future pharmacology

MDPI

Review

Chasing Uterine Cancer with NK Cell-Based Immunotherapies

Vijay Kumar [1,*], Caitlin Bauer [1] and John H. Stewart IV [1,2,*]

[1] Department of Interdisciplinary Oncology, Stanley S. Scott Cancer Center, School of Medicine, Louisiana State University Health Science Center (LSUHSC), 1700 Tulane Avenue, New Orleans, LA 70012, USA
[2] Louisiana Children's Medical Center Cancer Center, Stanley S. Scott Cancer Center, School of Medicine, Louisiana State University Health Science Center (LSUHSC), 1700 Tulane Avenue, New Orleans, LA 70012, USA
* Correspondence: vkuma2@lsuhsc.edu or vij_tox@yahoo.com (V.K.); jste17@lsuhsc.edu (J.H.S.IV); Tel.: +1-504-210-2047 (V.K.); +1-504-702-5514 (J.H.S.IV); Fax: +1-504-210-2970 (V.K. & J.H.S.IV)

Abstract: Gynecological cancers, including endometrial adenocarcinoma, significantly contribute to cancer incidence and mortality worldwide. The immune system plays a significant role in endometrial cancer pathogenesis. NK cells, a component of innate immunity, are among the critical innate immune cells in the uterus crucial in menstruation, embryonic development, and fighting infections. NK cell number and function influence endometrial cancer development and progression. Hence, it becomes crucial to understand the role of local (uterine) NK cells in uterine cancer. Uterine NK (uNK) cells behave differently than their peripheral counterparts; for example, uNK cells are more regulated by sex hormones than peripheral NK cells. A deeper understanding of NK cells in uterine cancer may facilitate the development of NK cell-targeted therapies. This review synthesizes current knowledge on the uterine immune microenvironment and NK cell-targeted uterine cancer therapeutics.

Keywords: NK cells; uterine cancer; endometrial cancer; uNK cells; immunotherapy

check for updates

Citation: Kumar, V.; Bauer, C.; Stewart, J.H., IV. Chasing Uterine Cancer with NK Cell-Based Immunotherapies. *Future Pharmacol.* **2022**, *2*, 642–659. https://doi.org/10.3390/futurepharmacol2040039

Academic Editor: Fabrizio Schifano

Received: 8 November 2022
Accepted: 5 December 2022
Published: 9 December 2022

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Copyright: © 2022 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).

1. Introduction

Uterine cancer (UC) is the most common invasive gynecologic malignancy among American women (lifetime risk of one out of every forty women) [1,2]. For example, more than 61,880 cases of UC were diagnosed in the US, with 12,160 deaths in 2019 [3]. Between 2010–2014 the average annual age-adjusted incidence of UC from the Surveillance, Epidemiology, and End Results Program (SEER) was 25.7 per 100,000 women [4]. Increases in UC incidence have significant implications on healthcare expenditures. For example, the annual medical expenditure for gynecological cancers in the United States between 2007 and 2014 was $3.8 billion. Breaking this down further, the cost of care for each patient with UC was approximately $9164 [5]. Early immune-based tumor detection and rapid intervention with effective treatments can mitigate these costs.

The immune system controls cancer pathogenesis by maintaining immune homeostasis and tumor surveillance [6]. For instance, the immune system has evolved to eliminate endogenous dead cells and cells that express damage/death-associated molecular patterns (DAMPs) [7]. During cellular homeostasis, the immune system guards against changes in the microenvironment that support tumor development through tumor immune surveillance [8]. However, this immune surveillance is disrupted during cancer progression, hence giving rise to the emerging field of immuno-oncology [9–12]. Future opportunities in UC immuno-oncology include understanding the UC tumor immune microenvironment (TIME), detailing approaches to reprograming immune cells to perform antitumor duties, and developing cancer-specific immune cell-based novel immunotherapies [12,13].

Natural Killer (NK) cells are central to maintaining immune homeostasis, including organ-specific immunotolerance [14,15]. They are one of the first described anticancer and antiviral innate immune cells with direct cytotoxic action. Since NK cells do not rely on

antigens to detect mutated cells, they act as first responders against cancer cells [16,17]. Furthermore, NK cell cytotoxicity (NKCC) against cancer cells makes them a strong cancer immunotherapy candidate [18,19]. NK cell-based therapies have been evaluated in several cancers, but information on their potential in UC is scarce [20–22]. Hence, the current article discusses NK cells' role in UC pathogenesis and their therapeutic targeting.

2. NK Cells Maintain Immune Homeostasis and Function

NK cells were recognized as cytotoxic lymphocytes in the late 1970s [23,24]. The discovery of the NK cell-deficient beige (bg/bg) mouse confirmed their importance in controlling hematogenous metastasis of cancer [25]. NK cells are among the first immune cells to arrive at the site of inflammation, expressing various cytokine and chemokine receptors as well as adhesion molecules [26–31]. For example, CXCR1, CXCR3, CXCR4, CXCR6, CCR5, CCR7, CCL3/4 or macrophage inflammatory protein-1 (MIP-1) α/β, CCL5 or regulated on activation, normal T cell expressed, and secreted (RANTES), and CXCL1 are crucial chemokines and chemokine receptors involved in NK cell trafficking to different tissues and organs [32,33]. These chemokines and their cognate receptors, including CXCR3/CCL10, CCL5/CCR5, CCL27/CCR10, CXCR4/CXCL12, and CX3CL1/CX3CR1 are also crucial for NK cell trafficking to different tumors and other inflammatory conditions [32,34–37]. For example, CXCR3/CCL9, 10 and CXCR4/CXCL12 chemokine/chemokine receptor axis is crucial for the migration of NK cells in the uterus during pregnancy [35,38]. Hence, the alteration in chemokine level and receptor expression affects NK cell infiltration in different diseases, including tumors [32,39,40]. The mature circulating NK cells in mice and humans express different chemokine receptors, including CXCR1 (only in humans), CXCR3, CXCR4, CCR1 (only in mice), and CXC3CR1 [39]. Of note, NK cells produce many cytokines and chemokines that exert direct antitumor actions, including interferon-γ (IFN-γ), TNF-α, IL-8 (CXCL-8), and granulocyte-monocyte colony-stimulating factor (GM-CSF) [15]. NK cells can also recruit potential immune cells ($CD8^+$T cells, neutrophils, and macrophages) with antitumor activity to control the growth and proliferation of the tumor cells. Hence, they are crucial in recruiting immune cells and targeting abnormal cells (tumor and virus-infected cells) to maintain homeostasis [15,41–43] (Figure 1).

NK cells are categorized as group 1 innate lymphoid cells (ILCs). ILCs have been classified into three major groups (group 1 ILCs or ILC1s, group 2 ILCs or ILC2s, group 3 ILCs or ILC3s) depending on their function and transcription factors [44,45]. A detailed discussion of ILCs and their interaction with adaptive immune cells has been discussed elsewhere [46–48]. Like any other immune cell, NK cells are characterized by specific cell-surface markers, including $CD56^{high}CD16^{low}$ and $CD16^{high}CD56^{low}$. Interestingly, NK cells do not express CD3, CD14, CD19, and TCR. Circulating mature NK cells include Lin^-IL-7R$\alpha^-CD56^{dim}CD16^+$ [49]. NK cells develop from common lymphoid progenitors (CLPs), which also give rise to T and B cells [50]. However, unlike T and B cells, NK cells do not undergo the gene recombination process regulated by recombination activating genes (RAGs). Instead, NK cell development requires a common γ chain of the IL-2R and IL-15 complex [51]. Details regarding the development of various ILCs, including NK cells, are beyond the scope of this article and discussed extensively elsewhere [52–55].

NK cells are the third largest lymphocyte population, following T and B cells [56]. Although NK cells have traditionally been regarded as prominent members of the innate immune system, recent studies revealed that NK cells are also present in adaptive and memory-like phenotypes, indicating that they serve as borderline cells for innate and adaptive immunity [57–59]. In addition, NK cells have unique direct cytotoxic action against infected and cancer cells [60–62] (Figure 1). Notably, NK cell cytotoxic abilities are distinct from T cells, which require antigen-presenting cells (APCs) for their activation. Furthermore, NK cells protect against oncogenic virus-induced cancers as evidenced by the fact that patients with NK cell deficiencies are more prone to develop virus-induced cancers [63]. Thus, NK cells are important targets for cancer immunotherapy due to their enhanced ability to distinguish between tumors and healthy cells. Furthermore, NK cells

can identify tumor cells that have mitigated MHC expression, as they do not rely on MHC expression or antibodies to identify targets [64,65].

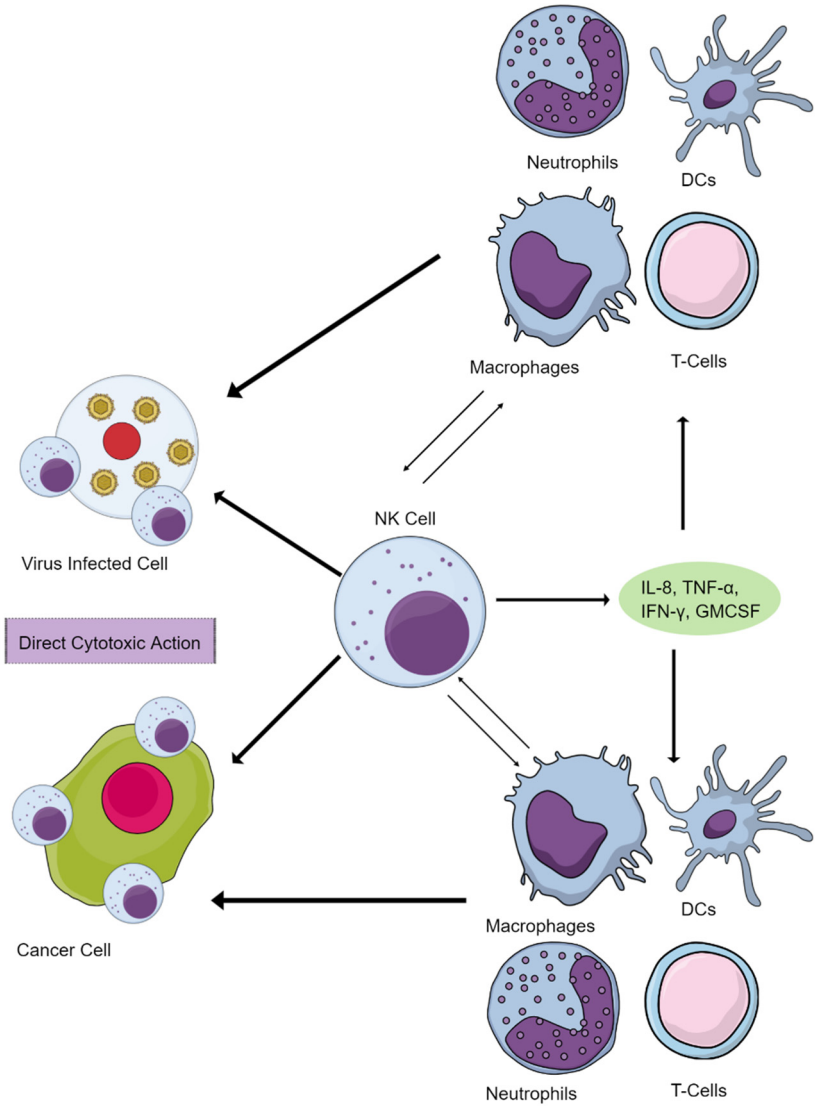


Figure 1. Diagrammatic representation of NK cells in immunoregulation during virus infections and cancer. NK cells are crucial to maintaining immune homeostasis due to their key role in cytokine and chemokine production. Cytokines and chemokines can interact with immune cells to induce a proinflammatory response, thus protecting the host.

