CrossRef]

77. Seaman, W.; Sieisenger, M.; Eriksson, E.; Koo, G. Depletion of natural killer cells in mice by monoclonal antibody to NK-1.1. Reduction in host defense against malignancy without loss of cellular or humoral immunity. J. Immunol. 1987, 138, 4539–4544. [PubMed]
78. Biron, C.A.; Nguyen, K.B.; Pien, G.C.; Cousens, L.P.; Salazar-Mather, T.P. Natural killer cells in antiviral defense: Function and regulation by innate cytokines. *Annu. Rev. Immunol.* **1999**, *17*, 189–220. [CrossRef]

79. Yu, J.; Freud, A.G.; Caligiuri, M.A. Location and cellular stages of natural killer cell development. *Trends Immunol.* **2013**, *34*, 573–582. [CrossRef]

80. Kumar, R.; Fossati, V.; Israel, M.; Snoeck, H.-W. Lin− Sca1+ Kit− bone marrow cells contain early lymphoid-committed precursors that are distinct from common lymphoid progenitors. *J. Immunol.* **2008**, *181*, 7507–7513. [CrossRef]

81. Adolfsson, J.; Borge, O.J.; Bryder, D.; Theilgaard-Mönch, K.; Åstrand-Grundström, I.; Sitnicka, E.; Sasaki, Y.; Jacobsen, S.E. Upregulation of Flt3 expression within the bone marrow Lin− Sca1+ c-kit+ stem cell compartment is accompanied by loss of self-renewal capacity. *Immunity* **2001**, *15*, 659–669. [CrossRef]

82. Karsunky, H.; Inlay, M.A.; Serwold, T.; Bhattacharya, D.; Weissman, I.L. Flk2+ common lymphoid progenitors possess equivalent differentiation potential for the B and T lineages. *Blood J. Am. Soc. Hematol.* **2008**, *111*, 5562–5570. [CrossRef] [PubMed]

83. Nozad Charoudeh, H.; Tang, Y.; Cheng, M.; Cilio, C.M.; Jacobsen, S.E.W.; Sitnicka, E. Identification of an earliest natural killer cell–committed progenitor in murine bone marrow. *Blood J. Am. Soc. Hematol.* **2010**, *116*, 183–192. [CrossRef] [PubMed]

84. Abel, A.M.; Yang, C.; Thakar, M.S.; Malarkannan, S. Natural killer cells: Development, maturation, and clinical utilization. *Front. Immunol.* **2018**, *9*, 1869. [CrossRef]

85. Liu, C.-C.; Perussia, B.; Young, J.D.-E. The emerging role of IL-15 in NK-cell development. *Immunol. Today* **2000**, *21*, 113–116. [CrossRef]

86. Huntington, N.D.; Legrand, N.; Alves, N.L.; Jaron, B.; Plet, A.; Mortier, E.; Jacques, Y.; Spits, H. IL-15 trans-presentation promotes human NK cell development and differentiation in vivo. *J. Exp. Med.* **2009**, *206*, 25–34. [CrossRef]

87. Fehniger, T.A.; Herbein, G.; Yu, H.; Para, M.I.; Bernstein, Z.P.; O’Brien, W.A.; Caligiuri, M.A. Natural killer cells from HIV-1+ patients produce C-C chemokines and inhibit HIV-1 infection. *J. Immunol.* **1998**, *161*, 6433–6438. [PubMed]

88. Smyth, M.J.; Zachariae, C.O.; Norihisa, Y.; Ortaldo, J.R.; Hishinuma, A.; Matsushima, K. IL-8 gene expression following activation with IL-18 or IL-15 in combination with IL-12: Implications for the innate immune response. *J. Immunol.* **1999**, *162*, 4511–4520.

89. Loza, M.J.; Perussia, B. Final steps of natural killer cell maturation: A model for type 1-type 2 differentiation? *Nat. Immunol.* **2001**, *2*, 917–924. [CrossRef]
98. Wallace, K.L.; Marshall, M.A.; Ramos, S.I.; Lannigan, J.A.; Field, J.J.; Strieter, R.M.; Linden, J.J.B. NKT cells mediate pulmonary inflammation and dysfunction in murine sickle cell disease through production of IFN-γ and CXCR3 chemokines. *Blood J. Am. Soc. Hematol.* 2009, 114, 667–676.

99. Bluman, E.M.; Bartynski, K.J.; Avalos, B.R.; Caligiuri, M.A. Human natural killer cells produce abundant macrophage inflammatory protein-1 alpha in response to monocyte-derived cytokines. *J. Clin. Investig.* 1996, 97, 2722–2727. [CrossRef]

100. Gascoyne, D.M.; Long, E.; Veiga-Fernandes, H.; De Boer, J.; Williams, O.; Seddon, B.; Coles, M.; Kioussis, D.; Brady, H.J. The basic leucine zipper transcription factor E4BP4 is essential for natural killer cell development. *Nat. Immunol.* 2009, 10, 1118. [CrossRef]

101. Cortez, V.S.; Fuchs, A.; Cella, M.; Gilfillan, S.; Colonna, M. Cutting edge: Salivary gland NK cells develop independently of Nfil3 in steady-state. *J. Immunol.* 2014, 192, 4487–4491. [CrossRef] [PubMed]

102. Vossen, C.A.; García-Ojeda, M.E.; Samson-Villegas, S.I.; Pasqualotto, V.; Enault, L.; Richard-Le Goff, O.; Corcuff, E.; Guy-Grand, D.; Rocha, B.; Cumano, A. A thymic pathway of mouse natural killer cell development characterized by expression of GATA-3 and CD127. *Nat. Immunol.* 2006, 7, 1217–1224. [CrossRef] [PubMed]

103. Klose, C.S.; Blatz, K.; d’Hargues, Y.; Hernandez, P.P.; Kofoed-Nielsen, M.; Ripka, J.F.; Ebert, K.; Arnold, S.J.; Diefenbach, A.; Palmer, E.; et al. The transcription factor T-bet is induced by IL-15 and thymic agonist selection and controls CD8αα(+) intraepithelial lymphocyte development. *Immunity* 2014, 41, 230–243. [CrossRef] [PubMed]

104. Peng, H.; Tian, Z. Diversity of tissue-resident NK cells. *Semin. Immunol.* 2017, 31, 3–10. [CrossRef]

105. Zhang, L.H.; Shin, J.H.; Haggadone, M.D.; Sunwoo, J.B. The aryl hydrocarbon receptor is required for the maintenance of liver-resident natural killer cells. *J. Exp. Med.* 2016, 213, 2249–2257. [CrossRef] [PubMed]

106. Zhou, Y.; Fu, B.; Xu, X.; Zhang, J.; Tong, X.; Wang, Y.; Dong, Z.; Zhang, X.; Shen, N.; Zhai, Y.; et al. PBX1 expression in uterine natural killer cells drives fetal growth. *Sci. Transl. Med.* 2020, 12. [CrossRef]

