Chasing Uterine Cancer with NK Cell-Based Immunotherapies

Subjects: Immunology

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Gynecological cancers, including endometrial adenocarcinoma, significantly contribute to cancer incidence and mortality worldwide. The immune system plays a significant role in endometrial cancer pathogenesis. (uterine) 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.

NK cells uterine cancer endometrial cancer

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][10][11][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][21][22].

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][27][28][29][30][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][35][36][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.

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 [41][42]. A detailed discussion of ILCs and their interaction with adaptive immune cells has been discussed elsewhere [43][44][45]. 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 $Lin^-IL\text{-}7R\alpha^-CD56^{dim}CD16^+$ [46]. NK cells develop from common lymphoid progenitors (CLPs), which also give rise to T and B cells [47]. 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 [48].

NK cells are the third largest lymphocyte population, following T and B cells [49]. 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 [50][51][52]. In addition, NK cells have unique direct cytotoxic action against infected and cancer cells [53][54]62. 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 [55]. 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 [56][57].

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 [58][59]. 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 [60]. 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 [61][62]. 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 [63][64]. KIR expression is also heterogenous due to allelic variation in KIR genes [62].

3. NK Cell-Based Therapies in Different Cancers

Larger tumors have fewer NK cells than less advanced tumors [65], 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 [66][67]. Tumor immunotherapy approaches include stimulating the patient's immune system or in vitro stimulation of immune cells later introduced to the patient [68]. 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 [69]. 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. 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 [70]. NK cell-targeted therapies could be instrumental to fighting resistant ECs, as they have already shown potential in other cancers [71][72]. In addition, NK cells will preferentially kill cancer stem cells over non-cancer stem cells in solid tumors, such as breast or prostate cancer [73]. Given cancer stem cell resilience to traditional cytotoxic cancer treatment, targeted NK cell immunotherapy may be game-changing [73].

Understanding the cytokine milieu may inform NK cell-targeted treatment approaches [57]. Previous pre-clinical studies have successfully used IL-15 to activate NK cells in vitro [56]. High trans-cellular IL-15 alters NKCC in murine colon cancer models, thereby limiting cancer metastasis. 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 [74]. 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 [75]. Another study has also supported that CXCR4 overexpression increases NK cell migration to the target site [76]. Hence, TRACKs and other CAR-NK cell-based immunotherapies have great potential for different tumors, including overcoming the tumor resistance mechanisms [77][78][79][80].

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. 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 [81]. Interestingly, NK-92 has also been shown to be a promising carrier for oncolytic enteroviruses, potentially treating various cancers [82].

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 [83]. This approach has been used safely in other malignancies in phase I and II clinical trials [84][85][86][87][88]. 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 [89][90][91]. Furthermore, memory-like NK cells armed with a neoepitope-specific chimeric antigen receptor (CAR) are potent antitumor immune cells [92]. CAR-NK cell-based therapies can overcome resistant tumors, including glioblastoma [77][93][94]. The details of CIML NK cells are discussed elsewhere [91][95][96][97]. 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.

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