NK cell activation and inhibition are regulated by different activating and inhibitory receptors (NKG2D, Ly49 or KIR, CD94–NKG2 heterodimers and natural cytotoxicity receptors or NCRs) as described in detail elsewhere [66,67] (Table 1). For example, inhibitory receptors regulate NKCC by preventing NK cell-mediated attacks against normal cells. However, they are also crucial to directing NK cells to target cells with altered MHC class I expression, as seen during tumor or viral infection [68]. The effector response of NK cells toward tumor cells involves activation and inhibition signals mediated by NK cell surface receptors. A primary inhibitory receptor class is the Killer immunoglobulin (Ig)-like receptor (KIR) family, including KIR2DL1-3, KIR2DL5, and KIR3DL1-3, which recognizes MHC class I peptides [69,70] (Table 1). KIRs are type 1 transmembrane proteins expressed on NK cells and a subset of T cells that bind to the peptide-binding region of the HLA-A, -B, and -C particles [71,72]. KIR expression is also heterogenous due to allelic variation in KIR genes [70]. Of note, KIRs can exhibit both an inhibitory and activating type, and a decrease

in the KIR2DS2 (an activating KIR that recognizes HLA-C1 allotypes and HLA-A*11:01) is associated with an increased risk of endometriosis, which is well-correlated with EC risk (Table 1) [73–77]. Integrins, such as α5(CD49e) and β1(CD29) (fibronectin receptor), are receptors of extracellular matrix proteins that typically exhibit low levels of expression on NK cells in adults but increase in some tumors [33,78] (Table 1).

Table 1. Alteration of different NK cells receptors and ligands in uterine or endometrial cancer patients. Arrows indicate the increase or decrease in their expression or activity.

	Receptors	**Ligands**
Activating Receptors	α5β1 integrin ↑	Vascular Cell Adhesion Molecule 1 (VCAM-1)
	CD226 (DNAM-1) ↑/↓	CD112 (Nectin-2), CD155 (Nec15)
	CD16	Immunoglobin B ↑
	NKp46 ↓	Viral hemagglutinins
	KIR2DS2 ↓	HLA-C1 allotypes and HLA-A*11:01
	CD94-NKG2C	HLA-E ↑
	CD94-NKG2E	HLA-E ↑
	NKG2D ↓	ULBP (RAET), MICA, MICB
	CD96 (Tactile) ↑	CD155 (Necl5) ↑/↓
	NKp30 ↓	pp65, BAT-3
Inhibitory Receptors	KIR-L ↑	HLA-A, HLA-B, HLA-C
	CD94-NKG2A	HLA-E ↑
	KLRG1 ↑	Cadherins
	LILRB1 or ILT2 (CD85) ↑	HLA class 1 ↓

NK cells orchestrate the engagement of additional anti-tumor immune cells through IFN-γ and TNF-α secretion [56]. The secreted IFN-γ and TNF-α engages other immune cells, including macrophages and dendritic cells (DCs), thereby promoting an inflammatory microenvironment that, at the initial stages of cancer, serves to remove tumor cells (Figure 1). Specifically, IFN-γ secretion is achieved via a STAT4-dependent pathway, while IL-12 secretion occurs via $XCR1^+$ conventional DCs (cDCs) after activation by local DCs. This inflammatory microenvironment protects the host from pathogens before circulating lymphocytes enter the TME [19,79,80] (Figure 1). In addition, NK cells exhibit perforin-dependent direct cytotoxicity and induce apoptosis among abnormal cells through different mechanisms, including lytic granule release, Fas ligand (FasL), and tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) expression [19,79,81]. These lytic granules consist of granzymes and perforin, where granzymes are serine proteases that are also expressed in cytotoxic T cells. Hence, NK cells are crucial innate immune lymphocytes or group 1 ILCs required to maintain immune homeostasis to fight and kill virus-infected and tumor cells.

3. Human Uterine NK (uNK) Cells

The uterine NK (uNK) cell population increases during early human pregnancy, which are also called decidual NK (dNK) cells. dNK cells comprise about 70% of all feto-maternal interface lymphocytes during first-trimester pregnancy in humans, and they support trophoblast invasion and angiogenesis [82–85]. dNK cells in the uterus highly express CXCR3, with relatively low expression of CXCR4 [32]. Very low CXCR1, CXCR2, CX3CR1, or CCR1, 2, 3 expression has also been observed in dNK cells. uNK cells acquire a trained innate immune memory phenotype in subsequent pregnancies [86]. The pregnancy-exposed uNK cells have been labeled as pregnancy-trained decidual or uterine NK cells (PTdNKs). PTdNKs exhibit unique transcriptome and epigenetic characteristics,

including high levels of NKG2-C type II integral membrane protein, NKG2C (CD159c), and leukocyte immunoglobulin-like receptor B1 (LILRB1) (Table 1) [86]. PTdNKs ensure proper placentation during subsequent pregnancies by producing higher IFN-γ and VEGF-α levels than naïve uNK cells, although studies have indicated a reduced risk of EC following pregnancy [87]. The role of PTdNKs in the UC carcinogenesis is still unknown. Hence, future work that delineates the correlation between PTdNKs and EC risk is warranted.

Unlike peripheral NK cells, uNK cells are highly regulated by sex hormones and IL-15. $CD56^{bright}CD16^{low}$ marker expression on uNK cells characterize them through the beginning of each menstrual cycle, and they undergo proliferation and granulation during the secretory phase of the menstrual cycle. In the absence of fertilization, they then apoptose two days before menstruation and shed with menstrual blood [88]. Notably, immature uNK cells are present in the human endometrium and uterine mucosa [89]. uNK cells do not produce copious cytokines, chemokines, or growth factors [90]. Before pregnancy, endometrial NK cells remain inactive and do not have the same cytotoxicity as dNK cells of the uterine mucosa. However, IL-15 can stimulate the cytotoxic activity of endometrial NK cells, suggesting that IL-15 levels may increase in the decidua during pregnancy and that dNK cells may arise from endometrial NK cells [91]. Additionally, pregnant women have NK cells with more significant migratory abilities than non-pregnant women, potentially due to increased progesterone levels [92]. Nevertheless, uNK cells are crucial innate immune cells that play a critical role in maintaining uterine immune homeostasis. Therefore, it is essential to understand the role of uNK cells in UC.

4. NK Cells in the UC Immune Microenvironment (UCIM)

The human uterus is a unique mucosal immune organ that undergoes a menstrual cycle every month (from menarche to menopause) and serves as a site of implantation for the developing embryo to support reproduction. uNK cells serve as central innate immune cells of the endometrium with few $CD8^+$T, regulatory T cells (T_{regs}), and B cells [93–95]. DCs, mast cells, and macrophages are also present in the typical uterine immune environment [93,96–98]. The uterine immune cell number changes cyclically with the menstrual cycle and inflammatory insult. Chronic inflammation without resolution may induce cancer, including endometrial cancer (EC), and systemic inflammatory markers, including C-reactive protein (CRP), serve as prognostic markers [99–101]. Hence, systemic and local inflammation may affect predisposition to the EC and its severity. Immune cells and secreted cytokines and chemokines are the critical mediators of the inflammatory cascade, including initiation, progression, and resolution [7,102,103]. Moreover, uterine immune cells, including uNK cells, play a significant role in the uterine remodeling seen during menstruation, embryonic development, and parturition [84,90,104]. Therefore, dysregulated uterine immune cell population and function that results in chronic inflammation may lead to EC. Notably, aging and obesity potentially alter the uterine or endometrial immune environment as both can induce chronic low-grade systemic inflammation [105–109]. Consequently, UC prevalence increases with aging and in females with obesity [110]. Thus, it becomes crucial to understand the EC immune microenvironment (ECIM or UCIM).

EC is the most common cancer of the female reproductive tract (FRT); however, little is known about the ECIM. The high expression of indoleamine 2,3-dioxygenase (IDO), PDL1, and B7-H4 found in EC suggest the development and persistence of an immunosuppressive TME [111]. Hence, EC can be targeted via known immunotherapeutics, including checkpoint inhibitors. Additionally, elevated arginase 1 expression observed in EC indicates the accumulation of tumor-promoting immunosuppressive M2 or alternatively activated macrophages (AAMs) along with myeloid-derived suppressor cells (MDSCs). Elevated M2 macrophages may hinder NK cell activation and mitigate cytotoxicity against tumor cells [112] (Figure 2). Blocking neuropilin-1 expression in hypoxic cells prevents recruitment and M2 macrophage polarization [113].

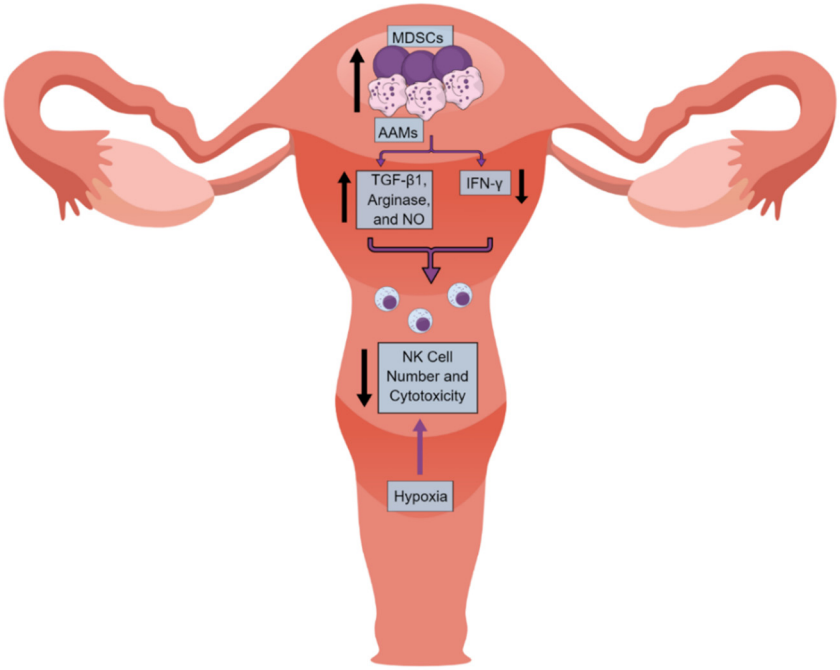


Figure 2. NK cell dysregulation in the immunosuppressive UCIM. Increased concentrations of MDSCs and AAMs in the tumor microenvironment (TME) increase TGF-β1, NO., and arginase, as well as decrease IFN-γ levels, all of which contribute to NK cell dysregulation and depletion. The hypoxic environment characteristic of some uterine tumors can also contribute to NK cell dysregulation and depletion.

MDSC migration in advanced stage EC hinders $CD8^+$ T cell accumulation, causing resistance to current therapies [114]. In addition, MDSCs can overexpress arginase and inducible nitric oxide synthase (iNOS), which converts arginine into nitric oxide (NO.), which subsequently reduces NK cell antibody-dependent cellular cytotoxicity (ADCC) [115] (Figure 2). High levels of TGF-β1 and low IFN-γ concentrations perpetuate an immunosuppressive microenvironment in ECs [116]. For example, TGF-β decreases mitochondrial metabolism in NK cells by hindering IL-2 [115,117]. The low IFN-γ level in the UC TME indicates fewer or non-functional $CD8^+$T and NK cells, which are the primary source of this cytokine (Figure 2). Additionally, EC cells show an increased CXCR4 expression that via CXCL12 recognition increases their metastasis to distant organs, including lungs and liver [118,119]. The CXCR4/CXCL12 axis also plays a crucial role in the NK cell chemotaxis and infiltration to different tissues and organs [120]. Thus, along with a nutrient-competitive TME, a chemokine and cytokine competitive UC time supports its growth and metastasis. For example, an increased CXCL12 usage by CXCR4 expressing EC cells for their metastasis decreases CXCL12 availability for chemotaxis of antitumor and cytotoxic NK cells [121]. Additionally, EC TME also has a decreased CCL27 or cutaneous T-cell-attracting chemokine (CTACK) level that further suppresses NK cell infiltration [121,122]. Furthermore, a highly hypoxic region in EC interrupts metabolic and biosynthetic genes in NK cells that are crucial for their antitumor function, including IFN-γ release [115,123]. Hypoxic EC tumors often have elevated lactate levels, a significant hurdle for NK cell-based immunotherapies [124].

