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Short Review

Natural killer cells in host defense against veterinary pathogens

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ABSTRACT

Natural Killer (NK) cells constitute a major subset of innate lymphoid cells that do not express the T- and B-cell receptors and play an important role in antimicrobial defense. NK cells not only induce early and rapid innate immune responses, but also communicate with dendritic cells to shape the adaptive immunity, thus bridging innate and adaptive immunity. Although the functional biology of NK cells is well-documented in a variety of infections in humans and mice, their role in protecting domestic animals from infectious agents is only beginning to be understood. In this article, we summarize the current state of knowledge about the contribution of NK cells in pathogen defense in domestic animals, especially cattle and pigs. Understanding the immunobiology of NK cells will translate into strategies to manipulate these cells for preventive and therapeutic purposes.

Contents

1. Introduction

Innate lymphoid cells (ILCs) represent a family of lymphoid cells that do not express the antigen-specific receptors (Artis and Spits, 2015). These cells play crucial roles in microbial immunity, autoimmunity, inflammation, and homeostasis (Walker et al., 2013). Broadly, ILCs are classified into 2 groups – cytotoxic and non-cytotoxic ILCs. The cytotoxic ILCs are comprised of natural killer (NK) cells, whereas the non-cytotoxic ILCs can be subclassified into 3 groups – group 1, 2, and 3 ILCs – based on their cytokine and transcriptional profile (Artis and Spits, 2015; Lanier, 2013). Group 1 ILCs (ILC1s) secrete type 1 cytokines (IFN-γ and TNF-α) and require Tbet for their development and function. They have been implicated in host defense against microbial pathogens, including bacteria and parasites. Group 2 ILCs (ILC2s), which are characterized by the production of a range of type 2 cytokines (IL-4, IL-5, and IL-13) and expression of GATA3, exert type 2 immunity that is critical for protective immunity, allergy, and tissue formation (Walker et al., 2013). In addition, group 3 ILCs comprise ILC3s and lymphoid tissue-inducer T (LTi) cells that mainly produce IL-17 and/or IL-22 and are dependent on RORγt. ILC3s elicit immunity against bacterial pathogens, promote inflammation, and augment tissue generation (Spits et al., 2013).

Natural killer (NK) cells are the most widely studied subset of ILCs conserved among all mammalian species (Trinchieri, 1989). Because of their ability to induce early and rapid immune responses, NK cells are considered as a first line of defense against microbial pathogens. Spontaneous production of effector cytokines and robust cytotoxic activity are important functional

Abbreviations: NK, natural killer cell; DC, dendritic cell; NO, nitric oxide; IFN-γ, interferon-γ; TNF-α, tumor necrosis factor-α; Ab, antibody; Ag, antigen; UC, uninfected cell; IC, infected cell; P, intracellular pathogen; T, T cell; ADCC, antibody-dependent cell-mediated cytotoxicity; KIR, killer inhibitory receptor; MHC-I, major histocompatibility complex-I.

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characteristics of NK cells (Hamerman et al., 2005; Vivier, 2006). Recent studies further indicate that the function of NK cells is much more sophisticated and broader than previously thought. Cooperation between NK and dendritic cells (DCs) not only regulates innate immunity but also dictates the direction and intensity of adaptive immunity (Münz et al., 2005). Most of what is known about NK-cell-mediated immunity to microbial infections comes from mice and human studies. However, the role of NK cells in pathogen defense in domestic animals is still unclear, mainly due to interspecies variations and limited availability of specific reagents and transgenic/knockout for these animals. Herein we review the current literature on the role of NK cells in inducing immunity against various pathogens in domestic animals, particularly cattle and pigs. Taking into account the worldwide veterinary and zoonotic significance of infectious diseases in domestic animals, it is crucial to better understand the immunobiology of NK cells for prophylactic and therapeutic purposes.

2. Phenotype and function of NK cells

NK cells are large granular lymphocytes that do not express T- and B-cell receptors. They constitute 5–10% of the total lymphocytes in the tissues such as the liver, lung and blood (Trinchieri, 1989; Inngjerdingen et al., 2011). Phenotypically, NK cells are characterized as CD3−CD56+CD8+ and CD3−CD56−CD11b+ lymphocytes in humans and mice, respectively (Inngjerdingen et al., 2011). In pigs, NK cells are characterized as perforin+CD3−CD4−CD5−CD6−CD8α+CD8β−CD11b+CD16+ (Denyer et al., 2006; Pintaric et al., 2008). Recently, porcine CD3−CD8α+ and CD8α$^{dim/-}$NKp46^{high} NK-cell subsets were reported to have distinct functional features (Mair et al., 2013). Using anti-bovine antibodies against NKp46, NK cells have been characterized as NKp46+CD3−CD2−CD25+CD8+ cells in cattle (Storset et al., 2004). Similar to bovine NK cells, Connelley et al. identified a population of ovine NKp46+ lymphocytes that show the characteristics of NK cells (Connelley et al., 2011).

