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Review

Human NK cell response to pathogens

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ABSTRACT

NK cells represent important effectors of the innate immunity in the protection of an individual from microbes. During an NK-mediated anti-microbial response, the final fate (survival or death) of a potential infected target cell depends primarily on the type and the number of receptor/ligand interactions occurring at the effector/target immune synapse. The identification of an array of receptors involved in NK cell triggering has been crucial for a better understanding of the NK cell biology. In this context, NCR play a predominant role in NK cell activation during the process of natural cytotoxicity. Regarding the NK-mediated pathogen recognition and NK cell activation, an emerging concept is represented by the involvement of TLRs and activating KIRs.

NK cells express certain TLRs in common with other innate cell types. This would mean that specific TLR ligands are able to promote the simultaneous and synergistic stimulation of these innate cells, providing a coordinated mechanism for regulating the initiation and amplification of immune responses.

Evidences have been accumulated indicating that viral infections may have a significant impact on NK cell maturation, promoting the expansion of phenotypically and functionally aberrant NK cell subpopulations. For example, during chronic HIV-infection, an abnormal expansion of a dysfunctional CD56neg NK cell subset has been detected that may explain, at least in part, the defective NK cell-mediated antiviral activity. An analogous imbalance of NK cell subsets has been detected in patients receiving HSCT to cure high risk leukemias and experiencing HCMV infection/reactivation. Remarkably, NK cells developing after CMV reactivation may contain "memory-like" or "long-lived" NK cells that could exert a potent anti-leukemia effect.

1. Introduction

Innate and adaptive immune responses cooperate to protect the host against microbial infections [1–3]. NK cells are innate immune cells whose function is critical in the first-line of defense against different types of pathogens, including viruses, bacteria and fungi [4,5]. Pathogen recognition by NK cell is mediated by different types of receptors, including Toll-like receptors (TLRs), that display broad specificities for conserved and invariant features of microorganisms, and a series of activating receptors, able to recognize specific ligands on infected/transformed cells [6,7]. NK cells also express inhibitory receptors that may counteract the function of activating receptors. The expression or the lack of ligands specific for inhibitory or activating NK receptors by target cells is thought to determine the final outcome, i.e. to determine whether a given target cell will be killed or spared by NK cells [8–12].

NK cells can also respond to signals/cytokines derived from accessory cells including IL-12 which is crucial for IFN-γ production in response to various pathogen-associated TLR agonists [13,14].

Remarkably, several recent studies reported that during infection with some viruses, a progressive, impairment of NK cell function may occur as a consequence of a progressive perturbation of NK cell compartment [15–17].

In this review, we will discuss some of the molecular mechanisms by which NK cells recognize pathogens or virus-infected cells, mediate appropriate innate immune effector responses

Abbreviations: HIV, human immunodeficiency virus; HCMV, human cytomegalovirus; MCMV, murine cytomegalovirus; HSCT, hematopoietic stem cell transplantation; TLRs, Toll-like receptors; PRR, pattern recognition receptor; PAMPs, pathogen-associated molecular pattern; poly I:C, polyinosinic–polycytidylic acid; NCR, natural cytotoxicity receptor; BCG, bacillus Calmette-Guerin; UCBT, umbilical cord blood transplantation; SOT, solid organ transplantation; PB, peripheral blood.

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and favor the development of efficacious downstream adaptive immune responses to viral antigens. In this context, the impact of human CMV (HCMV) infection on NK cell development and function will be analyzed in more detail. In addition, we will describe some aberrant redistribution of dysfunctional NK cell subsets, during HIV or HCMV infection/reactivation [17–19].

2. NK and TLRs

2.1. TLR-mediated recognition of pathogens by NK cells

TLRs are germ-line encoded pattern-recognition receptors (PRRs) that are essential for the recognition of invading pathogens, triggering of innate responses and shaping of subsequent adaptive immune responses [20,21]. Currently, at least 11 mammalian TLRs have been identified, but only nine have been well characterized. Each TLR has a broad specificity for conserved molecular structures that are unique to microorganisms. These targets are referred to as pathogen associated molecular patterns (PAMPs), although they may actually be components of both pathogenic and non-pathogenic microorganisms. PAMPs include: lipopolysaccharide (LPS), an essential structure of the outer membrane of Gram-negative bacteria, which is recognized by TLR4; bacterial lipoproteins and lipoteichoic acids, recognized by TLR2; flagellin, a bacterial protein recognized by TLR5; microbial unmethylated CpG DNA motifs, recognized by TLR9; double-stranded RNA (dsRNA), recognized by TLR3; and single-stranded RNA (ssRNA), recognized by TLR7/TLR8 [20].

TLRs are expressed on various cells of the innate immunity, including NK cells [1], monocytes/macrophages [22], neutrophils [22], basophils [23], eosinophils [24], myeloid dendritic cells (DCs) [25], plasmacytoid DCs (pDCs) [25] and mast cells [6,26]. TLR expression is dependent on the cell type and in most instances, a given cell type expresses a small number of TLR. Moreover, TLRs differ in their signal transduction pathways. Certain TLRs (TLR1,2,4,5,6) are expressed on the cell surface, whereas others (TLR3,7,8,9) are localized in intracellular compartments (i.e. endosomes). Therefore, their ligands require internalization to generate signals [21].