It is critical to understand the differential activity and prevalence of NK cells within the EC TME to advance targeted immune treatment. Although NK cells are present in the EC TME, their antitumoral response is less effective than those in surrounding healthy tissue [121] (Figure 2). This finding is primarily related to the fact that EC-associated fibroblasts suppress NK cell-killing activity more efficiently than normal endometrial fibroblasts [125]. As a result, there are fewer NK cells in EC tumors compared to the surrounding healthy tissue, and these NK cells are also less cytotoxic. In addition, a subset

of NK cells in patients with cancer behave more similarly to dNK cells by expressing CD56, CD9, CD49a, and CXCR3. Hence, these NK cells are more immunosuppressive and promote tumor growth rather than cell death [82] (Figure 2). Furthermore, approximately 40% of total NK cells in the EC TME express CD103, the marker for tumor resident NK cells with diminished cytotoxic function [121] (Figure 2). In addition, decreased levels of NK cell chemo-attractants in the TME decrease NK cell recruitment, further promoting an immunosuppressive environment [121].

Tumor cells alter the major histocompatibility complex (MHC) or human leukocyte antigen (HLA) molecules' expression to escape from antitumor tumor immune response [126–128]. HLA-E is one such molecule (a non-classical HLA class I molecule) that affects NK cell function [129]. For example, NK cell interaction with the HLA-E molecule occurs via C-type lectin-like NKG2 receptor family [130]. NKG2A or CD94 (an inhibitory receptor) has a six times higher affinity to HLA-E than the NKG2C (an activating receptor) [130–132]. Notably, NKG2A and NKG2C bind the HLA-E top through mostly shared but partly distinct sets of HLA-E residues discriminating between two NK cell receptors [133]. Additionally, HLA-E regulates NKG2C only when HLA-E is in complex with restricted peptide repertoire, specifically HLA-G leader peptide [134]. Hence, HLA-E can have dual (activating or inhibitory) action. NK cell loss may be attributed to the increased HLA-E expression which, thorough interacting with inhibitory NKG2A of residual NK cells, suppresses their antitumor function (Table 1). This has clinical implications as altered HLA-E expression in EC cells affects the disease prognosis, depending on NK cell number and function [135,136]. Forcing the expression of specially engineered HLA-E may hinder the 'missing self' response in NK cells responsible for attacking other cells. HLA-engineered pluripotent stem cells (PSCs) could evade $CD8^+$ T-cells' detection and prevent NK cell-mediated cell death. Therefore, HLA-E-expressing PSCs may serve as donor cells to individuals lacking HLA class II expression [137]. This approach could prove helpful in treating certain gynecological malignancies, including UCs, where changes in HLA-E regulation are linked to NK cell survival. While research into NK cell-targeted therapies in EC is severely lacking, we have extensive research into cellular processes and early trials in other cancers to guide novel studies in this direction.

5. NK Cell-Based Therapies in Different Cancers

Larger tumors have fewer NK cells than less advanced tumors [138] (Figure 3A), suggesting that NK cell-targeted therapies in gynecological cancers could have the most significant impact when implemented early. The unique immunological functions of NK cells make them ideal targets for cancer therapy and could prove pivotal to improving treatment. Targeted therapies may be vital to treating highly mutated ECs that can impact their function [139,140]. Tumor immunotherapy approaches include stimulating the patient's immune system or in vitro stimulation of immune cells later introduced to the patient [141]. One way to utilize the existing antitumor properties of NK cells for treatment is to target cytokines that promote their activity, given their reduced concentration in the tumor. For example, a recent study found that while the volume of NK cell-stimulating cytokine IL-15 is reduced in EC tumors, the volume of NK cell-inhibiting IL-6 was increased [121] (Figure 3A). Such interactions should serve to inform new targeted therapies.

Existing vaccines leverage human papilloma (HPV) Virus-Like Particles (VLPs) to stimulate NK cells and DCs (Figure 3B). In this process, NK cells enhance DC maturation and upregulate IL-12p70 production and CD86 and HLA-DR expression. Conversely, DCs stimulate NK cells by upregulating CD69 and HLA-DR through CD40-mediated interaction and IL-12p70 release [142]. NK cell-targeted therapies could be instrumental to fighting resistant ECs, as they have already shown potential in other cancers [143,144]. In addition, NK cells will preferentially kill cancer stem cells over non-cancer stem cells in solid tumors, such as breast or prostate cancer (Figure 3B) [145]. Given cancer stem cell resilience to traditional cytotoxic cancer treatment, targeted NK cell immunotherapy may be game-changing [145].

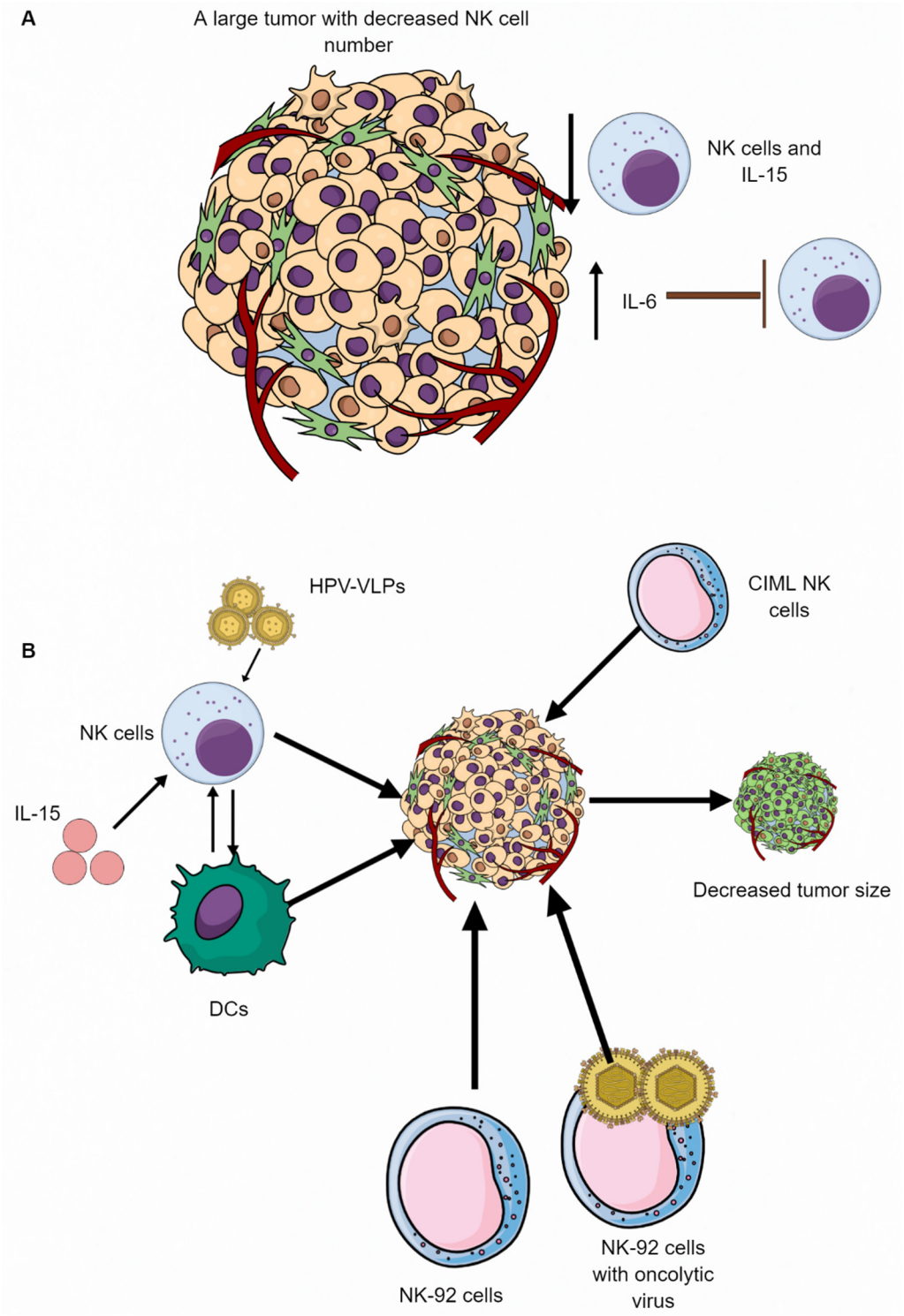


Figure 3. NK cell in TME or TIME and strategies to enhance their antitumor action. (**A**). Large tumors show a decreased NK cell number with dysregulated function due to the immunosuppressive TIME, including a decreased IL-15 level. Additionally, their TIME has elevated IL-6 level that suppresses NK cell function (**B**). Different strategies have been developed to enhance NK cell antitumor functions, including HPV virus like particles (VLPs), IL-15 treatment, NK-92 cells, NK-92 cells carrying oncolytic viruses, and CIML-NK cells. These therapies have potentially decreased the tumor size and burden in animal studies and in different clinical trials. Kindly see text for details.

Understanding the cytokine milieu may inform NK cell-targeted treatment approaches [65]. Previous pre-clinical studies have successfully used IL-15 to activate NK cells

in vitro [64]. High trans-cellular IL-15 alters NKCC in murine colon cancer models, thereby limiting cancer metastasis (Figure 3B). Exposure to IL-15α^+ does not induce NK cell production. However, the addition of membrane-bound IL-15 to IL-15α^+ enhances NK cell proliferation, thereby suggesting the requirement for IL-15 for in vivo NK cells development in vivo [146]. Additionally, transgenically augmented chimeric antigen receptor (CAR) NK cells (TRACKs), which are huCAR19 NK cells overexpressing human CXCR4, have increased migration capacity compared to conventional NK cells in response to CXCL12 or stromal-derived factor-1 (SDF-1) to targeted tumor (Table 2) [147]. Another study has also supported that CXCR4 overexpression increases NK cell migration to the target site [148]. Hence, TRACKs and other CAR-NK cell-based immunotherapies have great potential for different tumors, including overcoming the tumor resistance mechanisms [149–152].

Table 2. Possible NK cell-based immunotherapeutic strategies to leverage NK cells to target UC.

Therapeutic Agent	Goal
Peripheral blood or umbilical cord derived NK cells + Cetuximab	Increase cytotoxicity against cancer cells
Irradiated haNK cells	Induce CD16 expression to increase cancer cell lysis.
NK cell derived extracellular vesicles	Regulate APC response
Antibody based NK cell engager therapeutics	Induce NK cell proliferation, cytotoxicity, and cytokine release.
Block NKG2A with Monalizumab to enhance NK and T cells	Stimulate T cells and NK cells; promote NK cell antitumor activity.
TRACKs, expressing human CXCR4	Increased NK cell migration to tumor site

Early clinical trials have proven that NK-targeted therapy is safe for humans, but more research is needed to understand its effectiveness. Nevertheless, NK-92 (a IL-2-dependent NK cell line) infusion is safe for end-stage, chemotherapy-resistant cancers of various types, even at high dosages (Figure 3B). NK cells may even remain in the body for at least 48 h, capable of targeting the tumor without provoking an immune response against themselves [153]. Interestingly, NK-92 has also been shown to be a promising carrier for oncolytic enteroviruses, potentially treating various cancers [154] (Figure 3B).