107. Cong, J.; Wei, H. Natural Killer Cells in the Lungs. *Front. Immunol.* 2019, 10, 1416. [CrossRef]

108. Greenwood, J.D.; Minhas, K.; di Santo, J.P.; Makita, M.; Kiso, Y.; Croy, B.A. Ultrastructural studies of implantation sites from mice deficient in uterine natural killer cells. *Placenta* 2000, 21, 693–702. [CrossRef]

109. Ashkar, A.A.; Di Santo, J.P.; Croy, B.A. Interferon gamma contributes to initiation of uterine vascular modification, decidual integrity, and uterine natural killer cell maturation during normal murine pregnancy. *J. Exp. Med.* 2000, 192, 259–270. [CrossRef]

110. Ratsep, M.T.; Felker, A.M.; Kay, V.R.; Tolusso, L.; Hofmann, A.P.; Croy, B.A. Uterine natural killer cells: Supervisors of vasculature construction in early decidua basalis. *Reproduction* 2015, 149, R91–R102. [CrossRef]

111. Carson, W.E.; Fehniger, T.A.; Caligiuri, M.A. CD56bright natural killer cell subsets: Characterization of distinct functional responses to interleukin-2 and the c-kit ligand. *Eur. J. Immunol.* 1997, 27, 354–360. [CrossRef]

112. Jacobs, R.; Hintzen, G.; Kemper, A.; Beul, K.; Kempf, S.; Behrens, G.; Sykora, K.W.; Schmidt, R.E. CD56bright cells differ in their KIR repertoire and cytotoxic features from CD56dim NK cells. *Eur J. Immunol.* 2001, 31, 3121–3127. [CrossRef]

113. Carrega, P.; Bonacorsii, I.; Di Carlo, E.; Morandi, B.; Paul, P.; Rizzello, V.; Cipollone, G.; Navarra, G.; Mingari, M.C.; Moretta, L. CD56brightperforinlow noncytotoxic human NK cells are abundant in both healthy and neoplastic solid tissues and recirculate to secondary lymphoid organs via afferent lymph. *J. Immunol.* 2014, 192, 3805–3815. [CrossRef] [PubMed]

114. Fehniger, T.A.; Cooper, M.A.; Nuovo, G.J.; Cella, M.; Facchetti, F.; Colonna, M.; Caligiuri, M.A. CD56bright natural killer cells are present in human lymph nodes and are activated by T cell-derived IL-2: A potential new link between adaptive and innate immunity. *Blood J. Am. Soc. Hematol.* 2003, 101, 3052–3057. [CrossRef] [PubMed]

115. Manaster, I.; Mizrahi, S.; Goldman-WohI, D.; Sela, H.Y.; Stern-Ginossar, N.; Lankry, D.; Gruda, R.; Hurwitz, A.; Bdlolah, Y.; Haimov-Kochman, R. Endometrial NK cells are special immature cells that await pregnancy. *J. Immunol.* 2008, 181, 1869–1876. [CrossRef] [PubMed]

116. Ferlazzo, G.; Thomas, D.; Lin, S.-L.; Goodman, K.; Morandi, B.; Muller, W.A.; Moretta, A.; Münz, C. The abundant NK cells in human secondary lymphoid tissues require activation to express killer cell Ig-like receptors and become cytolytic. *J. Immunol.* 2004, 172, 1455–1462. [CrossRef]
117. Dogra, P.; Rancan, C.; Ma, W.; Toth, M.; Senda, T.; Carpenter, D.J.; Kubota, M.; Matsumoto, R.; Thapa, P.; Szabo, P.A. Tissue Determinants of Human NK Cell Development, Function, and Residence. Cell 2020, 180, 749–763.e13. [CrossRef] [PubMed]
118. Boulenouar, S.; Doisne, J.-M.; Sferruzzi-Perrin, A.; Gaynor, L.M.; Kieckbusch, J.; Balmas, E.; Yung, H.W.; Javadzadeh, S.; Volmer, L.; Hawkes, D.A. The residual innate lymphoid cells in NFIL3-deficient mice support suboptimal maternal adaptations to pregnancy. Front. Immunol. 2016, 7, 43. [CrossRef]
119. Matson, B.C.; Caron, K.M. Uterine natural killer cells as modulators of the maternal-fetal vasculature. Int. J. Dev. Biol. 2014, 58, 199–204. [CrossRef]
120. Lash, G.E.; Schiessl, B.; Kirkley, M.; Innes, B.A.; Cooper, A.; Searle, R.F.; Robson, S.C.; Bulmer, J.N. Expression of angiogenic growth factors by uterine natural killer cells during early pregnancy. J. Leukoc. Biol. 2006, 80, 572–580. [CrossRef]
121. Gamliel, M.; Goldman-Wohl, D.; Isaacson, B.; Gur, C.; Stein, N.; Yamin, R.; Berger, M.; Grunewald, M.; Kesher, E.; Rais, Y. Trained memory of human uterine NK cells enhances their function in subsequent pregnancies. Immunity 2018, 48, 951–962.e5. [CrossRef] [PubMed]
122. Rodewald, H.R.; Moingeon, P.; Lucich, J.L.; Dosiou, C.; Lopez, P.; Reinherz, E.L. A population of early fetal thymocytes expressing Fc gamma RIII/III contains precursors of T lymphocytes and natural killer cells. Cell 1992, 69, 139–150. [CrossRef]
123. Douagi, I.; Colucci, F.; Di Santo, J.P.; Cumano, A.J.B. Identification of the earliest prethymic bipotent T/NK progenitor in murine fetal liver. J. Am. Soc. Hematol. 2002, 99, 463–471. [CrossRef] [PubMed]
124. Ikawa, T.; Kawamoto, S.; Katsura, Y.J.T. Commitment of common T/natural killer (NK) progenitors to unipotent T and NK progenitors in the murine fetal thymus revealed by a single progenitor assay. J. Exp. Med. 1999, 190, 1617–1626. [CrossRef]
125. Michie, A.M.; Carlyle, J.R.; Schmitt, T.M.; Ljutic, B.; Cho, S.K.; Fong, Q.; Zuñiga-Piñuck, J.C.J.T. Clonal characterization of a bipotent T cell and NK cell progenitor in the mouse fetal thymus. J. Immunol. 2000, 164, 1730–1733. [CrossRef]
126. Hosoya, T.; Kuroha, T.; Moriguchi, T.; Cummings, D.; Maillard, I.; Lim, K.-C.; Engel, J.D. GATA-3 is required for early T lineage progenitor development. J. Exp. Med. 2009, 206, 2987–3000. [CrossRef]
127. Barik, S.; Miller, M.M.; Cattin-Roy, A.N.; Ukah, T.K.; Chen, W.; Zaghouani, H. IL-4 and Id2 promotes the expansion of human NK progenitor cells, which can be counteracted by the E protein assay. J. Exp. Med. 2009, 206, 1617–1626. [CrossRef]
128. Vargas, C.L.; Poursine-Laurent, J.; Yang, L.; Yokoyama, W.M.J.B. Development of thymic NK cells from double negative 1 thymocyte precursors. J. Am. Soc. Hematol. 2011, 118, 3570–3578. [CrossRef]
129. Yui, M.A.; Feng, N.; Rothenberg, E.V. Fine-scale staging of T cell lineage commitment in adult mouse thymus. J. Immunol. 2010, 185, 284–293. [CrossRef]
130. Gabrielli, S.; Sun, M.; Bell, A.; Zook, E.C.; de Pooter, R.F.; Zamai, L.; Kee, B.L. Murine thymic NK cells are distinct from ILC1s and have unique transcription factor requirements. Eur J. Immunol. 2017, 47, 800–805. [CrossRef]
131. Crotta, S.; Gkioka, A.; Male, V.; Duarte, J.H.; Davidson, S.; Nisoli, I.; Brady, H.J.; Wack, A. The transcription factor E4BP4 is not required for extramedullary pathways of NK cell development. J. Immunol. 2014, 192, 2677–2688. [CrossRef] [PubMed]
132. Ramirez, K.; Chandler, K.J.; Spaulding, C.; Zandi, S.; Sigvarydsson, M.; Graves, B.J.; Kee, B.L. Gene deregulation and chronic activation in natural killer cells deficient in the transcription factor ETS1. Immunity 2012, 36, 921–932. [CrossRef] [PubMed]
133. Schotte, R.; Donjé, W.; Nagasawa, M.; Yasuda, Y.; Bakker, A.Q.; Spits, H.; Blom, B. Synergy between IL-15 and Id2 promotes the expansion of human NK progenitor cells, which can be counteracted by the E protein HEB required to drive T cell development. J. Immunol. 2010, 184, 6670–6679. [CrossRef]
134. Smyth, M.J.; Nutt, S.L. IL-7 and the thymus dictate the NK cell’labor market’. Nat. Immunol. 2006, 7, 1134–1136. [CrossRef] [PubMed]
135. García-Peydró, M.; de Yebenes, V.G.; Toribio, M.L. Notch1 and IL-7 receptor interplay maintains proliferation of human thymic progenitors while suppressing non-T cell fates. J. Immunol. 2006, 177, 3711–3720. [CrossRef]
136. Wisse, E.v.; Van’t Noordende, J.; Van der Meulen, J.; Daems, W.T. The pit cell: Description of a new type of cell occurring in rat liver sinusoids and peripheral blood. Cell Tissue Res. 1976, 173, 423–435. [CrossRef] [PubMed]
137. Racanelli, V.; Rehermann, B.J. The liver as an immunological organ. Hepatology 2006, 43, S54–S62. [CrossRef]
138. Mikulak, J.; Bruni, E.; Oriolo, F.; Di Vito, C.; Mavilio, D. Hepatic Natural Killer Cells: Organ-Specific Sentinels of Liver Immune Homeostasis and Physiopathology. *Front. Immunol.* **2019**, *10*, 946. [CrossRef]

