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MINIREVIEW

Major Histocompatibility Complex Class I Antigens and the Control of Viral Infections by Natural Killer Cells

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Natural killer (NK) cells are large, granular cytotoxic lymphocytes which represent a major portion of the lymphocyte infiltrate of infected tissue at early stages of viral infections (35, 37). NK cells become cytolytically activated and proliferate in vivo after exposure either to alpha, beta, or gamma interferon (IFN-α, -β or -γ) or interleukin-2 (4, 6–8, 50). The peak in NK cell activation and proliferation occurs early in viral infections, in parallel with the IFN-α/β response (7, 50); at later stages of infection, when there is substantial T-cell proliferation and production of IFN-γ and interleukin-2, the NK cells are inhibited by large quantities of transforming growth factor β produced by macrophages receiving signals from the activated T cells (4, 46). Considerable evidence has amassed to indicate that NK cells provide natural resistance to a number of viral infections (52). NK cell depletion and reconstitution experiments in mice have been reported to demonstrate a role for NK cells in the control of murine cytomegalovirus (MCMV), vaccinia virus (VV), mouse hepatitis virus, herpes simplex virus (HSV), influenza virus, coxsackievirus, and other viral infections (reviewed in reference 52). Examples of human NK cell deficiencies are rare, but at our institution an adolescent presenting with a complete and selective NK cell deficiency had unusually severe infections with varicella-zoster virus, human cytomegalovirus (HCMV), and HSV (5).

The control of virus infections by NK cells in vivo is not well understood but is likely to be a consequence of the direct lysis of virus-infected cells and/or of the antiviral or immunomodulatory properties of NK cell-produced cytokines such as IFN-γ or tumor necrosis factor alpha (28, 38, 52). Direct lysis of virus-infected cells but not of uninfected cells would require either some form of selective NK cell recognition of targets at the binding or triggering steps or else would result from an increased sensitivity of virus-infected cells to cytolytic mechanisms. How NK cells recognize targets is not understood, but it has now become clear that altered class I major histocompatibility complex (MHC) expression can render target cells more sensitive to NK cell-mediated lysis and that viruses, through a variety of mechanisms, can alter class I MHC expression (32, 39, 43).

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NEGATIVE REGULATION OF NK CELL-MEDIATED CYTOTOXICITY BY CLASS I MHC ANTIGENS ON TARGET CELLS

NK cells stimulated in vivo by viral infections were shown in the 1970s to preferentially lyse allogeneic targets and to lyse at high levels targets expressing no class I MHC antigens, the latter being a criterion used initially to distinguish NK cell-from cytotoxic T lymphocyte (CTL)-mediated lysis (30, 50, 53). A series of elegant studies by Karre and Ljunggren and coworkers next demonstrated that class I expression in lymphoid targets correlated inversely with the sensitivity of the targets to NK cells and that the resistance of certain mutant cell lines to NK cells could be restored by transfection with genes which rescued class I expression (32, 33). IFN protects target cells from NK cell-mediated lysis at least in part by virtue of its ability to upregulate class I expression; target cells deficient in class I expression as a consequence of a mutation in the β_2 microglobulin (β_2m) gene could not be protected by IFN, but protection could be restored after transfection with a normal β_2m gene (33, 48).

Recent discoveries of the nature of receptors on NK cells have revealed an explanation for this type of recognition. A cluster of NK receptor genes encoding type II integral membrane proteins of the type C lectin family are located in the distal region of mouse chromosome 6 (18, 23, 27, 48, 55). These include genes encoding NK-associated proteins NK1.1, NKR-P1, CD69, and Ly-49. Of interest is the finding that genetic resistance of mice to the highly NK-sensitive MCMV is governed by another, less well-defined gene locus, *Cmv-1*, which maps in this region close to NK1.1 (41). In the C57BL/6 mouse, a subpopulation of $NK1.1^+$ NK cells express Ly-49 and mediate lysis with different specificities than do Ly-49^- cells. The Ly-49^+ NK cells are unable to lyse target cells expressing H-$2D^d$, but antibodies to either Ly-49 or to D^d abrogate this resistance. This indicates that engagement of certain class I molecules by this NK cell receptor molecule delivers a negative signal to NK cells and protects the targets from lysis (18, 19, 26, 27). Similar observations have been made with humans, from whom cloned NK cell lines have shown selectivity in lysing targets, and those targets which expressed specific class I antigens resisted lysis (15, 31, 34, 36, 48). One group of human NK cell receptors delivers negative signals to cells when engaging HLA-Cw3 (15), whereas another group of human NK receptor molecules delivers negative signals when exposed to certain HLA-B alleles (31, 36). Within a totally syngeneic system, the NK cells that survive education in the bone marrow environment during their development may constitute cells expressing various combinations of receptors that would direct them not to lyse targets expressing high levels of self class I MHC.