NK cell therapy can also be used with current treatment regimens to improve clinical outcomes. For example, treatment with combination NK cell-targeted therapy and radiotherapy in mice greatly improved survival relative to either therapy alone [20]. Furthermore, a dual therapeutic approach that combines adoptively transferred NK cells from haploidentical donors is also practical in advanced-stage cancer patients receiving pre-treatment immunosuppressive regimens, including cyclophosphamide and fludarabine [155]. This approach has been used safely in other malignancies in phase I and II clinical trials [156–160]. Hence, using haploidentical NK cells in a variety of tumors has been found to be safe and this approach can be used in patients with EC. However, patients who do not respond to haploidentical NK cell-based therapy can be treated with adoptively transferred cytokine-induced memory-like (CIML) NK cells. This approach has performed well in phase I clinical trials [161–163]. Furthermore, memory-like NK cells armed with a neoepitope-specific chimeric antigen receptor (CAR) are potent antitumor immune cells [164]. CAR-NK cell-based therapies can overcome resistant tumors, including glioblastoma [149,165,166]. The details of CIML NK cells are discussed elsewhere [163,167–169]. Hence, understanding tumor immunology and NK cell biology have opened new avenues for NK cell-based immunotherapies for different cancers with the potential to extrapolate to UCs or ECs.

6. Future Perspective and Conclusions

Immunotherapies can leverage the inherent cytotoxic function of NK cells to engineer tumor-targeting treatments [170]. The positive response of these techniques in differ-

ent gynecological cancers strongly supports their future use in patients with EC [171]. Peripheral-blood- and umbilical-cord-derived stem-cell-derived NK cells show increased cytotoxicity against cancer cells when combined with anticancer drugs [172]. However, the anticancer immune response that is generated by NK cells from umbilical cord blood stem cells has shown adverse reactions in other cancers [155]. Future research into UC treatment should leverage existing knowledge of cellular processes to generate more targeted cellular responses. While existing NK-92 cells lack CD16, they can be engineered into high-affinity NK (haNK) cells to express CD16 (a high-affinity FcγRIIIa receptor). Under certain conditions, irradiated haNK cells can target and lyse CC cells with a more robust response over increased periods (Table 2). The addition of the EGFR inhibitor Cetuximab is crucial for ADCC, even though Cetuximab does not perform well on its own [173].

Furthermore, NK cells secrete extracellular vesicles (EVs) or exosomes that transport different molecules to adjacent or distant cells. These EVs have strong immunomodulatory properties depending on their source and target, for example, NK cell-derived EVs shuttle different miRNAs, which regulate T cell responses and other APCs. Hence, NK cell-derived EVs have a novel potential in cancer immunotherapeutics, including one for UCs (Table 2) [174,175]. Recently, a versatile NK cell engager platform referred as antibody-based NK cell engager therapeutics (ANKETs) has been used to generate a tetra antibody-based CD20-ANKETs (IL-2v/aNKp46/Fc/aCD20) [176,177]. This ANKET comprises an IL-2v peptide activating IL-2R independently of CD25 engagement, an antibody fragment recognizing NKp46 (aNKp46-1), a Fc domain of human IgG1 interacting with Fcγ receptors, including CD16a, and a specific antibody fragment for CD20 (aCD20) as a model tumor-associated antigen. This ANKET has highly induced NK cell proliferation, antitumor cytokine release, and NKCC against different tumors in vivo (Table 2) [176]. Hence, ANKETs specifically targeting NK cells have a great potential in EC patients.

In some cases, combining various stimulatory and inhibitory cellular signals may be the most effective way to treat a malignancy. For example, the NKG2A receptor stimulates T and NK cell function, which is enhanced when the PD-1 (CD279) axis is blocked. Since NKG2A-positive cells are present in EC, this technique could be used as a targeted approach. In addition, the antibody Monalizumab can promote NK cell antitumor activity and is an existing drug that can be investigated as a repurposed drug for UC treatment [178]. NK cell-targeted therapies may also increase the quality of life for patients during treatment by mitigating side effects. For example, allogenic NK cell therapy does not have debilitating side effects nor induce graft-versus-host disease (GVHD) [179]. Furthermore, a phase I clinical trial for patients with various advanced cancers did not find any treatment-related side effects associated with using NK cell therapy [153], thereby suggesting that this approach may improve the quality of life in patients with EC. Additionally, strategies able to enhance clonal expansion epigenetic inheritance of long lasting memory among NK cells derived from the patients may serve a novel NK cell-based adoptive cell transfer strategy for EC [180]. Thus, inducing antitumor immunity memory in vitro among patient-derived NK cells and then their adoptive transfer seems a promising approach for EC patients.

In conclusion, direct anticancer effects and lower cytotoxic adverse events support using NK cell-based immunotherapeutic approaches as personalized medicine. Furthermore, developing and implementing novel NK cell-targeted treatments are pivotal to creating complete treatment regimens for UC. Hence, improved therapies targeting NK cells in patients with EC comprise an adjunct therapy to currently available chemotherapies with potential for future immunotherapeutic approaches.

Author Contributions: Conceptualization, V.K.; Writing, review, and editing, V.K.; Writing original draft, C.B.; Final editing and proof reading, J.H.S.IV. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

AAMs	Alternatively activated macrophages
ADCC	Antibody-dependent cellular cytotoxicity
ANKETs	Antibody-based natural killer cell engager therapeutics
APCs	Antigen presenting cells
CAR	Chimeric antigen receptor
cDCs	Conventional dendritic cells
CIML NK cells	Cytokine-induced memory-like NK cells
CIN	Cervical intraepithelial neoplasia
CLPs	Common lymphoid progenitors
DAMPs	Damage/death-associated molecular patterns
DCs	Dendritic cells
EC	Endometrial Cancer
ECIM	Endometrial cancer immune microenvironment
EVs	Extracellular vesicles
FRT	Female reproductive tract
GM-CSF	granulocyte-monocyte colony stimulating factor
GVHD	Graft-versus-host disease
haNK	High affinity NK
HLA	Human Leukocyte Antigen
IDO	Indoleamine 2,3-dioxygenase
ILCs	Innate lymphoid cells
LILRB1	Leukocyte immunoglobulin-like receptor B1
MDSCs	Myeloid-derived suppressor cells
NCT	Normal ectocervical tissue
NKCC	Natural Killer cell cytotoxicity
PD-1	Programmed death-1
PSCs	Pluripotent stem cells
PTdNKs	Pregnancy trained decidual or uterine NK cells
RAGs	Recombination activating genes
TIME	Tumor Immune Microenvironment
TME	Tumor microenvironment
UC	Uterine Cancer
UCIM	Endometrial cancer immune microenvironment
uNK	Uterine NK
VLPs	Virus-like particles

References

1. Centers for Disease Control and Prevention. *Gynecologic Cancer Incidence, United States—2012–2016*; Centers for Disease Control and Prevention, US Department of Health and Human Services: Atlanta, GA, USA, 2019; Volume 2022.
2. Siegel, R.L.; Miller, K.D.; Jemal, A. Cancer statistics, 2018. *CA Cancer J. Clin.* **2018**, *68*, 7–30. [CrossRef]
3. Siegel, R.L.; Miller, K.D.; Jemal, A. Cancer statistics, 2019. *CA Cancer J. Clin.* **2019**, *69*, 7–34. [CrossRef]
4. Siegel, R.L.; Miller, K.D.; Jemal, A. Cancer Statistics, 2017. *CA Cancer J. Clin.* **2017**, *67*, 7–30. [CrossRef]
5. Yue, X.; Pruemer, J.M.; Hincapie, A.L.; Almalki, Z.S.; Guo, J.J. Economic burden and treatment patterns of gynecologic cancers in the United States: Evidence from the Medical Expenditure Panel Survey 2007–2014. *J. Gynecol. Oncol.* **2020**, *31*, e52. [CrossRef]
6. Chen, D.S.; Mellman, I. Oncology Meets Immunology: The Cancer-Immunity Cycle. *Immunity* **2013**, *39*, 1–10.
7. Kumar, V. Inflammation research sails through the sea of immunology to reach immunometabolism. *Int. Immunopharmacol.* **2019**, *73*, 128–145. [CrossRef]
8. Swann, J.B.; Smyth, M.J. Immune surveillance of tumors. *J. Clin. Investig.* **2007**, *117*, 1137–1146. [CrossRef]
9. Fridman, W.H. From Cancer Immune Surveillance to Cancer Immunoediting: Birth of Modern Immuno-Oncology. *J. Immunol.* **2018**, *201*, 825–826. [CrossRef]
10. Kim, R.; Emi, M.; Tanabe, K. Cancer immunoediting from immune surveillance to immune escape. *Immunology* **2007**, *121*, 1–14. [CrossRef]