139. Phillips, J.H.; Horis, T.; Nagler, A.; Bhat, N.; Spits, H.; Lanier, L.L.J.T. Ontogeny of human natural killer (NK) cells: Fetal NK cells mediate cytolytic function and express cytoplasmic CD3 epsilon, delta proteins. *J. Exp. Med.* **1992**, *175*, 1055–1066. [CrossRef]

140. Serafini, N.; Vosshenrich, C.A.; Di Santo, J.P. Transcriptional regulation of innate lymphoid cell fate. *Nat. Rev. Immunol.* **2015**, *15*, 415–428. [CrossRef]

141. Huntington, N.D.; Vosshenrich, C.A.; Di Santo, J.P. Developmental pathways that generate natural-killer-cell diversity in mice and humans. *Nat. Rev. Immunol.* **2007**, *7*, 703–714. [CrossRef] [PubMed]

142. Crispe, I.N. The liver as a lymphoid organ. *Annu. Rev. Immunol.* **2009**, *27*, 147–163. [CrossRef]

143. Bouwens, L.; Remels, L.; Baekeland, M.; Van Bossuyt, H.; Wisse, E.J. Large granular lymphocytes or “pit cells” from rat liver: Isolation, ultrastructural characterization and natural killer activity. *Eur. J. Immunol.* **1987**, *17*, 37–42. [CrossRef] [PubMed]

144. Geissmann, F.; Cameron, T.O.; Sidobre, S.; Manlongat, N.; Kronenberg, M.; Briskin, M.J.; Dustin, M.L.; Littman, D.R. Intravascular immune surveillance by CXCR6+ NKT cells patrolling liver sinusoids. *PLoS Biol.* **2005**, *3*, e113. [CrossRef] [PubMed]

145. Peng, H.; Jiang, X.; Chen, Y.; Sojka, D.K.; Wei, H.; Gao, X.; Sun, R.; Yokoyama, W.M.; Tian, Z. Liver-resident NK cells confer adaptive immunity in skin-contact inflammation. *J. Clin. Investig.* **2013**, *123*, 1444–1456. [CrossRef]

146. Takeda, K.; Cretney, E.; Hayakawa, Y.; Ota, T.; Akiba, H.; Ogasawara, K.; Yagita, H.; Kinoshita, K.; Okumura, K.; Smyth, M.J. TRAIL identifies immature natural killer cells in newborn mice and adult mouse liver. *Blood* **2005**, *105*, 2082–2089. [CrossRef] [PubMed]

147. Harmon, C.; Robinson, M.W.; Fahey, R.; Whelan, S.; Houilhan, D.D.; Geoghegan, J.; O’Farrelly, C. Tissue-resident Eomeshi T-betlo CD56bright NK cells with reduced proinflammatory potential are enriched in the adult human liver. *Eur. J. Immunol.* **2016**, *46*, 2111–2120. [CrossRef]

148. Stegmann, K.A.; Robertson, E.; Hansi, N.; Gill, U.; Pallant, C.; Christophides, T.; Pallett, L.J.; Peppa, D.; Dunn, C.; Fusai, G. CXCR6 marks a novel subset of T-bet lo Eomes hi natural killer cells residing in human liver. *Sci. Rep.* **2016**, *6*, 1–10. [CrossRef]

149. Lunemann, S.; Martus, G.; Goebels, H.; Kautz, T.; Langeneckert, A.; Salzberger, W.; Koch, M.; Bunders, M.J.; Nashan, B.; van Gisbergen, K.P. Hobit expression by a subset of human liver-resident CD56 bright natural killer cells. *Sci. Rep.* **2017**, *7*, 1–9. [CrossRef]