Studies in human C1R cells transfected with various HLA-A genes showed that certain but not other class I molecules protected the C1R cells from NK cells, and exon-shuffling and point mutation studies indicated that a region near the peptide-binding domains of the class I molecule was crucial for the protective effect (43–45). This has led to the belief that the peptides presented by class I molecules may be of importance in NK cell recognition. Some studies have shown that exposure of normal class I-expressing target cells to class I-binding peptides can selectively alter their sensitivity to NK cells (14, 45), but these results have been difficult to repeat and require confirmation (9). Peptides capable of binding to specific class I allotypes can stabilize the conformation of empty class I molecules on the cell surface, resulting in higher detectable levels, and that may explain reports in which peptides have altered the sensitivity of targets to NK cells. RMA/S cells have a defect in their T-cell peptide transporter system and express on their cell surfaces class I MHC molecules in an abnormal confirmation. Stabilization of transfected D^d class I molecules by any of a variety of peptides rendered these targets resistant to lysis by Ly-49^+ NK cells, arguing that the specificity of the peptide is important mainly in its ability to stabilize the MHC on the cell surfaces (17). However, if NK cells do manifest a peptide-specific recognition of MHC molecules, this may be detectable only at the clonal level, and studies with cloned human NK cells and MHC molecules bearing mutations near the peptide-binding region support the concept of some level of peptide specificity (34).

Very recent work has shown that some NKR proteins bind to oligosaccharide structures on the cell surface and suggests that differences in glycosylation may affect NK cell-mediated lysis either negatively or positively (3, 19). The specificity of these oligosaccharide interactions is quite complex, but glycosylation of the class I D^d molecule is required for its binding to Ly-49 (19). There also is a glycosylation site on the class I molecule α1 domain near residues required for NK cell recognition and near the peptide-binding domain, perhaps accounting for studies associating the peptide-binding region with NK cell sensitivity (19). These recent studies help explain earlier work which correlated glycosylation and, specifically, sialation with altered sensitivity to NK cells. It is noteworthy that IFN can protect from NK cell-mediated lysis target cells expressing high levels of class I MHC before IFN treatment; IFN was shown to markedly alter the levels of sialic acid, glycoprotein, and glycosphingolipid expression on these target cells, which then became resistant to NK cells (54). These data on the importance of glycosylation may also explain findings that treatment of human NK cell populations with glycoproteins purified from a variety of viruses enhanced NK cell activity; perhaps the carbohydrate domains on these viral glycoproteins either helped drive positive signaling events or else interfered with the negative signaling events mediated by other cell surface proteins (52).