11. Mittal, D.; Gubin, M.M.; Schreiber, R.D.; Smyth, M.J. New insights into cancer immunoediting and its three component phases–elimination, equilibrium and escape. *Curr. Opin. Immunol.* **2014**, *27*, 16–25. [CrossRef]
12. O'Donnell, J.S.; Teng, M.W.L.; Smyth, M.J. Cancer immunoediting and resistance to T cell-based immunotherapy. *Nat. Rev. Clin. Oncol.* **2019**, *16*, 151–167. [CrossRef]
13. Darcy, P.K.; Neeson, P.; Yong, C.S.M.; Kershaw, M.H. Manipulating immune cells for adoptive immunotherapy of cancer. *Curr. Opin. Immunol.* **2014**, *27*, 46–52. [CrossRef]
14. Sun, H.; Sun, C.; Tian, Z.; Xiao, W. NK cells in immunotolerant organs. *Cell. Mol. Immunol.* **2013**, *10*, 202–212. [CrossRef]
15. Vivier, E.; Tomasello, E.; Baratin, M.; Walzer, T.; Ugolini, S. Functions of natural killer cells. *Nat. Immunol.* **2008**, *9*, 503–510. [CrossRef]
16. Carotta, S. Targeting NK Cells for Anticancer Immunotherapy: Clinical and Preclinical Approaches. *Front. Immunol.* **2016**, *7*, 152. [CrossRef]
17. Liu, S.; Galat, V.; Galat, Y.; Lee, Y.K.A.; Wainwright, D.; Wu, J. NK cell-based cancer immunotherapy: From basic biology to clinical development. *J. Hematol. Oncol.* **2021**, *14*, 7. [CrossRef]
18. 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]
19. Wu, S.Y.; Fu, T.; Jiang, Y.Z.; Shao, Z.M. Natural killer cells in cancer biology and therapy. *Mol. Cancer* **2020**, *19*, 120. [CrossRef]
20. Kim, K.W.; Jeong, J.U.; Lee, K.H.; Uong, T.N.T.; Rhee, J.H.; Ahn, S.J.; Kim, S.K.; Cho, D.; Quang Nguyen, H.P.; Pham, C.T.; et al. Combined NK Cell Therapy and Radiation Therapy Exhibit Long-Term Therapeutic and Antimetastatic Effects in a Human Triple Negative Breast Cancer Model. *Int. J. Radiat. Oncol. Biol. Phys.* **2020**, *108*, 115–125. [CrossRef]
21. Lamb, M.G.; Rangarajan, H.G.; Tullius, B.P.; Lee, D.A. Natural killer cell therapy for hematologic malignancies: Successes, challenges, and the future. *Stem Cell Res. Ther.* **2021**, *12*, 211. [CrossRef]
22. Veluchamy, J.P.; Spanholtz, J.; Tordoir, M.; Thijssen, V.L.; Heideman, D.A.M.; Verheul, H.M.W.; de Gruijl, T.D.; van der Vliet, H.J. Combination of NK Cells and Cetuximab to Enhance Anti-Tumor Responses in RAS Mutant Metastatic Colorectal Cancer. *PLoS ONE* **2016**, *11*, e0157830. [CrossRef] [PubMed]
23. Kiessling, R.; Petranyi, G.; Kärre, K.; Jondal, M.; Tracey, D.; Wigzell, H. Killer cells: A functional comparison between natural, immune T-cell and antibody-dependent in vitro systems. *J. Exp. Med.* **1976**, *143*, 772–780. [CrossRef] [PubMed]
24. Kiessling, R.; Klein, E.; Pross, H.; Wigzell, H. "Natural" killer cells in the mouse. II. Cytotoxic cells with specificity for mouse Moloney leukemia cells. Characteristics of the killer cell. *Eur. J. Immunol.* **1975**, *5*, 117–121. [CrossRef]
25. Greenberg, A. The origins of the NK cell, or a Canadian in King Ivan's court. *Clin. Investig. Med.* **1994**, *17*, 626–631.
26. Trinchieri, G. Biology of natural killer cells. *Adv. Immunol.* **1989**, *47*, 187–376.
27. Biron, C.A. Activation and function of natural killer cell responses during viral infections. *Curr. Opin. Immunol.* **1997**, *9*, 24–34. [CrossRef] [PubMed]
28. 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] [PubMed]
29. Fogler, W.E.; Volker, K.; McCormick, K.L.; Watanabe, M.; Ortaldo, J.R.; Wiltrout, R.H. NK cell infiltration into lung, liver, and subcutaneous B16 melanoma is mediated by VCAM-1/VLA-4 interaction. *J. Immunol.* **1996**, *156*, 4707–4714.
30. Castriconi, R.; Carrega, P.; Dondero, A.; Bellora, F.; Casu, B.; Regis, S.; Ferlazzo, G.; Bottino, C. Molecular Mechanisms Directing Migration and Retention of Natural Killer Cells in Human Tissues. *Front. Immunol.* **2018**, *9*, 2324. [CrossRef]
31. Gismondi, A.; Santoni, A. Migration of NK cells. In *Lymphocyte Trafficking in Health and Disease*; Badolato, R., Sozzani, S., Eds.; Birkhäuser Basel: Basel, Switzerland, 2006; pp. 95–112.
32. Ran, G.H.; Lin, Y.Q.; Tian, L.; Zhang, T.; Yan, D.M.; Yu, J.H.; Deng, Y.C. Natural killer cell homing and trafficking in tissues and tumors: From biology to application. *Signal Transduct. Target. Ther.* **2022**, *7*, 205. [CrossRef]
33. Shannon, M.J.; Mace, E.M. Natural Killer Cell Integrins and Their Functions in Tissue Residency. *Front. Immunol.* **2021**, *12*, 647358. [CrossRef] [PubMed]
34. Cursons, J.; Souza-Fonseca-Guimaraes, F.; Foroutan, M.; Anderson, A.; Hollande, F.; Hediyeh-Zadeh, S.; Behren, A.; Huntington, N.D.; Davis, M.J. A Gene Signature Predicting Natural Killer Cell Infiltration and Improved Survival in Melanoma Patients. *Cancer Immunol. Res.* **2019**, *7*, 1162–1174. [CrossRef] [PubMed]
35. Maghazachi, A.A. Role of chemokines in the biology of natural killer cells. *Curr. Top. Microbiol. Immunol.* **2010**, *341*, 37–58. [PubMed]
36. Robertson, M.J. Role of chemokines in the biology of natural killer cells. *J. Leukoc. Biol.* **2002**, *71*, 173–183. [CrossRef]
37. Lupo, K.; Matosevic, S. Chapter 16—Immunometabolic targeting of NK cells to solid tumors. In *Successes and Challenges of NK Immunotherapy*; Bonavida, B., Jewett, A., Eds.; Academic Press: Cambridge, MA, USA, 2021.
38. van den Heuvel, M.J.; Chantakru, S.; Xuemei, X.; Evans, S.S.; Tekpetey, F.; Mote, P.A.; Clarke, C.L.; Croy, B.A. Trafficking of circulating pro-NK cells to the decidualizing uterus: Regulatory mechanisms in the mouse and human. *Immunol. Investig.* **2005**, *34*, 273–293. [CrossRef]
39. Bernardini, G.; Antonangeli, F.; Bonanni, V.; Santoni, A. Dysregulation of Chemokine/Chemokine Receptor Axes and NK Cell Tissue Localization during Diseases. *Front. Immunol.* **2016**, *7*, 402. [CrossRef]
40. Yao, X.; Matosevic, S. Chemokine networks modulating natural killer cell trafficking to solid tumors. *Cytokine Growth Factor Rev.* **2021**, *59*, 36–45. [CrossRef]

41. Fauriat, C.; Long, E.O.; Ljunggren, H.G.; Bryceson, Y.T. Regulation of human NK cell cytokine and chemokine production by target cell recognition. *Blood* **2010**, *115*, 2167–2176. [CrossRef]
42. 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.
43. Mariani, E.; Pulsatelli, L.; Meneghetti, A.; Dolzani, P.; Mazzetti, I.; Neri, S.; Ravaglia, G.; Forti, P.; Facchini, A. Different IL-8 production by T and NK lymphocytes in elderly subjects. *Mech. Ageing Dev.* **2001**, *122*, 1383–1395. [CrossRef]
44. Spits, H.; Artis, D.; Colonna, M.; Diefenbach, A.; Di Santo, J.P.; Eberl, G.; Koyasu, S.; Locksley, R.M.; McKenzie, A.N.; Mebius, R.E.; et al. Innate lymphoid cells—A proposal for uniform nomenclature. *Nat. Rev. Immunol.* **2013**, *13*, 145–149. [CrossRef]
45. Kumar, V. Innate lymphoid cells: New paradigm in immunology of inflammation. *Immunol. Lett.* **2014**, *157*, 23–37. [CrossRef]
46. Kumar, V. Innate Lymphoid Cells: Immunoregulatory Cells of Mucosal Inflammation. *Eur. J. Inflamm.* **2014**, *12*, 11–20. [CrossRef]
47. Kumar, V. Innate lymphoid cell and adaptive immune cell cross-talk: A talk meant not to forget. *J. Leukoc. Biol.* **2020**, *108*, 397–417. [CrossRef] [PubMed]
48. Kumar, V. Innate Lymphoid Cells and Adaptive Immune Cells Cross-Talk: A Secret Talk Revealed in Immune Homeostasis and Different Inflammatory Conditions. *Int. Rev. Immunol.* **2021**, *40*, 217–251. [CrossRef]
49. O'Sullivan, T.E. Dazed and Confused: NK Cells. *Front. Immunol.* **2019**, *10*, 2235. [CrossRef] [PubMed]
50. Abel, A.M.; Yang, C.; Thakar, M.S.; Malarkannan, S. Natural Killer Cells: Development, Maturation, and Clinical Utilization. *Front. Immunol.* **2018**, *9*, 1869. [CrossRef]
51. Kumar, V. Natural killer cells in sepsis: Underprivileged innate immune cells. *Eur. J. Cell Biol.* **2019**, *98*, 81–93. [CrossRef] [PubMed]
52. Geiger, T.L.; Sun, J.C. Development and maturation of natural killer cells. *Curr. Opin. Immunol.* **2016**, *39*, 82–89. [CrossRef] [PubMed]
53. Kumar, V. Chapter 8—Innate lymphoid cells in autoimmune diseases. In *Translational Autoimmunity*; Rezaei, N., Ed.; Academic Press: Cambridge, MA, USA, 2022; Volume 1, pp. 143–175.
54. Perera Molligoda Arachchige, A.S. Human NK cells: From development to effector functions. *Innate Immun.* **2021**, *27*, 212–229. [CrossRef]
55. Sun, J.C.; Lanier, L.L. NK cell development, homeostasis and function: Parallels with $CD8^+$ T cells. *Nat. Rev. Immunol.* **2011**, *11*, 645–657. [CrossRef] [PubMed]
56. Zhang, Y.; Huang, B. The Development and Diversity of ILCs, NK Cells and Their Relevance in Health and Diseases. In *Regulation of Inflammatory Signaling in Health and Disease*; Xu, D., Ed.; Springer: Singapore, 2017; pp. 225–244.
57. Lam, V.C.; Lanier, L.L. NK cells in host responses to viral infections. *Curr. Opin. Immunol.* **2017**, *44*, 43–51. [CrossRef]
58. Sun, H.; Sun, C.; Xiao, W.; Sun, R. Tissue-resident lymphocytes: From adaptive to innate immunity. *Cell. Mol. Immunol.* **2019**, *16*, 205–215. [CrossRef] [PubMed]
59. Vivier, E.; Raulet, D.H.; Moretta, A.; Caligiuri, M.A.; Zitvogel, L.; Lanier, L.L.; Yokoyama, W.M.; Ugolini, S. Innate or adaptive immunity? The example of natural killer cells. *Science* **2011**, *331*, 44–49. [CrossRef] [PubMed]
60. Bald, T.; Krummel, M.F.; Smyth, M.J.; Barry, K.C. The NK cell–cancer cycle: Advances and new challenges in NK cell–based immunotherapies. *Nat. Immunol.* **2020**, *21*, 835–847. [CrossRef]
61. Chiossone, L.; Dumas, P.-Y.; Vienne, M.; Vivier, E. Natural killer cells and other innate lymphoid cells in cancer. *Nat. Rev. Immunol.* **2018**, *18*, 671–688. [CrossRef]
62. López-Soto, A.; Gonzalez, S.; Smyth, M.J.; Galluzzi, L. Control of Metastasis by NK Cells. *Cancer Cell* **2017**, *32*, 135–154. [CrossRef]
63. Moon, W.Y.; Powis, S.J. Does Natural Killer Cell Deficiency (NKD) Increase the Risk of Cancer? NKD May Increase the Risk of Some Virus Induced Cancer. *Front. Immunol.* **2019**, *10*, 1703. [CrossRef]
64. Cheng, M.; Chen, Y.; Xiao, W.; Sun, R.; Tian, Z. NK cell-based immunotherapy for malignant diseases. *Cell. Mol. Immunol.* **2013**, *10*, 230–252. [CrossRef]
65. Chu, J.; Gao, F.; Yan, M.; Zhao, S.; Yan, Z.; Shi, B.; Liu, Y. Natural killer cells: A promising immunotherapy for cancer. *J. Transl. Med.* **2022**, *20*, 240. [CrossRef]
66. Pegram, H.J.; Andrews, D.M.; Smyth, M.J.; Darcy, P.K.; Kershaw, M.H. Activating and inhibitory receptors of natural killer cells. *Immunol. Cell Biol.* **2011**, *89*, 216–224. [CrossRef]
67. Farag, S.S.; Fehniger, T.A.; Ruggeri, L.; Velardi, A.; Caligiuri, M.A. Natural killer cell receptors: New biology and insights into the graft-versus-leukemia effect. *Blood* **2002**, *100*, 1935–1947. [CrossRef] [PubMed]
68. Thielens, A.; Vivier, E.; Romagné, F. NK cell MHC class I specific receptors (KIR): From biology to clinical intervention. *Curr. Opin. Immunol.* **2012**, *24*, 239–245. [CrossRef] [PubMed]
69. Martin, J.H.; Mohammed, R.; Delforce, S.J.; Skerrett-Byrne, D.A.; Coribisier de Meaulsart, C.; Almzi, J.G.; Stephens, A.N.; Verills, N.M.; Dimitriadis, E.; Wang, Y.; et al. Role of the prorenin receptor in endometrial cancer cell growth. *Oncotarget* **2022**, *13*, 587–599. [CrossRef] [PubMed]
70. Rajalingam, R. Overview of the killer cell immunoglobulin-like receptor system. *Methods Mol. Biol.* **2012**, *882*, 391–414.
71. Paul, S.; Lal, G. The Molecular Mechanism of Natural Killer Cells Function and Its Importance in Cancer Immunotherapy. *Front. Immunol.* **2017**, *8*, 1124. [CrossRef]
72. Vilches, C.; Parham, P. KIR: Diverse, Rapidly Evolving Receptors of Innate and Adaptive Immunity. *Annu. Rev. Immunol.* **2002**, *20*, 217–251. [CrossRef]

