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Tricking the balance: NK cells in anti-cancer immunity

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ABSTRACT

Natural Killer (NK) cells are classically considered innate immune effector cells involved in the first line of defense against infected and malignant cells. More recently, NK cells have emerged to acquire properties of adaptive immunity in response to certain viral infections such as expansion of specific NK cell subsets and long-lasting virus-specific responses to secondary challenges. NK cells distinguish healthy cells from abnormal cells by measuring the net input of activating and inhibitory signals perceived from target cells through NK cell surface receptors. Acquisition of activating ligands in combination with reduced expression of MHC class I molecules on virus-infected and cancer cells activates NK cell cytotoxicity and release of immunostimulatory cytokines like IFN-γ. In the cancer microenvironment however, NK cells become functionally impaired by inhibitory factors produced by immunosuppressive immune cells and cancer cells. Here we review recent progress on the role of NK cells in cancer immunity. We describe regulatory factors of the tumor microenvironment on NK cell function which determine cancer cell destruction or escape from immune recognition. Finally, recent strategies that focus on exploiting NK cell anti-cancer responses for immunotherapeutic approaches are outlined.

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Introduction

Natural Killer (NK) cells have originally been described to belong to the innate arm of the immune system (Cerwenka and Lanier, 2001). More recently, conventional NK cells have been grouped among the emerging population of innate lymphocytes (ILC) as cytotoxic, interferon-γ (IFN-γ)-producing ILC (Artis and Spits, 2015). There is accumulating evidence that mature NK cells encompass a broad spectrum of phenotypic and functional diversity that may be shaped by epigenetic modifications by DNA methylation of NK cell genes and environmental influences (Bjorkstrom et al., 2010; Horowitz et al., 2013; Juelke et al., 2010; Lee et al., 2015; Luetke-Eversloh et al., 2014; Schlums et al., 2015). This diversity of human NK cells extends the typical $CD56^{bright}CD16^{-}$ (high cytokine producers) and $CD56^{dim}CD16^{+}$ (high cytotoxicity) NK cell subsets found in peripheral blood.

Like adaptive T and B lymphocytes, NK cells are thought to differentiate from the common lymphoid progenitor which arises

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from hematopoietic stem cells in the bone marrow. However, this concept may be more complex since in a recent study in rhesus macaques it was suggested that the $CD56^{dim}CD16^{+}$ NK cell lineage develops from a different progenitor than $CD56^{bright}CD16^{-}$ NK cells, T cells, B cells or myeloid cells (Wu et al., 2014). In the circulation, NK cells constitute 5–15% of peripheral blood lymphocytes in adult healthy individuals and can be detected at variable levels in peripheral tissues such as in the liver and the lung (Cerwenka and Lanier, 2001). Typically, NK cells are involved in the first line of defense against infection and cancer. NK cells were discovered in the 1970s as large granular lymphocytes distinct to B and cytotoxic T lymphocytes with the ability to kill virus-induced murine leukemic cells without the need for prior sensitization to these target cells (Herberman and Ortaldo, 1981; Kiessling et al., 1975). NK cells distinguish stressed, transformed and infected cells from healthy cells through an array of germline-encoded inhibitory, activating and adhesion receptors expressed on their cell surface (Vivier et al., 2011). In contrast to NK cells, adaptive T and B lymphocytes acquire a broad repertoire of antigen specificities by RAG recombinase-driven somatic recombination of their T and B cell receptor genes. Acquisition of NK cell receptors is independent of gene rearrangements. Yet, RAG proteins appear to play a critical role in NK cell functionality, since the lack of RAG1/2 activity during ontogeny affects genome stability and susceptibility to apoptosis of murine NK cells (Karo et al., 2014).

In the classical model of NK cell activation, NK cells are defined to respond to target cells with a reduced expression of MHC class I molecules, or an incomplete or incompatible repertoire of MHC class I molecules; a concept termed the 'missing-self hypothesis' (Karre et al., 1986; Vivier et al., 2008). Accordingly, NK cells recognize cells with a 'non-self' history such as from an allogeneic or haploidentical hematopoietic stem cell transplant. NK cells respond to virus-infected and malignant cells that frequently have reduced MHC class I expression. In addition, the responsiveness of NK cells is modulated by a complex spectrum of inhibiting and activating signals from target and accessory cells and their pro- and anti-inflammatory microenvironment (Fig. 1). Upon activation towards target cells, NK cells release cytotoxic proteins from pre-formed cytoplasmic granules by exocytosis into the immunological synapse at the NK–target cell interface (Krzewski and Strominger, 2008). After entry into the cytoplasm *via* the pore-forming protein perforin, members of the granzyme family of serine-proteases mediate target cell apoptosis through caspase-dependent and -independent pathways. In addition, target cell apoptosis can be mediated by Fas ligand or 'tumor necrosis-factor–related apoptosis-inducing ligand' (TRAIL) expressed on the cell surface or released from the cytoplasmic granules of NK cells (Smyth et al., 2005a,b). In this context, PTEN was shown to be a negative regulator of NK cell cytotoxicity by limiting actin accumulation, polarization of the microtubule organizing center, and the convergence of cytolytic granules at the NK–target cell interface (Briercheck et al., 2015).