INFLUENCE OF VIRAL INFECTIONS ON CLASS I MHC EXPRESSION

Viral infections have the capacity to alter class I MHC expression (39). As a consequence of virus-induced IFN and other cytokines, there are global increases in class I MHC expression in uninfected cells throughout the infected host (12). Class I expression on virus-infected cells, however, is often downregulated. Mechanisms of decreased class I MHC expression can involve global inhibitions of cellular RNA and protein synthesis that would block the expression not only of class I proteins but also that of other cell surface molecules required for positive interactions between the NK cell and the target; highly cytopathic viruses, such as HSV type 1 (HSV-1) or VV, can actually make virus-infected targets more resistant to NK cell-mediated lysis at later stages of infection, as the NK cells fail to bind to those targets (10, 51). Viruses also may more selectively alter class I expression, and selective downregulation in class I expression has been shown with adenoviruses (AdV), Epstein-Barr virus, HSV-1 and HSV-2, HCMV, MCMV, human immunodeficiency virus (HIV), mouse hepatitis virus, and Rous sarcoma virus (1, 2, 13, 21, 22, 24, 39, 42). AdV type 12 E1A gene products selectively inhibit class I mRNA transcription (22), whereas the AdV E3 gene-encoded 19-kDa protein complexes with class I molecules in the endoplasmic reticulum (ER), where it is retained (1). Impaired transport of class I molecules out of the ER or Golgi complex has also been observed with several herpesviruses, including HSV-1 (24), HSV-2 (24), HCMV (2), and MCMV (13). HCMV infection also causes enhanced degradation of class I molecules in the ER (2). A possible mechanism by which HIV escapes immune surveillance by CTLs may be the ability of the HIV Tat protein to decrease transcription of class I mRNA (42) (Table 1).

Viruses may also alter class I antigen expression by engaging the antigen-binding groove of the class I molecules with processed viral peptides. It is known that peptides can compete with each other for presentation by class I antigens, and it would be expected that class I antigens from virus-infected cells may, particularly under conditions of high levels of viral protein synthesis, compete for endogenous peptides. Consistent with that hypothesis is the fact that class I MHC molecules from VV-infected cells lose the ability to sensitize targets to allospecific CTLs as they sensitize the targets to virus-specific CTLs (10).

An additional mechanism of class I modulation which may be of great significance in vivo is that many viral infections interfere with the ability of virus-induced IFN to upregulate class I expression (11–13, 49). Uninfected cells isolated from mice during viral infections express high levels of class I antigens, are resistant to NK cells, and are very sensitive to allospecific CTLs (12). The ability of a virus infection to interfere with the IFN-mediated upregulation of class I antigens may thus allow for uninfected but not virus-infected cells to resist lysis by the highly activated NK cells generated during infection (11, 49). Of note is the finding that infection of fibroblasts with the NK-sensitive virus, MCMV, blocks the ability of IFN to protect targets from NK cells, but infection with the NK-resistant lymphocytic choriomeningitis virus does not (11; Fig. 1).

INFLUENCE OF VIRUS-INDUCED MODULATION OF CLASS I MHC ON THE SENSITIVITY OF INFECTED TARGET CELLS TO NK CELL-MEDIATED LYSIS

The question that must be answered is whether any or all of these mechanisms really do contribute to the regulation of viral infections by NK cells (Fig. 1 and Table 1). Work published to date has been inconclusive. In vitro studies have shown that a number of viruses (AdV, HSV-1, VV, HIV, and HCMV) that can downregulate class I MHC expression enhance the sensitivity of targets to NK cells, but convincing evidence that the enhanced sensitivity was due solely to reduced class I expression is still not available (52). Studies with AdV have led to conflicting data, with one report correlating increased sensitivity to downregulation of class I expression (20), whereas other studies have failed to find such a correlation (16, 40). In one report, HSV-1 enhanced the sensitivity of class I-expressing