150. Mackay, L.K.; Minnich, M.; Kragten, N.A.; Liao, Y.; Seillet, C.; Zaid, A.; Man, K.; Preston, S.; Freestone, D. Hobit and Blimp1 instruct a universal transcriptional program of tissue residency in lymphocytes. *Science* **2016**, *352*, 459–463. [CrossRef]

151. Martus, G.; Kautz, T.; Lunemann, S.; Richert, L.; Glau, L.; Salzberger, W.; Goebels, H.; Langeneckert, A.; Hess, L.; Poeh, T.; et al. Proliferative capacity exhibited by human liver-resident CD49a+CD25+ NK cells. *PLoS ONE* **2017**, *12*, e0182532. [CrossRef] [PubMed]

152. Culley, F.J. Natural killer cells in infection and inflammation of the lung. *Immunology* **2009**, *128*, 151–163. [CrossRef] [PubMed]

153. Carrega, P.; Morandi, B.; Costa, R.; Frumento, G.; Forte, G.; Altavilla, G.; Ratto, G.B.; Mingari, M.C.; Moretta, L.; Ferlazzo, G. Natural killer cells infiltrating human nonsmall-cell lung cancer are enriched in CD56brightCD16− cells and display an impaired capability to kill tumor cells. *Cancer* **2008**, *112*, 863–875. [CrossRef] [PubMed]

154. Calabrese, D.R.; Lanier, L.L.; Greenland, J.R. Natural killer cells in lung transplantation. *Thorax* **2019**, *74*, 397–404. [CrossRef] [PubMed]

155. Jaffar, Z.; Ferrini, M.; Roberts, K. Natural killer cells regulate allergic lung inflammation by acting on group 2 innate lymphoid cells. *J. Am. Assoc. Immunol.* **2018**, *200*, 44.5.

156. Vanderven, H.A.; Jegaskanda, S.; Wheatley, A.K.; Kent, S.J. Antibody-dependent cellular cytotoxicity and influenza virus. *Curr. Opin. Virol.* **2017**, *22*, 89–96. [CrossRef]

157. Wang, J.; Li, F.; Zheng, M.; Sun, R.; Wei, H.; Tian, Z. Lung natural killer cells in mice: Phenotype and response to respiratory infection. *Immunology* **2012**, *137*, 37–47. [CrossRef]

158. Bankovich, A.J.; Shiow, L.R.; Cyster, J.G. CD69 suppresses sphingosine 1-phosphate receptor-1 (SIP1) function through interaction with membrane helix 4. *J. Biol. Chem.* **2010**, *285*, 22328–22337. [CrossRef]
159. Shiow, L.R.; Rosen, D.B.; Brdičková, N.; Xu, Y.; An, J.; Lanier, L.L.; Cyster, J.G.; Matloubian, M. CD69 acts downstream of interferon-α/β to inhibit S1P 1 and lymphocyte egress from lymphoid organs. Nature 2006, 440, 540–544. [CrossRef]

160. Mackay, I.K.; Braun, A.; Macleod, B.L.; Collins, N.; Tebartz, C.; Bedou, S.; Carbone, F.R.; Gebhardt, T. Cutting edge: CD69 interference with sphingosine-1-phosphate receptor function regulates peripheral T cell retention. J. Immunol. 2015, 194, 2059–2063. [CrossRef]

161. Marquardt, N.; Kekäläinen, E.; Chen, P.; Lourda, M.; Wilson, J.N.; Scharenberg, M.; Bergman, P.; Al-Ameri, M.; Hård, J.; Mold, J.E. Unique transcriptional and protein-expression signature in human lung tissue-resident NK cells. Nat. Commun. 2019, 10, 1–12. [CrossRef] [PubMed]

162. Kumar, B.V.; Ma, W.; Miron, M.; Granot, T.; Guyer, R.S.; Carpenter, D.J.; Senda, T.; Sun, X.; Ho, S.-H.; Lerner, H. Human tissue-resident memory T cells are defined by core transcriptional and functional signatures in lymphoid and mucosal sites. Cell Rep. 2017, 20, 2921–2934. [CrossRef] [PubMed]

163. Hombrink, P.; Helbig, C.; Backer, R.A.; Piet, B.; Grunewald, J.; Eklund, A.; Katchar, K.; Söderström, K.; Wahlstrom, J.; Jonkers, R.E.; Stark, R.; Brasser, G.; Jongejan, A.; Kekäläinen, E.; Chen, P.; Marquardt, N.; Lourda, M.; Wilson, J.N.; Scharenberg, M.; Al-Ameri, M.; Hombrink, P.; Helbig, C.; Backer, R.A.; Piet, B.; Grunewald, J.; Eklund, A.; Katchar, K.; Söderström, K.; Wahlstrom, J.; Jonkers, R.E.; Stark, R.; Brasser, G.; Jongejan, A.; Kekäläinen, E.; Chen, P.; Marquardt, N.; Lourda, M.; Wilson, J.N.; Scharenberg, M.; Al-Ameri, M.; Nota, B. Programs for the persistence, vigilance and control of human CD8+ lung-resident memory T cells. Nat. Immunol. 2016, 17, 1467. [CrossRef]

164. Yamamoto, Y.; Miyazato, K.; Takahashi, K.; Yoshimura, N.; Tahara, H.; Hayakawa, Y. Lung-resident natural killer cells control pulmonary tumor growth in mice. Cancer Sci. 2018, 109, 2670–2676. [CrossRef] [PubMed]

165. Junqueira-Kipnis, A.P.; Kipnis, A.; Jamieson, A.; Juarrero, M.G.; Diefenbach, A.; Raulet, D.H.; Turner, J.; Hayakawa, Y.; Smyth, M.J. CD27 dissects mature NK cells into two subsets with distinct responsiveness and migratory capacity. J. Immunol. 2006, 176, 1517–1524. [CrossRef]

166. Girard, J.-P.; Moussion, C.; Förster, R. HEVs, lymphatics and homeostatic immune cell trafficking in lymph nodes. Nat. Rev. Immunol. 2012, 12, 762–773. [CrossRef]

167. Kohrt, H.E.; Nouri, N.; Nowels, K.; Johnson, D.; Holmes, S.; Lee, P.P. Profile of immune cells in axillary lymph nodes predicts disease-free survival in breast cancer. PLoS Med. 2005, 2, e284. [CrossRef]

168. Förster, R.; Braun, A.; Worbs, T. Lymph node homing of T cells and dendritic cells via afferent lymphatics. Trends Immunol. 2012, 33, 271–280. [CrossRef]

