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Regulation of innate immunity by paired receptors

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Abstract. NK cells show cytotoxicity and cytokine production upon recognition of virus-infected cells. When NK cells are removed from cytomegalovirus-resistant mice, the virus titer after infection is markedly increased and the mice are likely to die due to infection. However, the exact mechanism of how NK cells recognize virus-infected cells has remained unclear for a long time. Recent findings of the presence of virus-specific NK cell receptors and their ligands on virus-infected cells have provided a new vision of a protective role of NK cells in virus infection. Furthermore, the recognition of virus-infected cells by paired receptors consisting of activating and inhibitory receptors was found to correlate with the degree of host susceptibility to virus infection. Here, we would like to discuss the role of NK cells in anti-virus immunity. © 2005 Published by Elsevier B.V.

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1. Introduction

Immune-compromised patients who lack normal NK cells are susceptible to severe infectious diseases caused by several viruses even if they have functional T cells and B cells [1]. Similarly, certain mouse strains become susceptible to infection by some viruses, such as cytomegalovirus, when NK cells are deleted although NK cell-deficient mice are not always susceptible to virus infections [2]. From these observations, NK cells are thought to be a critical lymphocyte population for protection against certain virus infections [1]. Indeed, NK cells specifically recognize virus-infected cells and directly kill them. In addition, NK cells produce such cytokines as IFN-γ and regulate the immune response of T cells or B cells. Because NK cells show such effector functions against virus infection without prior sensitization, they play a role in immune response early in infection before the immune responses of T cells and B cells are established. Recent studies have

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revealed that virus-induced activation of NK cells may involve direct recognition of virus-infected cells via activating receptors such as Ly49H or NKG2D, or stimulation of NK cells by interferon-α/β and the cytokines, IL-12 and IL-18 and which are produced by myeloid or other cells at the site of infection.

2. NK cells in anti-virus immunity

The role of NK cells in anti-virus immunity has been well characterized using the MCMV system [1,3,4]. Newborn mice or NK cell-deficient mice are highly susceptible to MCMV infection. The adoptive transfer of mature NK cells into these mice protects the mice against MCMV infection. C57BL/6 mice are relatively resistant to MCMV infection; however, the virus titer after infection is increased by approximately one-thousand folds when NK cells are depleted. On the other hand, mice of inbred mouse strains such as BALB/c, DBA/2 and 129/J mice are quite susceptible to cytomegalovirus infection. They show a peak virus titer approximately one thousand times higher than that in resistant C57BL/6 mice. The genetic locus responsible for resistance to MCMV infection segregated as a single locus and was detected on mouse chromosome 6 and named *cmv-1* [5].

Recently, *cmv-1* has been reported to encode Ly49H, one of the activating NK receptors (see below). The *Ly49* gene family encodes receptors belonging to the C-type lectin superfamily and is polygenic and polymorphic [6]. Although Ly49 receptors are highly homologous to each other in amino acid sequence, different *Ly49* genes encode either inhibitory or activating receptors that are expressed on subsets of NK cells and T cells. Activating Ly49 receptors possess positively charged amino acids, lysine or arginine, in its transmembrane region and associate with the DAP12 adaptor molecule that has negatively charged amino acids in the transmembrane region [7]. DAP12 has an ITAM possessing a consensus sequence, Y-x-x-(L/I)-x(6-8)-Y-x-x-(L/I) in the cytoplasmic region and delivers activation signals by the recruitment of the Syk and ZAP70 tyrosine kinases. Activating Ly49 receptors require DAP12 for their cell surface expression as well as for activating signal transduction. On the other hand, inhibitory Ly49 receptors contain an ITIM with a consensus sequence, (I/V/L/S)-x-Y-x-x-(L/V), in the cytoplasmic region and delivers inhibitory signals via the SHP-1 or SHP-2 tyrosine phosphatase [8]. Inhibitory Ly49 receptors do not have positively charged amino acids in the transmembrane region and hence do not associate with DAP12. Daniels et al. showed that NK cells expressing the activating Ly49H receptors produce IFN-γ upon MCMV infection [9]. Furthermore, they showed that resistance to MCMV infection is lost when Ly49H-positive cells are removed. These results indicated that *cmv-1* gene encodes Ly49H. Other groups also identified Ly49H as a *cmv-1* gene by genomic mapping of the MCMV-resistance gene using BXD-8 recombinant inbred mouse [10,11]. BXD-8, a recombinant inbred strain generated by a cross between MCMV-resistant C57BL/6 mice and MCMV-sensitive DBA/2 mice, had a defect in the C57BL/6-derived Ly49H gene that rendered the mice susceptible to MCMV. Namely, MCMV-resistant mice expressed Ly49H whereas MCMV-susceptible mice did not. These results are also supported by the observation that DAP12-deficient mice are susceptible to MCMV infection [12].