73. Chou, Y.C.; Chen, C.H.; Chen, M.J.; Chang, C.W.; Chen, P.H.; Yu, M.H.; Chen, Y.J.; Tsai, E.M.; Yang, P.S.; Lin, S.Y.; et al. Killer cell immunoglobulin-like receptors (KIR) and human leukocyte antigen-C (HLA-C) allorecognition patterns in women with endometriosis. *Sci. Rep.* **2020**, *10*, 4897. [CrossRef]
74. Yu, H.C.; Lin, C.Y.; Chang, W.C.; Shen, B.J.; Chang, W.P.; Chuang, C.M. Increased association between endometriosis and endometrial cancer: A nationwide population-based retrospective cohort study. *Int. J. Gynecol. Cancer* **2015**, *25*, 447–452. [CrossRef]
75. Hermens, M.; van Altena, A.M.; Velthuis, I.; van de Laar DC, M.; Bulten, J.; van Vliet, H.; Siebers, A.G.; Bekkers, R.L.M. Endometrial Cancer Incidence in Endometriosis and Adenomyosis. *Cancers* **2021**, *13*, 4592. [CrossRef]
76. Ye, J.; Peng, H.; Huang, X.; Qi, X. The association between endometriosis and risk of endometrial cancer and breast cancer: A meta-analysis. *BMC Womens Health* **2022**, *22*, 455. [CrossRef] [PubMed]
77. Pende, D.; Falco, M.; Vitale, M.; Cantoni, C.; Vitale, C.; Munari, E.; Bertaina, A.; Moretta, F.; Del Zotto, G.; Pietra, G.; et al. Killer Ig-Like Receptors (KIRs): Their Role in NK Cell Modulation and Developments Leading to Their Clinical Exploitation. *Front. Immunol.* **2019**, *10*, 1179. [CrossRef] [PubMed]
78. Ganguly, K.K.; Pal, S.; Moulik, S.; Chatterjee, A. Integrins and metastasis. *Cell Adhes. Migr.* **2013**, *7*, 251–261. [CrossRef] [PubMed]
79. Zamai, L.; Ponti, C.; Mirandola, P.; Gobbi, G.; Papa, S.; Galeotti, L.; Cocco, L.; Vitale, M. NK Cells and Cancer. *J. Immunol.* **2007**, *178*, 4011–4016. [CrossRef] [PubMed]
80. Weizman, O.E.; Adams, N.M.; Schuster, I.S.; Krishna, C.; Pritykin, Y.; Lau, C.; Degli-Esposti, M.A.; Leslie, C.S.; Sun, J.C.; O'Sullivan, T.E. ILC1 Confer Early Host Protection at Initial Sites of Viral Infection. *Cell* **2017**, *171*, 795–808.e712. [CrossRef]
81. Prager, I.; Watzl, C. Mechanisms of natural killer cell-mediated cellular cytotoxicity. *J. Leukoc. Biol.* **2019**, *105*, 1319–1329. [CrossRef]
82. Albini, A.; Noonan, D.M. Decidual-Like NK Cell Polarization: From Cancer Killing to Cancer Nurturing. *Cancer Discov.* **2021**, *11*, 28–33. [CrossRef]
83. Sojka, D.K. Uterine Natural Killer Cell Heterogeneity: Lessons From Mouse Models. *Front. Immunol.* **2020**, *11*, 290. [CrossRef] [PubMed]
84. Kumar, V.; Medhi, B. Emerging role of uterine natural killer cells in establishing pregnancy. *Iran J. Immunol.* **2008**, *5*, 71–81.
85. Moffett-King, A. Natural killer cells and pregnancy. *Nat. Rev. Immunol.* **2002**, *2*, 656–663. [CrossRef]
86. Gamliel, M.; Goldman-Wohl, D.; Isaacson, B.; Gur, C.; Stein, N.; Yamin, R.; Berger, M.; Grunewald, M.; Keshet, E.; Rais, Y.; et al. Trained Memory of Human Uterine NK Cells Enhances Their Function in Subsequent Pregnancies. *Immunity* **2018**, *48*, 951–962.e955. [CrossRef] [PubMed]
87. Husby, A.; Wohlfahrt, J.; Melbye, M. Pregnancy duration and endometrial cancer risk: Nationwide cohort study. *BMJ* **2019**, *366*, l4693. [CrossRef] [PubMed]
88. Male, V.; Sharkey, A.; Masters, L.; Kennedy, P.R.; Farrell, L.E.; Moffett, A. The effect of pregnancy on the uterine NK cell KIR repertoire. *Eur. J. Immunol.* **2011**, *41*, 3017–3027. [CrossRef]
89. Male, V.; Hughes, T.; McClory, S.; Colucci, F.; Caligiuri, M.A.; Moffett, A. Immature NK cells, capable of producing IL-22, are present in human uterine mucosa. *J. Immunol.* **2010**, *185*, 3913–3918. [CrossRef] [PubMed]
90. Meyer, N.; Zenclussen, A.C. Immune Cells in the Uterine Remodeling: Are They the Target of Endocrine Disrupting Chemicals? *Front. Immunol.* **2020**, *11*, 246. [CrossRef] [PubMed]
91. Manaster, I.; Mizrahi, S.; Goldman-Wohl, D.; Sela, H.Y.; Stern-Ginossar, N.; Lankry, D.; Gruda, R.; Hurwitz, A.; Bdolah, Y.; Haimov-Kochman, R.; et al. Endometrial NK cells are special immature cells that await pregnancy. *J. Immunol.* **2008**, *181*, 1869–1876. [CrossRef] [PubMed]
92. Carlino, C.; Stabile, H.; Morrone, S.; Bulla, R.; Soriani, A.; Agostinis, C.; Bossi, F.; Mocci, C.; Sarazani, F.; Tedesco, F.; et al. Recruitment of circulating NK cells through decidual tissues: A possible mechanism controlling NK cell accumulation in the uterus during early pregnancy. *Blood* **2008**, *111*, 3108–3115. [CrossRef] [PubMed]
93. Agostinis, C.; Mangogna, A.; Bossi, F.; Ricci, G.; Kishore, U.; Bulla, R. Uterine Immunity and Microbiota: A Shifting Paradigm. *Front. Immunol.* **2019**, *10*, 2387. [CrossRef]
94. Shen, M.; O'Donnell, E.; Leon, G.; Kisovar, A.; Melo, P.; Zondervan, K.; Granne, I.; Southcombe, J. The role of endometrial B cells in normal endometrium and benign female reproductive pathologies: A systematic review. *Hum. Reprod. Open* **2022**, *2022*, hoab043. [CrossRef]
95. Wang, Y.; He, M.; Zhang, G.; Cao, K.; Yang, M.; Zhang, H.; Liu, H. The immune landscape during the tumorigenesis of cervical cancer. *Cancer Med.* **2021**, *10*, 2380–2395. [CrossRef]
96. De Leo, B.; Esnal-Zufiaurre, A.; Collins, F.; Critchley, H.O.D.; Saunders, P.T.K. Immunoprofiling of human uterine mast cells identifies three phenotypes and expression of ERβ and glucocorticoid receptor. *F1000Research* **2017**, *6*, 667. [CrossRef] [PubMed]
97. Drudy, L.; Sheppard, B.; Bonnar, J. Mast cells in the normal uterus and in dysfunctional uterine bleeding. *Eur. J. Obstet. Gynecol. Reprod. Biol.* **1991**, *39*, 193–201. [CrossRef] [PubMed]
98. Schulke, L.; Manconi, F.; Markham, R.; Fraser, I.S. Endometrial dendritic cell populations during the normal menstrual cycle. *Hum. Reprod.* **2008**, *23*, 1574–1580. [CrossRef]
99. Friedenreich, C.M.; Langley, A.R.; Speidel, T.P.; Lau, D.C.; Courneya, K.S.; Csizmadi, I.; Magliocco, A.M.; Yasui, Y.; Cook, L.S. Case-control study of inflammatory markers and the risk of endometrial cancer. *Eur. J. Cancer Prev.* **2013**, *22*, 374–379. [CrossRef]
100. Yang, Y.; Li, X.; Qian, H.; Di, G.; Zhou, R.; Dong, Y.; Chen, W.; Ren, Q. C-Reactive Protein as a Prognostic Biomarker for Gynecologic Cancers: A Meta-Analysis. *Comput. Intell. Neurosci.* **2022**, *2022*, 6833078. [CrossRef] [PubMed]