169. Louie, D.A.P.; Liao, S. Lymph node subcapsular sinus macrophages as the frontline of lymphatic immune defense. Front. Immunol. 2019, 10, 347. [CrossRef] [PubMed]

170. Moore Jr, J.E.; Bertram, C.D. Lymphatic system flows. Annu. Rev. Fluid Mech. 2018, 50, 459–482. [CrossRef] [PubMed]

171. Rezende, R.M.; Lopes, M.E.; Menezes, G.B.; Weiner, H.L. Visualizing Lymph Node Structure and Cellular Localization using Ex-Vivo Confocal Microscopy. J. Vis. Exp. Jove 2019; p. 111900J. [PubMed]

172. Cutts, T.; Moore, G.; Heys, D.; Tresadern, G.; Kibby, G. Multicellular innate immune response in lymph nodes limits systemic pathogen spread. Cell 2012, 150, 1235–1248. [CrossRef]

173. Kastenmüller, W.; Torabi-Parizi, P.; Subramanian, N.; Lämmermann, T.; Germain, R.N. A spatially-organized multicellular innate immune response in lymph nodes limits systemic pathogen spread. Cell 2012, 150, 1235–1248. [CrossRef]

174. Grant, S.M.; Lou, M.; Yao, L.; Germain, R.N.; Radtke, A.J. The lymph node at a glance–how spatial organization optimizes the immune response. J. Cell Sci. 2020, 133, jcs241828. [CrossRef]

175. Renner, C.; Thun, C.; Griesbeck, L.; Viehweger, T.; Voolstra, R.; Kleinhans, R.; Aicher, T.; Schild, H.; Kastenmüller, W.; Torabi-Parizi, P. Unique transcriptional and protein-expression signature in human lung tissue-resident NK cells. Nat. Commun. 2019, 10, 1–12. [CrossRef] [PubMed]

176. Hombrink, P.; Helbig, C.; Backer, R.A.; Piet, B.; Oja, A.E.; Stark, R.; Grunewald, J.; Eklund, A.; Katchar, K.; Söderström, K.; Wahlstrom, J.; Jonkers, R.E.; Stark, R.; Brasser, G.; Jongejan, A.; Kekäläinen, E.; Chen, P.; Marquardt, N.; Lourda, M.; Wilson, J.N.; Scharenberg, M.; Al-Ameri, M.; Nota, B. Programs for the persistence, vigilance and control of human CD8+ lung-resident memory T cells. Nat. Immunol. 2016, 17, 1467. [CrossRef]

177. Yamamoto, Y.; Miyazato, K.; Takahashi, K.; Yoshimura, N.; Tahara, H.; Hayakawa, Y. Lung-resident natural killer cells control pulmonary tumor growth in mice. Cancer Sci. 2018, 109, 2670–2676. [CrossRef] [PubMed]

178. Junqueira-Kipnis, A.P.; Kipnis, A.; Jamieson, A.; Juarrero, M.G.; Diefenbach, A.; Raulet, D.H.; Turner, J.; Hayakawa, Y.; Smyth, M.J. CD27 dissects mature NK cells into two subsets with distinct responsiveness and migratory capacity. J. Immunol. 2006, 176, 1517–1524. [CrossRef]

179. Girard, J.-P.; Moussion, C.; Förster, R. HEVs, lymphatics and homeostatic immune cell trafficking in lymph nodes. Nat. Rev. Immunol. 2012, 12, 762–773. [CrossRef]

180. Kohrt, H.E.; Nouri, N.; Nowels, K.; Johnson, D.; Holmes, S.; Lee, P.P. Profile of immune cells in axillary lymph nodes predicts disease-free survival in breast cancer. PLoS Med. 2005, 2, e284. [CrossRef]

181. Förster, R.; Braun, A.; Worbs, T. Lymph node homing of T cells and dendritic cells via afferent lymphatics. Trends Immunol. 2012, 33, 271–280. [CrossRef]

182. Louie, D.A.P.; Liao, S. Lymph node subcapsular sinus macrophages as the frontline of lymphatic immune defense. Front. Immunol. 2019, 10, 347. [CrossRef] [PubMed]

183. Moore Jr, J.E.; Bertram, C.D. Lymphatic system flows. Annu. Rev. Fluid Mech. 2018, 50, 459–482. [CrossRef] [PubMed]

184. Rezende, R.M.; Lopes, M.E.; Menezes, G.B.; Weiner, H.L. Visualizing Lymph Node Structure and Cellular Localization using Ex-Vivo Confocal Microscopy. J. Vis. Exp. Jove 2019; p. 111900J. [PubMed]

185. Suo, Y.; Yang, W.; Lu, F.; Xie, X.S. Label-free imaging of lymph nodes with stimulated Raman scattering. Cancers 2020, 12, 1553. [CrossRef]

186. Westermann, J.; Pabst, R. Distribution of lymphocyte subsets and natural killer cells in the human body. Clin. Investig. 1992, 70, 539–544. [CrossRef]

187. Grant, S.M.; Lou, M.; Yao, L.; Germain, R.N.; Radtke, A.J. The lymph node at a glance–how spatial organization optimizes the immune response. J. Cell Sci. 2020, 133, jcs241828. [CrossRef]
180. Eissens, D.N.; Spanholtz, J.; Van Der Meer, A.; Van Cranenbroek, B.; Dolstra, H.; Kwekkeboom, J.; Preijers, F.W.; Joosten, I. Defining early human NK cell developmental stages in primary and secondary lymphoid tissues. *PLoS ONE* **2012**, *7*, e30930. [CrossRef]

181. Ferlazzo, G.; Carrega, P. Natural killer cell distribution and trafficking in human tissues. *Front. Immunol.* **2012**, *3*, 347.

182. Campbell, J.J.; Qin, S.; Unutmaz, D.; Soler, D.; Murphy, K.E.; Hodge, M.R.; Wu, L.; Butcher, E.C. Unique subpopulations of CD56+ NK and NK-T peripheral blood lymphocytes identified by chemokine receptor expression repertoire. *J. Immunol.* **2001**, *166*, 6477–6482. [CrossRef] [PubMed]

183. Frey, M.; Packianathan, N.B.; Fehninger, T.A.; Ross, M.E.; Wang, W.-C.; Stewart, C.C.; Caligiuri, M.A.; Evans, S.S. Differential expression and function of L-selectin on CD56bright and CD56dim natural killer cell subsets. *J. Immunol.* **1998**, *161*, 400–408. [PubMed]

184. Freud, A.G.; Becknell, B.; Roychowdhury, S.; Mao, H.C.; Ferketich, A.K.; Nuovo, G.J.; Hughes, T.L.; Muzumdar, M.D.; Tasic, B.; Miyamichi, K.; Li, L.; Luo, L. A global double-fluorescent Cre reporter mouse. *J. Immunol.* **2005**, *175*, 295–304. [CrossRef] [PubMed]

