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Review

NK cells controlling virus-specific T cells: Rheostats for acute vs. persistent infections

Raymond M. Welsh*, Stephen N. Waggoner

Department of Pathology and Program for Immunology and Virology, University of Massachusetts Medical School, 55 Lake Avenue North, Worcester, MA 01655, USA

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ABSTRACT

Viral infections characteristically induce a cytokine-driven activated natural killer (NK) cell response that precedes an antigen-driven T cell response. These NK cells can restrain some but not all viral infections by attacking virus-infected cells and can thereby provide time for an effective T cell response to mobilize. Recent studies have revealed an additional immunoregulatory role for the NK cells, where they inhibit the size and functionality of the T cell response, regardless of whether the viruses are themselves sensitive to NK cells. This subsequent change in T cell dynamics can alter patterns of immunopathology and persistence and implicates NK cells as rheostat-like regulators of persistent infections.

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Introduction

Natural killer (NK) cells and T cells are regulatory and effector lymphocytes that get mobilized into the host response to viral infections. NK cells are cytotoxic antiviral cytokine-producing lymphocytes whose activities are regulated by cytokines and by a number of stochastically-expressed positive- and negative-signaling NK receptors (NKR) that recognize cellular stress-related molecules, adhesion molecules, and major histocompatibility complex (MHC) proteins (Lanier, 2008; Raulet, 2003). Some NKR have even evolved to directly recognize certain viral proteins (Daniels et al., 2001; Lee et al., 2001; Brown et al., 2001; Voigt et al., 2003). T cells, on the other hand, express randomly generated and clonally distributed T cell receptors (TCR) that recognize processed viral peptide epitopes presented to them in the grooves of MHC molecules expressed on the surface of antigen-presenting cells (Wilson et al., 2004). The activated T cells can be similar to NK cells in their acquisition of cytotoxic and

* Corresponding author. Fax: +1 508 856 0019.
E-mail address: Raymond.Welsh@umassmed.edu (R.M. Welsh).

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cytokine-producing effector functions; this is especially true for the CD8 T cells, which recognize peptide epitopes presented by class 1 MHC molecules. The activated CD4 T cells, which recognize peptides presented by class 2 MHC molecules, can secrete factors that regulate the T cells and the rest of the immune response in positive or negative ways. NK cells patrol the host at a moderate state of activation and at a relatively high frequency (~15% of peripheral blood lymphocytes), but will proliferate and become even more active during a viral infection (Biron et al., 1983; Welsh, 1978). However, immunologically naïve T cells specific to any peptide epitope exist at low frequency (~1/50,000) and in an inactive naïve state and require a substantial clonal expansion to increase in numbers and functions sufficient to control of infection (Blattman et al., 2002; Seedhom et al., 2009). Innate cytokines such as the type 1 interferons (IFN), IL-12, and IL-15 are rapidly induced during viral infections and can stimulate the activation and proliferation of NK cells and greatly augment the proliferation of T cells (Biron, 1995). The dynamics of this process follow the innate and adaptive immune response paradigm, first described in the 1970s: an early cytokine-driven activated NK cell innate response followed by a peak in clonally expanded T cells (Fig. 1) (Welsh, 1978).

The temporal relationship between the early activated NK cell vs. late T cell peak has historically engendered questions about whether these cell populations were influencing each other. Certainly, the T cell response may clear the pathogen that induces the cytokines that the NK cells need to stay highly active and proliferating. That is probably not the entire explanation of the waning of the NK cell response, however, as some work has shown that TGFβ made late in the response has a more suppressive effect on NK cells than T cells (Su et al., 1991). In the other direction, a number of papers described later have proposed that NK cells may either enhance or inhibit the T cell response, and earlier papers even suggested that the NK cells may turn into T cells! We can dismiss that latter suggestion, as it is now clear that NK cells and T cells represent different lineages, but the question of how well NK cells control T cells has recently come to the forefront. It would not be out of the question to think that NK cells could promote T cell proliferation, as they produce IFNγ, which itself can promote CD8 T cell expansion (Whitmire et al., 2007). Also, NK cells might indirectly promote T cell expansion by directly controlling viral load early in infection, thereby inhibiting the levels of virus that might cause immune suppression (Bukowski et al., 1984). It should also be of no surprise that NK cells could affect T cells in a negative way. T cell targets such as mouse YAC-1 cells were among the earliest target cells used in cytotoxicity assays to detect the activity of NK cells (Salazar-Onfray et al., 1997), and primary thymocytes were among the first documented targets in vivo (Hansson et al., 1980, 1979. Recent work has indicated that in the context of a viral infection the NK cells have the capacity to directly kill or indirectly regulate the numbers and activities of antiviral CD4 and CD8 T cells (Su et al., 2001; Waggoner et al., 2010, 2012; Lang et al., 2012; Narni-Mancinelli et al., 2012; Andrews et al., 2010; Robbins et al., 2007; Mitrovic et al., 2012; Ge et al., 2012; Lee et al., 2009; Stadnisky et al., 2011). As a consequence of this activity, NK cells may serve as rheostats regulating the T cells that control whether an infection becomes resolved, persistent, or lethal.

