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Review

Natural killer cell immunotherapies against cancer: checkpoint inhibitors and more

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ABSTRACT

After many years of research, recent advances have shed new light on the role of the immune system in advanced-stage cancer. Various types of immune cells may be useful for therapeutic purposes, along with chemical molecules and engineered monoclonal antibodies. The immune effectors suitable for manipulation for adoptive transfer or drug targeting *in vivo* include natural killer (NK) cells. These cells are of particular interest because they are tightly regulated by an array of inhibitory and activating receptors, enabling them to kill tumor cells while sparing normal cells. New therapeutic antibodies blocking the interactions of inhibitory receptors (immune checkpoint inhibitors, ICI) with their ligands have been developed and can potentiate NK cell functions *in vivo*.

1. Introduction

NK cells are a population of innate lymphoid cells (ILCs) that can induce the death of allogeneic and autologous cells undergoing malignant transformation or microbial infection [1]. They account for 5–15% of total peripheral blood mononuclear cells (PBMCs) in humans and they contribute to tumor immunosurveillance through their ability to circulate between peripheral organs. NK cells were shown, years ago, to be important in the anti-tumor response in mice [2,3]. In humans, cases of selective NK cell deficiency are rare and it is difficult to assess the contribution of these cells to the incidence of cancer. However, several studies have revealed the existence of a link between low levels of NK cell activity in peripheral blood and an increase in the risk of cancer [4,5]. In addition, the infiltration of NK cells into tumors has been shown to be associated with a favorable prognosis in non-small cell lung cancer (NSCLC), clear cell renal cell cancer and colorectal cancer [6–8].

NK cells express a repertoire of activating and inhibitory receptors enabling them to detect target cells while sparing normal cells (Fig. 1). The activation status of NK cells is determined by the integration of all these signals [9]. NK cells can detect an absence of major histocompatibility complex (MHC) class I ("missing self") [2] through the expression of KIRs (killer cell immunoglobulin-like receptors) in humans [10] and Ly49 receptors in mice [11]. The KIR gene family has been characterized in detail and shown to include a number of different genes and alleles giving rise to distinct haplotypes. Each receptor recognizes a group of classical HLA class I allotypes with particular features of the α1 domain in common [12]. Inhibitory KIRs signal through the immunoreceptor tyrosine-based inhibitory motif (ITIM) in their cytoplasmic domain [13]. The binding of inhibitory KIRs to their ligands leads to the tyrosine phosphorylation of their ITIMs and activation of the SHP-1 protein tyrosine phosphatase, resulting in an inhibition of NK cell activation. The engagement of NK cell receptors by MHC-I molecules during NK cell maturation is required, for the generation of functional effector cells adapted to the host-specific MHC-I environment; this process is referred to as NK cell education [14]. A related family of receptors recognizing MHC class I molecules, the Ig-like transcripts (ILT) or leukocyte Ig-like receptors (LIR), can be detected on subsets of NK cells. In particular, ILT2 (LIR-1) and ILT4 (LIR-2) contain cytoplasmic ITIMs that recruit SHP-1 and help to control NK cell activation [15]. NK cells also have another inhibitory receptor,

Abbreviations: NK, natural killer; ICI, immune checkpoint inhibitors; ILCs, innate lymphoid cells; PBMCs, peripheral blood mononuclear cells; NSCLC, non-small cell lung cancer; MHC, major histocompatibility complex; KIRs, killer cell immunoglobulin-like receptors; ITIM, immunoreceptor tyrosine-based inhibitory motif; ILT, Ig-like transcripts; LIR, leucocyte Ig-like receptors; MHC, major histocompatibility complex; HLA, human leukocyte antigen; ADCC, antibody-dependent cell-mediated cytotoxicity; TNF, tumor necrosis factor; TRAIL, tumor-necrosis factor-related apoptosis-inducing ligand; IFN, interferon; MCP-1, monocyte chemoattractant protein 1; MIP, macrophage inflammatory protein; RANTES, regulated on activation, normal T cell expressed and secreted; IL, interleukin; GM-CSF, granulocyte-macrophage colony-stimulating factor; mAb, monoclonal antibody; GVHD, graft versus host disease; CAR, chimeric antigen receptor; TGF, transforming growth factor; CLL, chronic lymphocytic leukemia; SHP, Src homology region 2 domain-containing phosphatase; SHIP, phosphatidylinositol-3,4,5-trisphosphate 5-phosphatase; AML, acute myeloid leukemia