101. Njoku, K.; Ramchander, N.C.; Wan, Y.L.; Barr, C.E.; Crosbie, E.J. Pre-treatment inflammatory parameters predict survival from endometrial cancer: A prospective database analysis. *Gynecol. Oncol.* **2022**, *164*, 146–153. [CrossRef] [PubMed]
102. Serhan, C.N.; Gupta, S.K.; Perretti, M.; Godson, C.; Brennan, E.; Li, Y.; Soehnlein, O.; Shimizu, T.; Werz, O.; Chiurchiù, V.; et al. The Atlas of Inflammation Resolution (AIR). *Mol. Asp. Med.* **2020**, *74*, 100894. [CrossRef]
103. Fullerton, J.N.; Gilroy, D.W. Resolution of inflammation: A new therapeutic frontier. *Nat. Rev. Drug Discov.* **2016**, *15*, 551–567. [CrossRef]
104. Wang, F.; Qualls, A.E.; Marques-Fernandez, L.; Colucci, F. Biology and pathology of the uterine microenvironment and its natural killer cells. *Cell. Mol. Immunol.* **2021**, *18*, 2101–2113. [CrossRef]
105. Kumar, V.; Kiran, S.; Kumar, S.; Singh, U.P. Extracellular vesicles in obesity and its associated inflammation. *Int. Rev. Immunol.* **2022**, *41*, 30–44. [CrossRef]
106. Chung, H.Y.; Kim, D.H.; Lee, E.K.; Chung, K.W.; Chung, S.; Lee, B.; Seo, A.Y.; Chung, J.H.; Jung, Y.S.; Im, E.; et al. Redefining Chronic Inflammation in Aging and Age-Related Diseases: Proposal of the Senoinflammation Concept. *Aging Dis.* **2019**, *10*, 367–382. [CrossRef] [PubMed]
107. Ferrucci, L.; Fabbri, E. Inflammageing: Chronic inflammation in ageing, cardiovascular disease, and frailty. *Nat. Rev. Cardiol.* **2018**, *15*, 505–522. [CrossRef] [PubMed]
108. Sanada, F.; Taniyama, Y.; Muratsu, J.; Otsu, R.; Shimizu, H.; Rakugi, H.; Morishita, R. Source of Chronic Inflammation in Aging. *Front. Cardiovasc. Med.* **2018**, *5*, 12. [CrossRef] [PubMed]
109. Patel, M.V.; Shen, Z.; Wira, C.R. Do endometrial immune changes with age prior to menopause compromise fertility in women? *Explor. Immunol.* **2022**, *2*, 677–692. [CrossRef]
110. van der Woude, H.; Hally, K.E.; Currie, M.J.; Gasser, O.; Henry, C.E. Importance of the endometrial immune environment in endometrial cancer and associated therapies. *Front. Oncol.* **2022**, *12*, 975201. [CrossRef] [PubMed]
111. Vanderstraeten, A.; Luyten, C.; Verbist, G.; Tuyaerts, S.; Amant, F. Mapping the immunosuppressive environment in uterine tumors: Implications for immunotherapy. *Cancer Immunol. Immunother.* **2014**, *63*, 545–557. [CrossRef] [PubMed]
112. Krneta, T.; Gillgrass, A.; Poznanski, S.; Chew, M.; Lee, A.J.; Kolb, M.; Ashkar, A.A. M2-polarized and tumor-associated macrophages alter NK cell phenotype and function in a contact-dependent manner. *J. Leukoc. Biol.* **2017**, *101*, 285–295. [CrossRef]
113. Chen, X.-J.; Wu, S.; Yan, R.-M.; Fan, L.-S.; Yu, L.; Zhang, Y.-M.; Wei, W.-F.; Zhou, C.-F.; Wu, X.-G.; Zhong, M.; et al. The role of the hypoxia-Nrp-1 axis in the activation of M2-like tumor-associated macrophages in the tumor microenvironment of cervical cancer. *Mol. Carcinog.* **2019**, *58*, 388–397. [CrossRef]
114. Mise, Y.; Hamanishi, J.; Daikoku, T.; Takamatsu, S.; Miyamoto, T.; Taki, M.; Yamanoi, K.; Yamaguchi, K.; Ukita, M.; Horikawa, N.; et al. Immunosuppressive tumor microenvironment in uterine serous carcinoma via CCL7 signal with myeloid-derived suppressor cells. *Carcinogenesis* **2022**, *43*, 647–658. [CrossRef]
115. Terrén, I.; Orrantia, A.; Vitallé, J.; Zenarruzabeitia, O.; Borrego, F. NK Cell Metabolism and Tumor Microenvironment. *Front. Immunol.* **2019**, *10*, 2278. [CrossRef]
116. Ni, Y.; Soliman, A.; Joehlin-Price, A.; Abdul-Karim, F.; Rose, P.G.; Mahdi, H. Immune cells and signatures characterize tumor microenvironment and predict outcome in ovarian and endometrial cancers. *Immunotherapy* **2021**, *13*, 1179–1192. [CrossRef] [PubMed]
117. Zaiatz-Bittencourt, V.; Finlay, D.K.; Gardiner, C.M. Canonical TGF-β Signaling Pathway Represses Human NK Cell Metabolism. *J. Immunol.* **2018**, *200*, 3934–3941. [CrossRef] [PubMed]
118. Gelmini, S.; Mangoni, M.; Castiglione, F.; Beltrami, C.; Pieralli, A.; Andersson, K.L.; Fambrini, M.; Taddei, G.L.; Serio, M.; Orlando, C. The CXCR4/CXCL12 axis in endometrial cancer. *Clin. Exp. Metastasis* **2009**, *26*, 261–268. [CrossRef] [PubMed]
119. Medina-Gutiérrez, E.; Céspedes, M.V.; Gallardo, A.; Rioja-Blanco, E.; Pavón, M.; Asensio-Puig, L.; Farré, L.; Alba-Castellón, L.; Unzueta, U.; Villaverde, A.; et al. Novel Endometrial Cancer Models Using Sensitive Metastasis Tracing for CXCR4-Targeted Therapy in Advanced Disease. *Biomedicines* **2022**, *10*, 1680. [CrossRef] [PubMed]
120. Noda, M.; Omatsu, Y.; Sugiyama, T.; Oishi, S.; Fujii, N.; Nagasawa, T. CXCL12-CXCR4 chemokine signaling is essential for NK-cell development in adult mice. *Blood* **2011**, *117*, 451–458. [CrossRef] [PubMed]
121. Degos, C.; Heinemann, M.; Barrou, J.; Boucherit, N.; Lambaudie, E.; Savina, A.; Gorvel, L.; Olive, D. Endometrial Tumor Microenvironment Alters Human NK Cell Recruitment, and Resident NK Cell Phenotype and Function. *Front. Immunol.* **2019**, *10*, 877. [CrossRef] [PubMed]
122. Gao, J.Q.; Tsuda, Y.; Han, M.; Xu, D.H.; Kanagawa, N.; Hatanaka, Y.; Tani, Y.; Mizuguchi, H.; Tsutsumi, Y.; Mayumi, T.; et al. NK cells are migrated and indispensable in the anti-tumor activity induced by CCL27 gene therapy. *Cancer Immunol. Immunother.* **2009**, *58*, 291–299. [CrossRef]
123. Parodi, M.; Raggi, F.; Cangelosi, D.; Manzini, C.; Balsamo, M.; Blengio, F.; Eva, A.; Varesio, L.; Pietra, G.; Moretta, L.; et al. Hypoxia Modifies the Transcriptome of Human NK Cells, Modulates Their Immunoregulatory Profile, and Influences NK Cell Subset Migration. *Front. Immunol.* **2018**, *9*, 2358. [CrossRef]
124. Jedlička, M.; Feglarová, T.; Janstová, L.; Hortová-Kohoutková, M.; Frič, J. Lactate from the tumor microenvironment—A key obstacle in NK cell-based immunotherapies. *Front. Immunol.* **2022**, *13*, 932055. [CrossRef]
125. Inoue, T.; Adachi, K.; Kawana, K.; Taguchi, A.; Nagamatsu, T.; Fujimoto, A.; Tomio, K.; Yamashita, A.; Eguchi, S.; Nishida, H.; et al. Cancer-associated fibroblast suppresses killing activity of natural killer cells through downregulation of poliovirus receptor (PVR/CD155), a ligand of activating NK receptor. *Int. J. Oncol.* **2016**, *49*, 1297–1304. [CrossRef]

126. Dhatchinamoorthy, K.; Colbert, J.D.; Rock, K.L. Cancer Immune Evasion Through Loss of MHC Class I Antigen Presentation. *Front. Immunol.* **2021**, *12*, 636568. [CrossRef] [PubMed]
127. Dersh, D.; Hollý, J.; Yewdell, J.W. A few good peptides: MHC class I-based cancer immunosurveillance and immunoevasion. *Nat. Rev. Immunol.* **2021**, *21*, 116–128. [CrossRef] [PubMed]
128. Axelrod, M.L.; Cook, R.S.; Johnson, D.B.; Balko, J.M. Biological Consequences of MHC-II Expression by Tumor Cells in Cancer. *Clin. Cancer Res.* **2019**, *25*, 2392–2402. [CrossRef] [PubMed]
129. Kaiser, B.K.; Barahmand-Pour, F.; Paulsene, W.; Medley, S.; Geraghty, D.E.; Strong, R.K. Interactions between NKG2x immunoreceptors and HLA-E ligands display overlapping affinities and thermodynamics. *J. Immunol.* **2005**, *174*, 2878–2884. [CrossRef] [PubMed]
130. Kaiser, B.K.; Pizarro, J.C.; Kerns, J.; Strong, R.K. Structural basis for NKG2A/CD94 recognition of HLA-E. *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 6696–6701. [CrossRef] [PubMed]
131. Lee, N.; Llano, M.; Carretero, M.; Ishitani, A.; Navarro, F.; López-Botet, M.; Geraghty, D.E. HLA-E is a major ligand for the natural killer inhibitory receptor CD94/NKG2A. *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 5199–5204. [CrossRef] [PubMed]
132. Iwaszko, M.; Bogunia-Kubik, K. Clinical Significance of the HLA-E and CD94/NKG2 Interaction. *Arch. Immunol. Ther. Exp.* **2011**, *59*, 353. [CrossRef]
133. Wada, H.; Matsumoto, N.; Maenaka, K.; Suzuki, K.; Yamamoto, K. The inhibitory NK cell receptor CD94/NKG2A and the activating receptor CD94/NKG2C bind the top of HLA-E through mostly shared but partly distinct sets of HLA-E residues. *Eur. J. Immunol.* **2004**, *34*, 81–90. [CrossRef]
134. Lauterbach, N.; Wieten, L.; Popeijus, H.E.; Voorter, C.E.M.; Tilanus, M.G.J. HLA-E regulates NKG2C+ natural killer cell function through presentation of a restricted peptide repertoire. *Hum. Immunol.* **2015**, *76*, 578–586. [CrossRef]
135. Versluis, M.A.C.; Marchal, S.; Plat, A.; de Bock, G.H.; van Hall, T.; de Bruyn, M.; Hollema, H.; Nijman, H.W. The prognostic benefit of tumour-infiltrating Natural Killer cells in endometrial cancer is dependent on concurrent overexpression of Human Leucocyte Antigen-E in the tumour microenvironment. *Eur. J. Cancer* **2017**, *86*, 285–295. [CrossRef]
136. Ben Yahia, H.; Boujelbene, N.; Babay, W.; Ben Safta, I.; Dhouioui, S.; Zemni, I.; Ali Ayadi, M.; Charfi, L.; Ouzari, H.I.; Rebmann, V.; et al. Expression analysis of immune-regulatory molecules HLA-G, HLA-E and IDO in endometrial cancer. *Hum. Immunol.* **2020**, *81*, 305–313. [CrossRef] [PubMed]
137. Gornalusse, G.G.; Hirata, R.K.; Funk, S.E.; Riolobos, L.; Lopes, V.S.; Manske, G.; Prunkard, D.; Colunga, A.G.; Hanafi, L.A.; Clegg, D.O.; et al. HLA-E-expressing pluripotent stem cells escape allogeneic responses and lysis by NK cells. *Nat. Biotechnol.* **2017**, *35*, 765–772. [CrossRef] [PubMed]
138. Tu, Y.; Pan, M.; Song, S.; Hua, J.; Liu, R.; Li, L. CD3+CD56+ natural killer T cell infiltration is increased in cervical cancer and negatively correlated with tumour progression. *Biotechnol. Biotechnol. Equip.* **2019**, *33*, 1380–1391. [CrossRef]
139. Piulats, J.M.; Matias-Guiu, X. Immunotherapy in Endometrial Cancer: In the Nick of Time. *Clin. Cancer Res.* **2016**, *22*, 5623–5625. [CrossRef]
140. Santin, A.D.; Bellone, S.; Buza, N.; Choi, J.; Schwartz, P.E.; Schlessinger, J.; Lifton, R.P. Regression of Chemotherapy-Resistant Polymerase epsilon (POLE) Ultra-Mutated and MSH6 Hyper-Mutated Endometrial Tumors with Nivolumab. *Clin. Cancer Res.* **2016**, *22*, 5682–5687. [CrossRef] [PubMed]
141. Di Tucci, C.; Capone, C.; Galati, G.; Iacobelli, V.; Schiavi, M.C.; Di Donato, V.; Muzii, L.; Panici, P.B. Immunotherapy in endometrial cancer: New scenarios on the horizon. *J. Gynecol. Oncol.* **2019**, *30*, e46. [CrossRef]
142. Langers, I.; Renoux, V.; Reschner, A.; Touze, A.; Coursaget, P.; Boniver, J.; Koch, J.; Delvenne, P.; Jacobs, N. Natural killer and dendritic cells collaborate in the immune response induced by the vaccine against uterine cervical cancer. *Eur. J. Immunol.* **2014**, *44*, 3585–3595. [CrossRef]
143. Laskowski, T.J.; Biederstädt, A.; Rezvani, K. Natural killer cells in antitumour adoptive cell immunotherapy. *Nat. Rev. Cancer* **2022**, *22*, 557–575. [CrossRef]
144. Maskalenko, N.A.; Zhigarev, D.; Campbell, K.S. Harnessing natural killer cells for cancer immunotherapy: Dispatching the first responders. *Nat. Rev. Drug Discov.* **2022**, *21*, 559–577. [CrossRef]
145. Ames, E.; Canter, R.J.; Grossenbacher, S.K.; Mac, S.; Chen, M.; Smith, R.C.; Hagino, T.; Perez-Cunningham, J.; Sckisel, G.D.; Urayama, S.; et al. NK Cells Preferentially Target Tumor Cells with a Cancer Stem Cell Phenotype. *J. Immunol.* **2015**, *195*, 4010–4019. [CrossRef]
146. Kobayashi, H.; Dubois, S.; Sato, N.; Sabzevari, H.; Sakai, Y.; Waldmann, T.A.; Tagaya, Y. Role of trans-cellular IL-15 presentation in the activation of NK cell-mediated killing, which leads to enhanced tumor immunosurveillance. *Blood* **2005**, *105*, 721–727. [CrossRef] [PubMed]
147. Jamali, A.; Hadjati, J.; Madjd, Z.; Mirzaei, H.R.; Thalheimer, F.B.; Agarwal, S.; Bonig, H.; Ullrich, E.; Hartmann, J. Highly Efficient Generation of Transgenically Augmented CAR NK Cells Overexpressing CXCR4. *Front. Immunol.* **2020**, *11*, 2028. [CrossRef] [PubMed]
148. Levy, E.; Reger, R.; Segerberg, F.; Lambert, M.; Leijonhufvud, C.; Baumer, Y.; Carlsten, M.; Childs, R. Enhanced Bone Marrow Homing of Natural Killer Cells Following mRNA Transfection With Gain-of-Function Variant CXCR4R334X. *Front. Immunol.* **2019**, *10*, 1262. [CrossRef]
149. Valeri, A.; García-Ortiz, A.; Castellano, E.; Córdoba, L.; Maroto-Martín, E.; Encinas, J.; Leivas, A.; Río, P.; Martínez-López, J. Overcoming tumor resistance mechanisms in CAR-NK cell therapy. *Front. Immunol.* **2022**, *13*, 953849. [CrossRef]