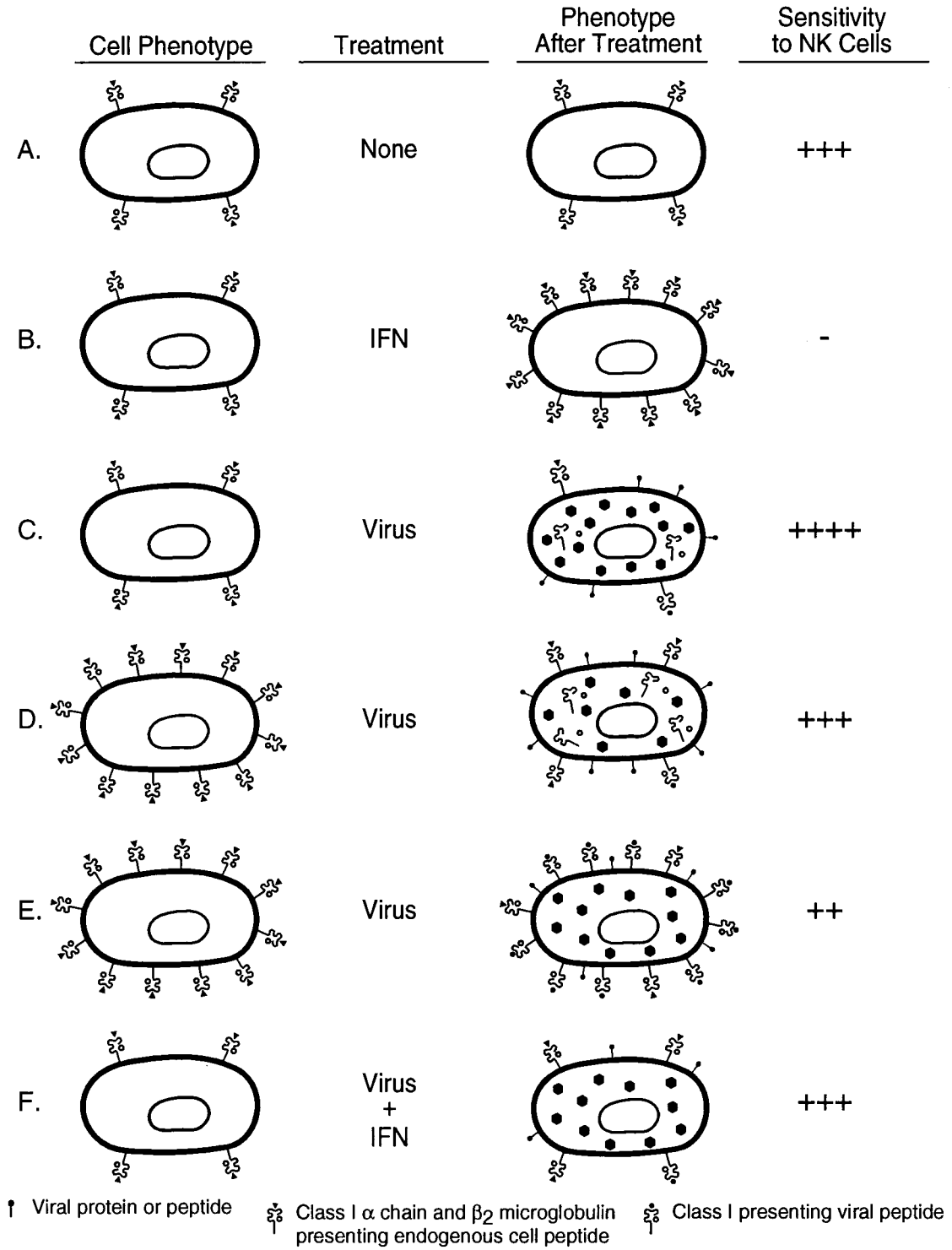

FIG. 1. Alterations in target cell class I antigens and sensitivity to NK cells by IFN and viral infections. (A) Target cells expressing low levels of class I MHC antigens are susceptible to NK cells, and the IFN induced by virus infections can upregulate class I expression (B) and thereby protect target cells from NK cell-mediated lysis. Viral infections, through a variety of mechanisms listed in Table 1, can downregulate class I expression and may through this mechanism render cells more susceptible to NK cells (C and D). It is possible though not yet definitively shown that viruses may interfere with the class I molecule-induced negative signal by the replacement of the presented cellular peptides with virus-encoded (or induced) peptides (E). Cells already infected with viruses may become resistant to IFN and may not upregulate class I antigens, thereby remaining sensitive to NK cells (F).

TABLE 1. Downregulation of class I MHC antigen expression by viruses discussed in this review