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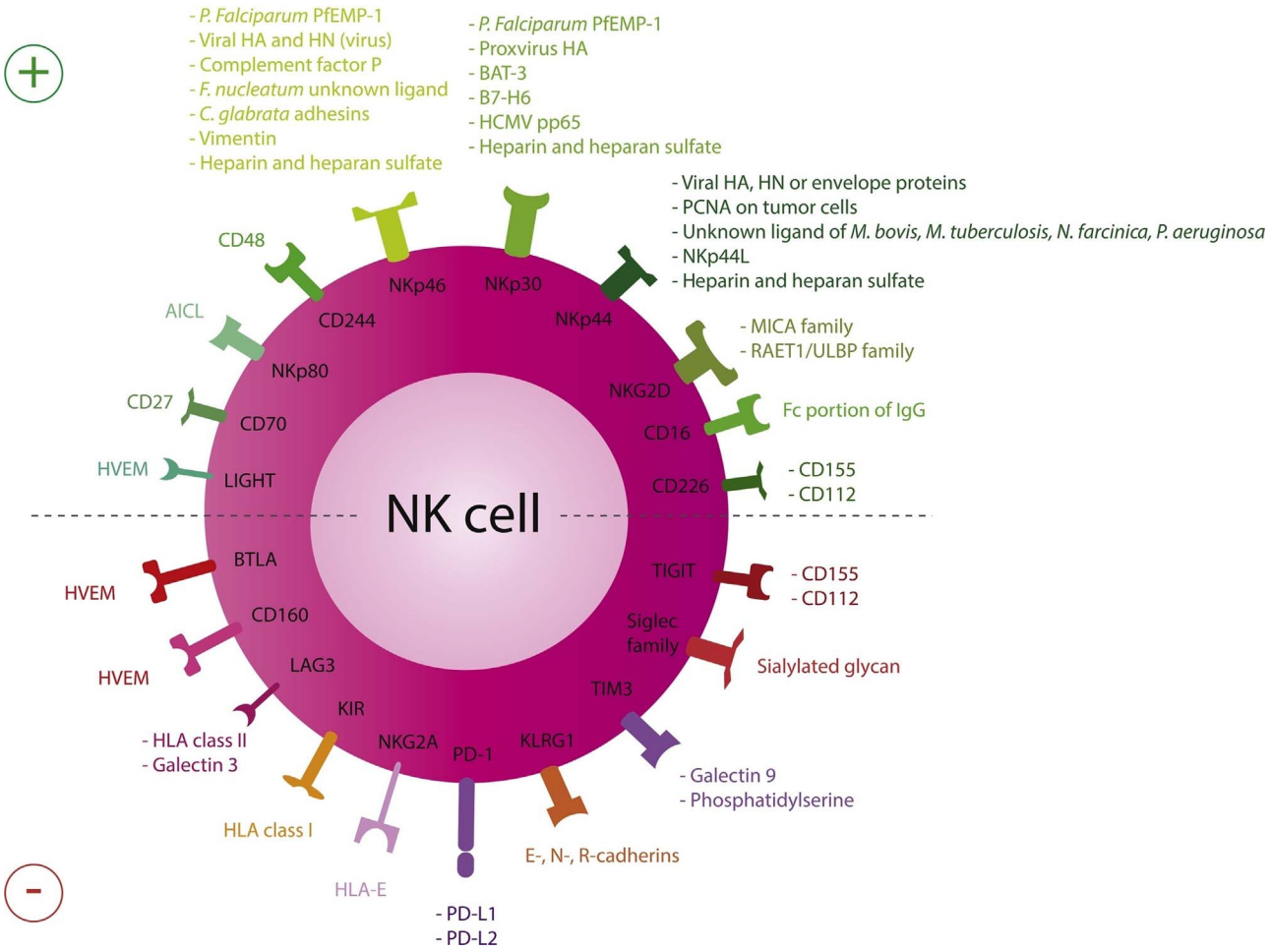