Patterns of viral pathogenesis and persistence

Viral infections can present themselves in many forms. Many acute viral infections induce sterilizing T and B cell immune responses that clear the infection, form long term memory, and leave the host resistant to re-infection. Other infections, such as

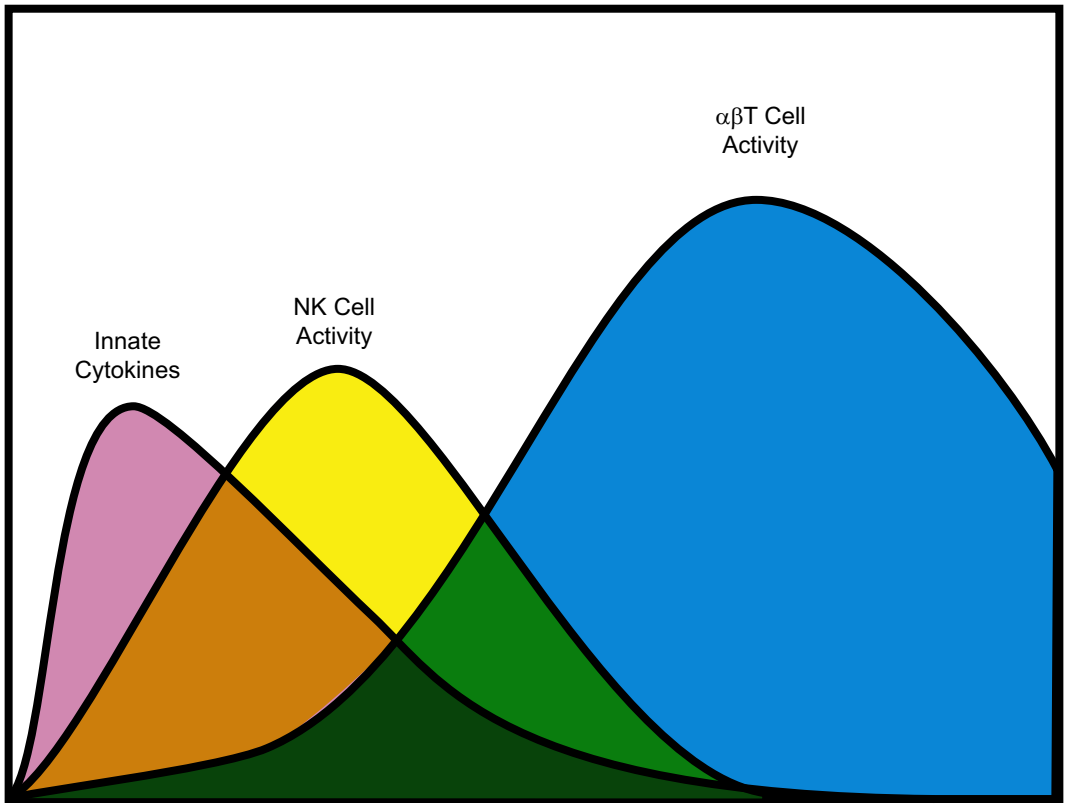

Fig. 1. Innate and adaptive host response to infection. This figure portrays the timing of the peaks in innate cytokines (type 1 IFN, etc.), NK cell cytolytic activity (not cell number), and T cell number and activity during an acute viral infection, based on Welsh (1978).

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