Virus	Known mechanism(s) of class I MHC downregulation	Reference(s)
RNA		
HIV-1	Tat protein-induced reduction in class I transcription	42
Mouse hepatitis virus	Allele-specific decrease in class I expression	39
Respiratory syncytial virus	Decrease in class I transcription	39
DNA		
AdV	Retention of class I in ER; reduced transcription and posttranscriptional processing of class I	1, 22, 39
Epstein-Barr virus	Allele-specific decrease in class I	39
HCMV	Degradation of class I heavy chain	2, 39
HSV-1	Impaired transport into Golgi	24
HSV-2	Impaired transport into Golgi	24
MCMV	Retention or degradation of class I in ER	2, 13
VV	Unknown	10

target cells but not that of class I-deficient target cells to NK cells; this occurred under conditions in which class I expression on the plasma membrane was not reduced, leading to speculation that modification of the class I molecules by a viral peptide may have led to enhanced sensitivity (29). However, the uninfected class I-negative cell line was so sensitive to lysis that it might have been difficult for a viral infection to enhance its sensitivity, and a class I-independent mechanism may have caused the virus-induced increased sensitivity of the class I-expressing target. In a similar type of study, VV infection rendered targets more sensitive to NK cells at a time after infection when their class I molecules were rendered resistant to allospecific CTLs, presumably because of their presentation of viral peptides (10). Proof that the peptides were indeed modulating the sensitivity to NK cells in that system was not forthcoming. Our own studies with 12 immunodominant T-cell peptides from seven different viruses, presented on either of six class I MHC molecules and using lymphocyte and fibroblast targets, have failed, under conditions that sensitize targets to CTLs, to sensitize targets to NK cells (9). These peptides included vesicular stomatitis virus $N_{53–59}$ (GYVYQGL, K^b); lymphocytic choriomeningitis virus $NP_{397–407}$ (QPQNGQFI HFY, D^b); HIV-1_{IIIB} $gp160_{315–329}$ (RIQRGPGRAFVTIGK, D^d); HSV-1 $gB_{497–507}$ (TSSIEFARLQF, K^b); influenza virus $HA_{147–161}$ (TYQRTRALVRTGMDP, K^d), $HA_{515–526}$ (ILAI YSTVASSL, K^d), $NP_{50–63}$ (SDYEGRLIQNSLI, K^k), and $NP_{365–379}$ (IASNENMETMESSTL, D^b); lymphocytic choriomeningitis virus $GP_{278–286}$ (VENPGGYCL, D^b) and $NP_{119–127}$ (PQASGVYMG, L^d); MCMV $IEpp89_{168–176}$ (YPHFMPTNL, L^d); and rabies virus $NS_{191–206}$ (EKDDLSVEAEIAHQI, K^k). The possibility exists, however, that these peptides may have affected certain subsets or clones within the NK cell population or that a glycosylated peptide may affect such interactions. It is also possible that nonimmunodominant peptides transported with class I molecules to the cell surface may rapidly dissociate and thereby render the class I molecules unable to deliver a negative signal, but such peptides are not well studied.

The importance of the nature of the target cell should not be overlooked in these studies, as the correlations between class I expression and resistance to NK cells are more convincing with lymphocyte targets than with fibroblast targets (32, 33, 43). Interestingly, the genetic resistance of mice to MCMV that is mediated by the NK1.1-linked *Cmv-1* locus affects resistance in the spleen, where MCMV is probably growing substantially in lymphocytes, but not in the liver, where it replicates in hepatocytes (41). MCMV is a virus which impairs transport of class I molecules out of the ER and which interferes with the ability of IFN-γ or IFN-β to upregulate class I molecules and to protect target cells from NK cell-mediated lysis (13, 21). The effect of MCMV infection on MHC expression in lymphocytes and sensitivity to NK cells should therefore be investigated. Control of MCMV infection by NK cells appears to be normal in β_2m knockout mice, which have very low cell surface class I MHC expression, but it remains possible that NK cells educated in a β_2m^--deficient environment might be able to detect subtle changes in aberrant class I expression in MCMV-infected β_2m^--deficient target cells (25, 47).

CONTROL OF VIRAL INFECTIONS BY CYTOTOXIC LYMPHOCYTES WITH DIVERGENT RECOGNITION SYSTEMS

Should further experimental data support the hypothesis that NK cells control viral infections by lysing targets whose class I protein expression is downregulated or otherwise altered, one could make speculations concerning evolutional significance. It would appear that the host is armed with two classes of cytotoxic lymphocytes: one, the NK cell, which lyses targets low in class I expression, and another, the CTL, which lyses targets high in class I molecules. Should a virus evolve to either up- or downregulate class I expression, infected target cells may become resistant to one of these mechanisms but should remain sensitive to the other.

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