Fig. 1. Human NK cell receptors.
Major activating (green) and inhibitory (red) receptors expressed by human NK cells are reperesented [9,91–94]. Abbreviations: AICL, activation-induced C-type lectin; BAT3, HLA-B-associated transcript 3; HA, hemagglutinins; HIV, human immunodeficiency virus; HN, hemagglutinin neuraminidases; HVEM, herpesvirus entry mediator; LIGHT, homologous to lymphotoxin, exhibits inducible expression and competes with HSV glycoprotein D for binding to herpesvirus entry mediator, a receptor expressed on T lymphocytes; NKp44L, NKp44 ligand; PCNA, proliferating cell nuclear antigen; Plasmodium falciparum erythrocyte membrane protein-1 (PfEMP1).

CD94/NKG2A, which is expressed as a heterodimer in humans and mice. This receptor recognizes the non-classical MHC class I molecules corresponding to HLA-E in humans and Qa-1b in mice. Unlike classical HLA-A, −B, and −C molecules, which bind and present self-peptides, HLA-E binds leader peptides derived from the signal sequences of certain HLA-A, −B, −C and −G molecules. The interaction between CD94/NKG2A complexes and HLA-E molecules therefore allows NK cells to monitor the expression of other MHC-I molecules indirectly [16].

During tumor transformation, cells often present a decrease in MHC-I molecule expression, which identifies them as potential targets for NK cells [17]. However, the destruction of these cells by NK cells also requires the recognition, by activating receptors on the NK cells, of their ligands on the tumor cell membrane. These activating receptors include NKp46, NKG2D, and DNAM-1, in both humans and mice, and NKp30 and NKp44, which are expressed only by human NK cells [18]. NKp30 and NKG2D detect molecules that are not present in the basal state, but for which expression increases in response to stress or pathogen infection. Other surface trigger molecules, such as 2B4, NKp80, NTB-A, and CD59 appear to function as coreceptors. Indeed, they can induce natural cytotoxicity only when co-engaged with a triggering receptor [18]. Most mature NK cells also express CD16 (FcγRIIIA), a low-affinity receptor for the Fc region of G-type immunoglobulins (IgG) responsible for antibody-dependent cell-mediated cytotoxicity (ADCC) [19].

Recognition of the target leads to NK cell activation and degranulation, a process involving the exocytosis of lytic granules containing perforin and granzymes. In addition to this degranulation-dependent pathway, another pathway involving interactions between the TNF family of death receptors and their ligands (such as TRAIL and FasL) may lead to target cell apoptosis [20]. NK cells also secrete pro-inflammatory cytokines, such as IFN-γ and TNFα, which have direct antitumor effects, many chemokines, including MCP-1, MIP1-α, MIP1-β, RANTES, lymphotactin and IL-8 (in decidua), and growth factors, such as GM-CSF, which help to determine the orientation of the adaptive immune response [21].

We discuss here the potential use of NK cells to treat solid and hematopoietic tumors, focusing particularly on the use of infusions of monoclonal antibodies (mAbs) blocking the interactions of inhibitory NK cell receptors with their ligands to enhance NK cell functions *in vivo*.

2. NK cell manipulations in therapeutic approaches

The discovery that NK cells can recognize and lyse tumor cells translated into hope that NK cells could be used as therapeutic tools. Many efforts have been made to exploit NK cells in clinical practice, and more than 200 (see on clinicaltrials.gov) clinical trials have been carried out with the aim of potentiating the effector capacities of these cells *in vivo* [17,22,23].