185. Gordon, S.M.; Chaix, J.; Rupp, L.J.; Wu, J.; Madera, S.; Sun, J.C.; Lindsten, T.; Reiner, S.L. The transcription factors T-bet and Eomes control key checkpoints of natural killer cell maturation. *Immunity* **2012**, *36*, 55–67. [CrossRef] [PubMed]

186. Luevano, M.E.; Madrigal, A.; Saudemont, A. Transcription factors involved in the regulation of natural killer cell development and function: An update. *Front. Immunol.* **2012**, *3*, 319. [CrossRef]

187. Aliahmad, P.; De La Torre, B.; Kaye, J. Shared dependence on the DNA-binding factor TOX for the development of lymphoid tissue–inducer cell and NK cell lineages. *Nat. Immunol.* **2010**, *11*, 945–952. [CrossRef]

188. Sojka, D.K.; Yang, L.; Plougastel-Douglas, B.; Hijiguchi, D.A.; Croy, B.A.; Yokoyama, W.M. Cutting edge: Local proliferation of uterine tissue-resident NK cells during decidualization in mice. *J. Immunol.* **2018**, *201*, 2551–2556. [CrossRef] [PubMed]

189. Sojka, D.K.; Yang, L.; Yokoyama, W.M. Uterine natural killer cells: To protect and to nurture. *Front. Immunol.* **2015**, *6*, 593–605. [CrossRef] [PubMed]

190. Kalkunte, S.; Chichester, C.O.; Gotsch, F.; Sentman, C.L.; Romero, R.; Sharma, S. Evolution of non-cytotoxic uterine natural killer cells. *An. J. Reprod. Immunol.* **2008**, *59*, 425–432. [CrossRef]

191. Keskin, D.B.; Allan, D.S.; Rybalov, B.; Andzelm, M.M.; Stern, J.N.; Kopcow, H.D.; Koopman, L.A.; Strominger, J.L. TGFβ promotes conversion of CD16+ peripheral blood NK cells into CD16− NK cells with similarities to decidual NK cells. *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 3378–3383. [CrossRef]

192. Sharkey, A.M.; Xiong, S.; Kennedy, P.R.; Gardner, L.; Farrell, L.E.; Chazara, O.; Ivarsson, M.A.; Hiby, S.E.; Colucci, F.; Moffett, A. Tissue-specific education of decidual NK cells. *J. Immunol.* **2015**, *195*, 3026–3032. [CrossRef] [PubMed]

193. Björkström, N.K.; Ljunggren, H.-G.; Michaelsson, J. Emerging insights into natural killer cells in human peripheral tissues. *Nat. Rev. Immunol.* **2016**, *16*, 310–320. [CrossRef] [PubMed]

194. Ni, F.; Guo, C.; Sun, R.; Fu, B.; Yang, Y.; Wu, L.; Ren, S.; Tian, Z.; Wei, H. MicroRNA transcriptomes of distinct human NK cell populations identify miR-362-5p as an essential regulator of NK cell function. *Sci. Rep.* **2015**, *5*, 9993. [CrossRef] [PubMed]

195. Muzumdar, M.D.; Tasic, B.; Miyamichi, K.; Li, L.; Luo, L. A global double-fluorescent Cre reporter mouse. *Genes* **2007**, *45*, 593–605. [CrossRef]

196. Sojka, D.K.; Yang, L.; Yokoyama, W.M. Uterine Natural Killer Cells. *Front. Immunol.* **2019**, *10*, 960. [CrossRef]

197. Sojka, D.K. Uterine Natural Killer Cell Heterogeneity: Lessons From Mouse Models. *Front. Immunol.* **2020**, *11*, 290. [CrossRef]

198. Kather, A.; Chantakru, S.; He, H.; Minhas, K.; Foster, R.; Markert, U.R.; Pfeffer, K.; Croy, B.A. Neither lymphotixin α nor lymphotixin β receptor expression is required for biogenesis of lymphoid aggregates or differentiation of natural killer cells in the pregnant mouse uterus. *Immunology* **2003**, *108*, 338–345. [CrossRef]

199. Redhead, M.L.; Portilho, N.A.; Felker, A.M.; Mohammad, S.; Mara, D.L.; Croy, B.A. The transcription factor NFIL3 is essential for normal placental and embryonic development but not for uterine natural killer (UNK) cell differentiation in mice. *Biol. Reprod.* **2016**, *91*, 101–116. [CrossRef]

200. Tayade, C.; Fang, Y.; Black, G.P.; Paffaro, V.A., Jr.; Erlebacher, A.; Croy, B.A. Differential transcription of Eomes and T-bet during maturation of mouse uterine natural killer cells. *J. Leukoc. Biol.* **2005**, *78*, 1347–1355. [CrossRef]
201. Hanna, J.; Goldman-Wohl, D.; Hamani, Y.; Avraham, I.; Greenfield, C.; Natanson-Yaron, S.; Prus, D.; Cohen-Daniel, L.; Arnon, T.I.; Manaster, I. Decidual NK cells regulate key developmental processes at the human fetal-maternal interface. Nat. Med. 2006, 12, 1065–1074. [CrossRef]

202. Moffett, A.; Colucci, F. Uterine NK cells: Active regulators at the maternal-fetal interface. J. Clin. Investig. 2014, 124, 1872–1879. [CrossRef]

203. Fu, B.; Li, X.; Sun, R.; Tong, X.; Ling, B.; Tian, Z.; Wei, H. Natural killer cells promote immune tolerance by regulating inflammatory TH17 cells at the human maternal-fetal interface. Proc. Natl. Acad. Sci. USA 2013, 110, E231–E240. [CrossRef] [PubMed]

204. Blois, S.M.; Freitag, N.; Tirado-Gonzalez, I.; Cheng, S.-B.; Heimesaat, M.M.; Bereswill, S.; Rose, M.; Conrad, M.L.; Barrientos, G.; Sharma, S. NK cell-derived IL-10 is critical for DC-NK cell dialogue at the maternal-fetal interface. Sci. Rep. 2017, 7, 2189. [CrossRef] [PubMed]

205. Huang, K.W.; Sabatini, B.L. Single-Cell Analysis of Neuroinflammatory Responses Following Intracranial Injection of G-Deleted Rabies Viruses. Front. Cell. Neurosci. 2020, 14, 65. [CrossRef] [PubMed]

206. Langers, I.; Renoux, V.M.; Thiry, M.; Delvenne, P.; Jacobs, N. Natural killer cells: Role in local tumor growth and metastasis. Biologics 2012, 6, 73–82. [CrossRef] [PubMed]

207. Diefenbach, A.; Jensen, E.R.; Jamieson, A.M.; Raulet, D.H. Rae1 and H60 ligands of the NKG2D receptor stimulate tumour immunity. Nature 2001, 413, 165–171. [CrossRef] [PubMed]