NK cells are considered to bridge innate and adaptive immunity by the secretion of IFN-γ, which enhances MHC class I expression on tumor cells and MHC class II expression on antigen-presenting cells like monocytes/macrophages and dendritic cells (Vivier et al., 2008). Aside from their role in initial responses against infection and cancer, it has become evident, that NK cells also contribute to the induction of adaptive anti-cancer T cell as well as B cell responses (Diefenbach et al., 2001; Kelly et al., 2002; Krebs et al., 2009; Smyth et al., 2005a,b). In addition, NK cells can exert immunoregulatory functions under certain conditions. Several reports have shown that NK cells control the number of dendritic cells and activated CD4 and CD8 T cells and constrain the formation of memory T and B cell responses, as observed in murine lymphocytic choriomeningitis virus and cytomegalovirus infection models (Crouse et al., 2014; Ferlazzo et al., 2002; Narni-Mancinelli et al., 2012; Rydyznski et al., 2015; Schuster et al., 2014; Soderquest et al., 2011; Waggoner et al., 2012, 2014; Xu et al., 2014). Hence, to some extent NK cells are able to prevent excessive immune activation and autoimmune pathology. Their classification as solely innate immune cells is currently further challenged since there is now evidence that under certain conditions NK cells can acquire similarities to adaptive immunity such as expansion of specific subsets and antigen-specific responses, as will be further discussed below (Sun et al., 2014).

Regulation of NK cell activity

During development, NK cells that fail to express inhibitory receptors to at least one 'self' MHC class I type are rendered anergic to prevent reactivity against healthy 'self' cells; a concept referred to as 'education' or 'licensing' (Anfossi et al., 2006; Kim et al., 2005). NK cells that express inhibitory receptors in combination with activating receptors are able to react against abnormal 'non-self' cells. Transfer of NK cells from an MHC class I-sufficient mouse to an MHC class I-deficient mouse (and vice versa) can reset NK cell responsiveness (Elliott et al., 2010; Joncker et al., 2010). Hence, the fate of reactivity or hyporesponsiveness of mature NK cells appears to be continuously modulated by trafficking through environments with changing levels of inhibitory molecules. Consistent with this hypothesis, persistent failure of engaging inhibitory receptors in an MHC class I-deficient tumor microenvironment reduces NK cell responsiveness unless NK cell are re-stimulated with NK cell-activating cytokines like interleukin-2 (IL-2) or IL-12/18 (Ardolino et al., 2014).

Target cell recognition by NK cells is regulated by the net input of inhibitory and activating signals perceived through NK cell receptor and target cell ligand interactions (Gasser and Raulet, 2006; Moretta et al., 2006). Thus, lysis of cancer cells is triggered by low expression of ligands for NK cell inhibitory receptors, such as killer cell immunoglobulin-like receptors (KIR), TIGIT and CD96, in combination with induced/increased expression of ligands for NK cell activating receptors, such as NKG2D, DNAM-1 and 'natural cytotoxicity receptors' (NCR). HLA-A/B/C molecules bind to inhibitory KIR receptors (Thielens et al., 2012). The non-classical HLA-E molecule, presenting MHC class I-derived leader peptides, binds to the lectin-like inhibitory CD94–NKG2A receptor complex as well as to the activating CD94–NKG2C receptor complex (Braud et al., 1998; Kabat et al., 2002). The inhibitory KIR receptors and NKG2A contain cytoplasmic 'immunoreceptor tyrosine-based inhibitory motif' (ITIM). NK cells express numerous activating receptors that engage 'stress'-induced ligands. These ligands are normally not expressed on healthy cells under non-inflammatory conditions but can be induced, for instance, in response to DNA damage as demonstrated for NKG2D ligands (Gasser et al., 2005). Human NKG2D binds to 'MHC class I chain-related genes' MICA and MICB as well as to the 'UL-binding proteins' ULBP1–6 and signals through the adaptor protein DAP10 (Bacon et al., 2004; Bauer et al., 1999; Chalupny et al., 2003; Cosman et al., 2001; Eagle et al., 2009). Murine NKG2D binds to its murine ligands retinoic acid early inducible 1 (Rae-1), ULBP-like transcript (MULT-1) and minor histocompatibility antigen H60 and signals through DAP10 and DAP12 (Cerwenka et al., 2000; Diefenbach et al., 2000; Ullrich et al., 2013). The co-stimulatory adhesion receptor DNAM-1 binds to CD112 and CD155 and recruits the tyrosine kinase Fyn and the serine–threonine kinase PKC (Bottino et al., 2003; Martinet and Smyth, 2015). Activation through DNAM-1 is counteracted by the inhibitory receptors TIGIT (ITIM motif) and CD96 (ITIM-like motif), sharing the common ligands CD112/CD155 and CD155, respectively (Chan et al., 2014; Stanietsky et al., 2009). B7-H6 was the first identified