Upon recognition of PAMPs, TLRs initiate a signaling cascade resulting in activation of tissue-resident innate cells (such as DCs, macrophages and mast cells) and in chemokine secretion. In turn, these factors recruit circulating leukocytes to the site of infection which further limit the spread of invading pathogens [1,21]. Among the recruited cells, an important role is played by NK cells, that, once reached the inflammatory sites, require activation in order to carry out their function [27]. NK cell activation occurs through different mechanisms, including engagement of different triggering NK cell receptors or recognition of appropriate ligands on transformed cells, and/or stimulation via TLRs [1]. NK cells express different functional TLRs, independent of their state of activation, including TLR2 [28,29], TLR3 [30,31], TLR5 [32], TLR7/8 [33,34] and TLR9 [30]. Thus, responses to TLR ligands occur in both fresh and IL-2-activated NK cells and, in most instances, are sharply increased in the presence of inflammatory cytokines, primarily IL-12. TLRs can activate NK cell function either directly or in cooperation with accessory cells in a cytokine or cell-to-cell contact-dependent manner [13] (Fig. 1).

Because certain TLRs are shared by different innate cells that participate to the early phases of an immune response, certain PAMPs are able to promote the simultaneous and synergistic stimulation of these cells. For example, since both NK cells and DCs express TLR3, the engagement of such receptor may represent a crucial step for promoting the cross-talk between these cells in peripheral tissues. In particular, in the presence of IL-12 (released by DCs upon TLR3 engagement), NK cells respond via TLR3 to dsRNA by increasing their anti-tumor/anti-viral cytotoxicity and acquire also the ability to kill immature DCs (iDCs). This activity favors the selective survival of mature DCs (NK cell-mediated 'editing' of DCs) [30]. Moreover, upon TLR stimulation, NK cells greatly increase their capability of secreting pro-inflammatory cytokines (such as TNF-α and IFN-γ), which promote further DC maturation and subsequent induction of Th1 responses in lymph nodes [35–37].

Remarkably, NK cell populations, derived from different donors may respond to TLR3 stimulation with different efficiency. Such heterogeneous response to poly I:C, a classic TLR3 ligand, has been explained with the observation that the percentage of NK cells expressing high levels of TLR3 mRNA transcripts may vary in different donors. Moreover, the analysis of NK cell clones revealed that heterogeneity exists not only among different donors, but also among NK cell clones derived from the same individual [38]. It has also been shown that NK cell clones expressing low levels of Natural Cytotoxicity Receptors [39–41](NCR dull phenotype) that are poorly cytotoxic, can up-regulate their cytolitic activity upon TLR3 engagement provided that they express high levels of TLR3 mRNA transcript. This capability of responding to TLR3 ligands may be critical in the context of some pathologic conditions, including HIV infection [42] or acute myeloid leukemia (AML) [43], in which down-regulation of NCR expression may represent a mechanism by which virus-infected or tumor cells escape NK-mediated lysis.

Notably, NK cells also express functional TLR9, which are present in pDCs, but not in conventional DCs. Thus, stimuli acting on TLR9 are able to simultaneously activate both NK cells and pDCs [44]. In particular, IFN-α, released by pDCs upon TLR9 engagement, may play an important role in supporting the activation of TLR9-responsive NK cells [45]. Moreover, the exposure of NK cells to IL-12 (produced by DCs) amplifies the response and further potentiates NK-mediated induction of IFN-α release by pDCs [46].

Also TLR2 is expressed by NK cells and other innate cells (including monocytes/macrophages and DCs). This TLR binds to products of bacterial origin. In particular, a direct involvement of TLR2 in the recognition of Mycobacterium tuberculosis by NK cells has been clearly demonstrated [29,47] (see Section 2.2).

Flagellin the TLR5 ligand, can directly act on NK cells by inducing the secretion of IFN-γ and α-defensins that contribute, respectively, to activate accessory cells (e.g., macrophages) and to exert an anti-microbial effect. In turn, accessory cells, activated by PAMPs and/or cytokines present in the inflammatory microenvironment, can release other cytokines (e.g., IL-12 and IL-2), which may modulate PAMP-mediated activation of NK cell effector functions [32].

Finally, Hart et al. demonstrated that human NK cells may also express functional TLR7 and TLR8 [33]. In this regard, Alter et al. showed that NK cells may be significantly activated by the TLR7/8 ligand uridine-rich ssRNA derived from HIV. The functional activation of NK cells is strictly dependent on the direct contact of NK cells with pDCs or $CD14^+$ monocytes resulting in increased IFN-γ secretion [34].

All these data indicate that, although in some cases NK cells can be directly activated by some TLR agonists, both the cross-talk with other innate cells (in particular DCs) and the cytokine milieu may play a crucial role in the activation of their effector function. Thus, NK cells, in addition to a direct TLR-engagement, require appropriate costimulatory signals, to elicit an optimal response, capable of modulating downstream adaptive immune responses [6,48] (Fig. 1).

2.2. Direct recognition of BCG by human NK cells

A number of experimental evidences indicate that NK cells are the main responsible of the anti-tumor responses induced