208. Ljunggren, H.G.; Karre, K. Host resistance directed selectively against H-2-deficient lymphoma variants. Analysis of the mechanism. J. Exp. Med. 1985, 162, 1745–1759. [CrossRef]

209. Imai, K.; Matsuyama, S.; Miyake, S.; Suga, K.; Nakachi, K. Natural cytotoxic activity of peripheral-blood lymphocytes and cancer incidence: An 11-year follow-up study of a general population. Lancet 2000, 356, 1795–1799. [CrossRef]

210. Bruno, A.; Mortara, L.; Baci, D.; Noonan, D.M.; Albini, A. Myeloid Derived Suppressor Cells Interactions with Natural Killer Cells and Pro-angiogenic Activities: Roles in Tumor Progression. Front. Immunol. 2019, 10, 771. [CrossRef]

211. Sun, C.; Sun, H.; Zhang, C.; Tian, Z. NK cell receptor imbalance and NK cell dysfunction in HBV infection and hepatocellular carcinoma. Cell Mol. Immunol. 2015, 12, 292–302. [CrossRef]

212. Sun, C.; Sun, H.Y.; Xiao, W.H.; Zhang, C.; Tian, Z.G. Natural killer cell dysfunction in hepatocellular carcinoma and NK cell-based immunotherapy. Acta Pharm. Sin. 2015, 36, 1191–1199. [CrossRef] [PubMed]

213. Coca, S.; Perez-Piqueras, J.; Martinez, D.; Colmenarejo, A.; Saez, M.A.; Vallejo, C.; Martos, J.A.; Moreno, M. The prognostic significance of intratumoral natural killer cells in patients with colorectal carcinoma. Cancer 1997, 79, 2320–2328. [CrossRef]

214. Ishigami, S.; Natsugoe, S.; Tokuda, K.; Nakajo, A.; Che, X.; Iwashige, H.; Aridome, K.; Hokita, S.; Aikou, T. Prognostic value of intratumoral natural killer cells subset CD57 in patients with squamous cell lung cancer. Lung Cancer 2002, 35, 23–28. [CrossRef]

215. Villegas, F.R.; Coca, S.; Villarrubia, V.G.; Jimenez, R.; Chillon, M.J.; Jareno, J.; Zuil, M.; Callol, L. Prognostic significance of tumor infiltrating natural killer cells subset CD57 in patients with squamous cell lung cancer. Front. Physiol. 2014, 5, 220. [CrossRef]

216. Sun, C.; Sun, H.; Zhang, C.; Tian, Z. NK cell receptor imbalance and NK cell dysfunction in HBV infection and hepatocellular carcinoma. Cell Mol. Immunol. 2015, 12, 292–302. [CrossRef] [PubMed]

217. Langers, I.; Renoux, V.M.; Thiry, M.; Delvenne, P.; Jacobs, N. Natural killer cells: Role in local tumor growth and metastasis. Biologics 2012, 6, 73–82. [CrossRef] [PubMed]

218. Diefenbach, A.; Jensen, E.R.; Jamieson, A.M.; Raulet, D.H. Rae1 and H60 ligands of the NKG2D receptor stimulate tumour immunity. Nature 2001, 413, 165–171. [CrossRef] [PubMed]

219. Ljunggren, H.G.; Karre, K. Host resistance directed selectively against H-2-deficient lymphoma variants. Analysis of the mechanism. J. Exp. Med. 1985, 162, 1745–1759. [CrossRef]

220. Imai, K.; Matsuyama, S.; Miyake, S.; Suga, K.; Nakachi, K. Natural cytotoxic activity of peripheral-blood lymphocytes and cancer incidence: An 11-year follow-up study of a general population. Lancet 2000, 356, 1795–1799. [CrossRef]

221. Bruno, A.; Mortara, L.; Baci, D.; Noonan, D.M.; Albini, A. Myeloid Derived Suppressor Cells Interactions with Natural Killer Cells and Pro-angiogenic Activities: Roles in Tumor Progression. Front. Immunol. 2019, 10, 771. [CrossRef]

222. Sun, C.; Sun, H.; Zhang, C.; Tian, Z. NK cell receptor imbalance and NK cell dysfunction in HBV infection and hepatocellular carcinoma. Cell Mol. Immunol. 2015, 12, 292–302. [CrossRef] [PubMed]

223. Sun, C.; Sun, H.Y.; Xiao, W.H.; Zhang, C.; Tian, Z.G. Natural killer cell dysfunction in hepatocellular carcinoma and NK cell-based immunotherapy. Acta Pharm. Sin. 2015, 36, 1191–1199. [CrossRef] [PubMed]

224. Coca, S.; Perez-Piqueras, J.; Martinez, D.; Colmenarejo, A.; Saez, M.A.; Vallejo, C.; Martos, J.A.; Moreno, M. The prognostic significance of intratumoral natural killer cells in patients with colorectal carcinoma. Cancer 1997, 79, 2320–2328. [CrossRef]

225. Ishigami, S.; Natsugoe, S.; Tokuda, K.; Nakajo, A.; Che, X.; Iwashige, H.; Aridome, K.; Hokita, S.; Aikou, T. Prognostic value of intratumoral natural killer cells in gastric carcinoma. Cancer 2000, 88, 577–583. [CrossRef]

226. Villegas, F.R.; Coca, S.; Villarrubia, V.G.; Jimenez, R.; Chillon, M.J.; Jareno, J.; Zuil, M.; Callol, L. Prognostic significance of tumor infiltrating natural killer cells subset CD57 in patients with squamous cell lung cancer. Lung Cancer 2002, 35, 23–28. [CrossRef]

227. Torelli, G.F.; Peragine, N.; Raponi, S.; Pagliara, D.; De Propris, M.S.; Vitale, A.; Bertaina, A.; Barberi, W.; Moretta, L.; Basso, G.; et al. Recognition of adult and pediatric acute lymphoblastic leukemia blasts by natural killer cells. Haematologica 2014, 99, 1248–1254. [CrossRef]

228. Handgretinger, R.; Lang, P.; Andre, M.C. Exploitation of natural killer cells for the treatment of acute leukemia. Blood 2016, 127, 3341–3349. [CrossRef]

229. Mehta, R.S.; Randolph, B.; Daher, M.; Rezvani, K. NK cell therapy for hematologic malignancies. Int J. Hematol 2018, 107, 262–270. [CrossRef]

230. Lim, O.; Jung, M.Y.; Hwang, Y.K.; Shin, E.C. Present and Future of Allogeneic Natural Killer Cell Therapy. Front. Immunol. 2015, 6, 286. [CrossRef]