NK cells express various activating (e.g. Ly49 and CD94) and inhibitory (e.g. killer-cell immunoglobulin-like receptors and leukocyte inhibitory receptors) receptors that do not undergo rearrangement. These receptors recognize their cognate ligands on the surface of infected cells, and the complex interplay between them determines the activation of NK cells (Finton and Strong, 2012). The mechanisms by which NK cells execute their effector functions include cytotoxicity, antibody-dependent cell-mediated cytotoxicity (ADCC), production of cytokines, and modulation of DCs (Vivier, 2006; Münz et al., 2005; Inngjerdingen et al., 2011). NK cells are able to recognize and kill the virus-infected cells that reduce or lack the expression of MHC-I antigens, often termed as missing self-hypothesis, through perforin and granzyme production (Fig. 1A) (Kärre et al., 1986; Ljunggren and Kärre, 1985; Lanier, 2005). Moreover, cytokines produced by NK cells such as IFN-γ and TNF-α contribute to the activation of macrophages to induce antimicrobial killing mechanisms, e.g. inducible or type-2 nitric oxide synthase (Fig. 1B) (Bogdan, 2001; Stetson et al., 2003; Laouar et al., 2005; Prajeeth et al., 2011). In ADCC, specific antibodies bind to their cognate antigens recognized by CD16 (FcYRIII) receptors expressed on NK cells, resulting in release of cytolytic granules, such as perforin and granzyme, and consequent apoptosis of aberrant cells like virus-infected and tumor cells (Fig. 1C) (Lanier, 2005).

Bidirectional communication between NK cells and DCs is crucial for induction of optimal immunity. Activation of NK cells causes DC maturation through cell-to-cell contact, cytokine production and receptor-ligand interactions (Walzer et al., 2005). Mature DCs secrete a variety of cytokines, such as IL-12, IL-23, IL-6, IL-21, IL-27, and TGFβ. IL-12 induces the differentiation of naïve T cells into Th1 cells, which are characterized by the production of IFN-γ and TNF-α, through activation of STAT4 (Walsh and Mills, 2013; Szabo et al., 2003). Although TGFβ, IL-6, and IL-21 are involved in development of Th17 cells by activating transcription factors like STAT3 and RORγt, IL-23 is important for promoting the maintenance of Th17 cells (Korn et al., 2009). However, IL-27, a member of IL-12 family, has been shown to suppress Th1/Th17 immunity (Kastelein et al., 2007). These cytokine signals from NK-cell-activated DCs control the T-cell responses (IFN-γ/IL-17) against viruses and intracellular bacteria. Moreover, NK cells modulate the DC-mediated T cell responses that induce the killing of infected cells through perforin and granzyme pathway (Fig. 1D). However, in addition to reportedly enhancing DC function, NK cells can also negatively regulate DCs by causing lysis of immature DCs (Inngjerdingen et al., 2011; Lanier, 2005). On the other hand, DCs can activate NK cells through cytokine signals and cell-to-cell contact. Cytokines produced by DCs such as IL-12, IL-18, IL-15, and IFN-α/β promote cytotoxicity and IFN-γ production by and proliferation of NK cells (Walzer et al., 2005). In addition, NK-cell activation by DCs requires a contact between these cell types that involves the formation of stimulatory synapses (Borg et al., 2004).

Recent studies have highlighted a unique role for NK cells in presenting antigens to naïve T cells. Activated mouse NK cells have been reported to express MHC-II molecules (Spits and Lanier, 2007; Blasius et al., 2007). Nakayama et al. demonstrated that MHC-II+ NK cells are generated by intercellular transfer of antigen-MHC-II complex from murine DCs to NK cells through a process referred to as trogocytosis. Furthermore, the MHC-II+ NK cells present antigen-MHC-II complexes to CD4+ T cells for regulating adaptive immunity (Nakayama et al., 2011). Similar to the antigen-presenting role of NK cells, ILC2s express MHC-II and prime T cells to produce IL-2, which in turn induces type 2 responses that contribute to anti-parasitic immunity (Oliphant et al., 2014). Overall, these findings suggest that ILCs including NK cells can perform additional functions such as antigen presentation under certain conditions.

3. NK cells in host defense against viral pathogens

The function of NK cells has been critically examined during infections of animals with foot-and-mouth disease virus (FMDV), a picornavirus that afflicts cloven-hoofed animals including cattle and pigs with significant morbidity and mortality (Toka and Golde, 2013). Initial studies using in vitro systems demonstrated that the stimulation of porcine NK cells with proinflammatory cytokines, in particular IL-2 and IL-15, not only activated these cells to express higher levels of IFN-γ and perforin but also induced the lysis of FMDV-infected cells, suggesting a protective role for porcine NK cells in FMDV infection (Toka et al., 2009). Similar anti-viral function was observed upon stimulation of these cells with TLR7/8 agonists (Toka et al., 2009a). In contrast to these in vitro findings, Toka et al. found a significant reduction in the proportion of NK cells, which had the ability to produce IFN-γ and store perforin, in pigs following infection with the o1 Campos strain of FMDV (Toka et al., 2009b). The NK cells isolated from the infected-pigs showed reduced lysis of target cells compared to the NK cells from uninfected animals. This reduced lytic ability of NK cells however could not be restored with in vitro TLR-agonist-stimulations (Toka et al., 2009b). In line, NK-cell functions are reported to be compromised during porcine respiratory and reproductive syndrome virus (PRRSV), and African swine fever virus (ASFV) infections (Jung et al., 2009; Hulst et al., 2013; Manickam et al., 2013; Renukaradhya et al., 2010). In addition, co-infection with PRRSV and porcine respiratory corona virus synergistically inhibited the NK-cell-mediated cytotoxicity (Fan et al., 2013). These in vivo data taken together indicate an inhibitory effect of viral infections on porcine NK-cell function