150. Xie, G.; Dong, H.; Liang, Y.; Ham, J.D.; Rizwan, R.; Chen, J. CAR-NK cells: A promising cellular immunotherapy for cancer. *EBioMedicine* **2020**, *59*, 102975. [CrossRef] [PubMed]
151. Biederstädt, A.; Rezvani, K. Engineering the next generation of CAR-NK immunotherapies. *Int. J. Hematol.* **2021**, *114*, 554–571. [CrossRef] [PubMed]
152. Marofi, F.; Abdul-Rasheed, O.F.; Rahman, H.S.; Budi, H.S.; Jalil, A.T.; Yumashev, A.V.; Hassanzadeh, A.; Yazdanifar, M.; Motavalli, R.; Chartrand, M.S.; et al. CAR-NK cell in cancer immunotherapy; A promising frontier. *Cancer Sci.* **2021**, *112*, 3427–3436. [CrossRef]
153. Tonn, T.; Schwabe, D.; Klingemann, H.G.; Becker, S.; Esser, R.; Koehl, U.; Suttorp, M.; Seifried, E.; Ottmann, O.G.; Bug, G. Treatment of patients with advanced cancer with the natural killer cell line NK-92. *Cytotherapy* **2013**, *15*, 1563–1570. [CrossRef]
154. Podshivalova, E.S.; Semkina, A.S.; Kravchenko, D.S.; Frolova, E.I.; Chumakov, S.P. Efficient delivery of oncolytic enterovirus by carrier cell line NK-92. *Mol. Ther. Oncolytics* **2021**, *21*, 110–118. [CrossRef]
155. Miller, J.S.; Soignier, Y.; Panoskaltsis-Mortari, A.; McNearney, S.A.; Yun, G.H.; Fautsch, S.K.; McKenna, D.; Le, C.; Defor, T.E.; Burns, L.J.; et al. Successful adoptive transfer and in vivo expansion of human haploidentical NK cells in patients with cancer. *Blood* **2005**, *105*, 3051–3057. [CrossRef]
156. Pérez-Martínez, A.; Fernández, L.; Valentín, J.; Martínez-Romera, I.; Corral, M.D.; Ramírez, M.; Abad, L.; Santamaría, S.; González-Vicent, M.; Sirvent, S.; et al. A phase I/II trial of interleukin-15–stimulated natural killer cell infusion after haplo-identical stem cell transplantation for pediatric refractory solid tumors. *Cytotherapy* **2015**, *17*, 1594–1603. [CrossRef] [PubMed]
157. Shaffer, B.C.; Le Luduec, J.B.; Forlenza, C.; Jakubowski, A.A.; Perales, M.A.; Young, J.W.; Hsu, K.C. Phase II Study of Haploidentical Natural Killer Cell Infusion for Treatment of Relapsed or Persistent Myeloid Malignancies Following Allogeneic Hematopoietic Cell Transplantation. *Biol. Blood Marrow Transplant.* **2016**, *22*, 705–709. [CrossRef] [PubMed]
158. 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 Transplant.* **2016**, *22*, 1290–1298. [CrossRef] [PubMed]
159. Nguyen, R.; Wu, H.; Pounds, S.; Inaba, H.; Ribeiro, R.C.; Cullins, D.; Rooney, B.; Bell, T.; Lacayo, N.J.; Heym, K.; et al. A phase II clinical trial of adoptive transfer of haploidentical natural killer cells for consolidation therapy of pediatric acute myeloid leukemia. *J. Immunother. Cancer* **2019**, *7*, 81. [CrossRef]
160. Arai, S.; Meagher, R.; Swearingen, M.; Myint, H.; Rich, E.; Martinson, J.; Klingemann, H. Infusion of the allogeneic cell line NK-92 in patients with advanced renal cell cancer or melanoma: A phase I trial. *Cytotherapy* **2008**, *10*, 625–632. [CrossRef]
161. Bednarski, J.J.; Zimmerman, C.; Berrien-Elliott, M.M.; Foltz, J.A.; Becker-Hapak, M.; Neal, C.C.; Foster, M.; Schappe, T.; McClain, E.; Pence, P.P.; et al. Donor memory-like NK cells persist and induce remissions in pediatric patients with relapsed AML after transplant. *Blood* **2022**, *139*, 1670–1683. [CrossRef]
162. Parihar, R. Memory NK cells to forget relapsed AML. *Blood* **2022**, *139*, 1607–1608. [CrossRef]
163. Romee, R.; Rosario, M.; Berrien-Elliott, M.M.; Wagner, J.A.; Jewell, B.A.; Schappe, T.; Leong, J.W.; Abdel-Latif, S.; Schneider, S.E.; Willey, S.; et al. Cytokine-induced memory-like natural killer cells exhibit enhanced responses against myeloid leukemia. *Sci. Transl. Med.* **2016**, *8*, 357ra123. [CrossRef]
164. Dong, H.; Ham, J.D.; Hu, G.; Xie, G.; Vergara, J.; Liang, Y.; Ali, A.; Tarannum, M.; Donner, H.; Baginska, J.; et al. Memory-like NK cells armed with a neoepitope-specific CAR exhibit potent activity against NPM1 mutated acute myeloid leukemia. *Proc. Natl. Acad. Sci. USA* **2022**, *119*, e2122379119. [CrossRef]
165. Hosseinalizadeh, H.; Habibi Roudkenar, M.; Mohammadi Roushandeh, A.; Kuwahara, Y.; Tomita, K.; Sato, T. Natural killer cell immunotherapy in glioblastoma. *Discov. Oncol.* **2022**, *13*, 113. [CrossRef]
166. Rafei, H.; Daher, M.; Rezvani, K. Chimeric antigen receptor (CAR) natural killer (NK)-cell therapy: Leveraging the power of innate immunity. *Br. J. Haematol.* **2021**, *193*, 216–230. [CrossRef] [PubMed]
167. Tarannum, M.; Romee, R. Cytokine-induced memory-like natural killer cells for cancer immunotherapy. *Stem. Cell Res. Ther.* **2021**, *12*, 592. [CrossRef] [PubMed]
168. Pahl, J.H.W.; Cerwenka, A.; Ni, J. Memory-like NK Cells: Remembering a Previous Activation by Cytokines and NK Cell Receptors. *Front. Immunol.* **2018**, *9*, 2796. [CrossRef] [PubMed]
169. Berrien-Elliott, M.M.; Wagner, J.A.; Fehniger, T.A. Human Cytokine-Induced Memory-like Natural Killer Cells. *J. Innate Immun.* **2015**, *7*, 563–571. [CrossRef]
170. Ljunggren, H.G.; Malmberg, K.J. Prospects for the use of NK cells in immunotherapy of human cancer. *Nat. Rev. Immunol.* **2007**, *7*, 329–339. [CrossRef] [PubMed]
171. Uppendahl, L.D.; Dahl, C.M.; Miller, J.S.; Felices, M.; Geller, M.A. Natural Killer Cell-Based Immunotherapy in Gynecologic Malignancy: A Review. *Front. Immunol.* **2017**, *8*, 1825. [CrossRef] [PubMed]
172. Veluchamy, J.P.; Heeren, A.M.; Spanholtz, J.; van Eendenburg, J.D.; Heideman, D.A.; Kenter, G.G.; Verheul, H.M.; van der Vliet, H.J.; Jordanova, E.S.; de Gruijl, T.D. High-efficiency lysis of cervical cancer by allogeneic NK cells derived from umbilical cord progenitors is independent of HLA status. *Cancer Immunol. Immunother.* **2017**, *66*, 51–61. [CrossRef]
173. Jochems, C.; Hodge, J.W.; Fantini, M.; Fujii, R.; Morillon, Y.M., 2nd; Greiner, J.W.; Padget, M.R.; Tritsch, S.R.; Tsang, K.Y.; Campbell, K.S.; et al. An NK cell line (haNK) expressing high levels of granzyme and engineered to express the high affinity CD16 allele. *Oncotarget* **2016**, *7*, 86359–86373. [CrossRef]

174. Farcas, M.; Inngjerdingen, M. Natural killer cell–derived extracellular vesicles in cancer therapy. *Scand. J. Immunol.* **2020**, *92*, e12938. [CrossRef]
175. Dosil, S.G.; Lopez-Cobo, S.; Rodriguez-Galan, A.; Fernandez-Delgado, I.; Ramirez-Huesca, M.; Milan-Rois, P.; Castellanos, M.; Somoza, A.; Gómez, M.J.; Reyburn, H.T.; et al. Natural killer (NK) cell-derived extracellular-vesicle shuttled microRNAs control T cell responses. *eLife* **2022**, *11*, e76319. [CrossRef]
176. Demaria, O.; Gauthier, L.; Vetizou, M.; Blanchard Alvarez, A.; Vagne, C.; Habif, G.; Batista, L.; Baron, W.; Belaïd, N.; Girard-Madoux, M.; et al. Antitumor immunity induced by antibody-based natural killer cell engager therapeutics armed with not-alpha IL-2 variant. *Cell Rep. Med.* **2022**, *3*, 100783. [CrossRef] [PubMed]
177. Gauthier, L.; Morel, A.; Anceriz, N.; Rossi, B.; Blanchard-Alvarez, A.; Grondin, G.; Trichard, S.; Cesari, C.; Sapet, M.; Bosco, F.; et al. Multifunctional Natural Killer Cell Engagers Targeting NKp46 Trigger Protective Tumor Immunity. *Cell* **2019**, *177*, 1701–1713.e1716. [CrossRef] [PubMed]
178. André, P.; Denis, C.; Soulas, C.; Bourbon-Caillet, C.; Lopez, J.; Arnoux, T.; Bléry, M.; Bonnafous, C.; Gauthier, L.; Morel, A.; et al. Anti-NKG2A mAb Is a Checkpoint Inhibitor that Promotes Anti-tumor Immunity by Unleashing Both T and NK Cells. *Cell* **2018**, *175*, 1731–1743.e1713. [CrossRef] [PubMed]
179. Hoogstad-van Evert, J.S.; Bekkers, R.; Ottevanger, N.; Jansen, J.H.; Massuger, L.; Dolstra, H. Harnessing natural killer cells for the treatment of ovarian cancer. *Gynecol. Oncol.* **2020**, *157*, 810–816. [CrossRef] [PubMed]
180. Rückert, T.; Lareau, C.A.; Mashreghi, M.-F.; Ludwig, L.S.; Romagnani, C. Clonal expansion and epigenetic inheritance of long-lasting NK cell memory. *Nat. Immunol.* **2022**, *23*, 1551–1563. [CrossRef]