231. Li, Y.; Yin, J.; Li, T.; Huang, S.; Yan, H.; Leavenworth, J.; Wang, X. NK cell-based cancer immunotherapy: From basic biology to clinical application. Sci China Life Sci 2015, 58, 1233–1245. [CrossRef]

232. Lee, D.A.; Denman, C.J.; Rondon, G.; Woodworth, G.; Chen, J.; Fisher, T.; Kaur, I.; Fernandez-Vina, M.; Cao, K.; Ciurea, S.; et al. Haploidentical Natural Killer Cells Infused before Allogeneic Stem Cell Transplantation for Myeloid Malignancies: A Phase I Trial. Biol. Blood Marrow Transpl. 2016, 22, 1290–1298. [CrossRef]

233. Fang, F.; Xiao, W.; Tian, Z. NK cell-based immunotherapy for cancer. Semin. Immunol. 2017, 31, 37–54. [CrossRef] [PubMed]
223. Shah, N.; Li, L.; McCarty, J.; Kaur, I.; Yvon, E.; Shaim, H.; Muftuoglu, M.; Liu, E.; Orlowski, R.Z.; Cooper, L.; et al. Phase I study of cord blood-derived natural killer cells combined with autologous stem cell transplantation in multiple myeloma. Br. J. Haematol. 2017, 177, 457–466. [CrossRef]

224. Liu, E.; Marin, D.; Banerjee, P.; Macapinlac, H.A.; Thompson, P.; Basar, R.; Nassif Kerbauy, L.; Overman, B.; Thall, P.; Kaplan, M.; et al. Use of CAR-Transduced Natural Killer Cells in CD19-Positive Lymphoid Tumors. N. Engl. J. Med. 2020, 382, 545–553. [CrossRef] [PubMed]

225. Amadei, B.; Urbani, S.; Caalay, A.; Fiscaro, P.; Zerhini, A.; Ahmed, P.; Missale, G.; Ferrari, C.; Khakoo, S.I. Activation of natural killer cells during acute infection with hepatitis C virus. Gastroenterology 2010, 138, 1536–1545. [CrossRef] [PubMed]

226. Hudspeth, K.; Pontarini, E.; Tentorio, P.; Cimino, M.; Donadon, M.; Torzilli, G.; Lugli, E.; Della Bella, S.; Gershwin, M.E.; Mavilio, D. The role of natural killer cells in autoimmune liver disease: A comprehensive review. J. Autoimmun 2013, 46, 55–65. [CrossRef]

227. Cooper, G.E.; Ostridge, K.; Khakoo, S.I.; Wilkinson, T.M.A.; Staples, K.J. Human CD49a(+) Lung Natural Killer Cell Cytotoxicity in Response to Influenza A Virus. Front. Immunol. 2018, 9, 1671. [CrossRef]

228. Kumar, P.; Thakar, M.S.; Ouyang, W.; Malarkannan, S. IL-22 from conventional NK cells is epithelial regenerative and inflammation protective during influenza infection. Mucosal Immunol. 2013, 6, 69–82. [CrossRef]

229. Kumar, P.; Rajasekaran, K.; Palmer, J.M.; Thakar, M.S.; Malarkannan, S. IL-22: An Evolutionary Missing-Link Authenticating the Role of the Immune System in Tissue Regeneration. J. Cancer 2013, 4, 57–65. [CrossRef]

230. Grundy, M.A.; Zhang, T.; Sentman, C.L. NK cells rapidly remove B16F10 tumor cells in a perforin and interferon-gamma independent manner in vivo. Cancer Immunol. Immunother. 2007, 56, 1153–1161. [CrossRef]

231. Shen, H.; Kanoh, M.; Maruyama, S.; Matsumoto, A.; Zhang, W.; Asano, Y. Attenuated Listeria infection and inflammation protective during influenza infection. Nat. Immunol. 2018, 19, 102–114. [CrossRef] [PubMed]

232. Nanbaksh, A.; Srinivasamani, A.; Holzhauer, S.; Riese, M.J.; Zheng, Y.; Burns, R.; Reimer, M.H.; Rao, S.; Lemke, A.; et al. Mirc11 Disrupts Inflammatory but Not Cytotoxic Responses of NK Cells. Cancer Immunol. Immunother. 2019, 68, 107–117. [CrossRef]

233. Scharton, T.M.; Scott, P. Natural killer cells are a source of interferon gamma that drives differentiation of CD4+ T cell subsets and induces early resistance to Leishmania major in mice. J. Exp. Med. 1993, 178, 567–577. [CrossRef] [PubMed]

234. Scharton-Kersten, T.; Caspar, P.; Sher, A.; Denkers, E.Y. Toxoplasma gondii: Evidence for interleukin-12-dependent and-independent pathways of interferon-gamma production induced by an attenuated parasite strain. Exp. Parasitol. 1996, 84, 102–114. [CrossRef] [PubMed]

235. Martin-Fontecha, A.; Thomsen, L.L.; Brett, S.; Gerard, C.; Lipp, M.; Lanzavecchia, A.; Sallusto, F. Induced recruitment of NK cells to lymph nodes provides IFN-γ for TH-1 priming. Nat. Immunol. 2004, 5, 1260–1265. [CrossRef] [PubMed]

236. Fang, V.; Chaluvadi, V.S.; Ramos-Perez, W.D.; Mendoza, A.; Baeyens, A.; Rivera, R.; Chun, J.; Cammer, M.; Schwab, S.R. Gradients of the signaling lipid SIP in lymph nodes position natural killer cells and regulate their interferon-γ response. Nat. Immunol. 2017, 18, 15. [CrossRef] [PubMed]

237. Chandrasekaran, S.; Chan, M.F.; Li, J.; King, M.R. Super natural killer cells that target metastases in the tumor draining lymph nodes. Biomaterials 2016, 77, 66–76. [CrossRef]

238. Frazao, A.; Messaoudene, M.; Nunez, N.; Dulphy, N.; Roussin, F.; Sedlik, C.; Zitvogel, L.; Piaggio, E.; Toubert, A.; Caignard, A. CD16+ NK2G2AHigh Natural Killer Cells Infiltrate Breast Cancer–Draining Lymph Nodes. Cancer Immunol. Res. 2019, 7, 208–218. [CrossRef]

239. Cross, J.C.; Hemberger, M.; Lu, Y.; Nozaki, T.; Whiteley, K.; Masutani, M.; Adamson, S.L. Trophoblast functions, angiogenesis and remodeling of the maternal vasculature in the placenta. Mol. Cell. Endocrinol. 2002, 187, 207–212. [CrossRef]

240. Fu, B.; Zhou, Y.; Ni, X.; Tong, X.; Xu, X.; Dong, Z.; Sun, R.; Tian, Z.; Wei, H. Natural killer cells promote fetal development through the secretion of growth-promoting factors. Immunity 2017, 47, 1100–1113.e6. [CrossRef]