Non-classical MHC Class I molecules regulating natural killer cell function

Mark J. Smyth,1,* Lucy C. Sullivan,1 Andrew G. Brooks2 and Daniel M. Andrews1

1Cancer Immunology Program; Sir Peter MacCallum Department of Oncology; University of Melbourne; Parkville, VIC Australia; 2Department of Microbiology and Immunology; University of Melbourne; Parkville, VIC Australia

Keywords: education, inhibitory, metastasis, tumor immunosurveillance

Abbreviations: KIR, killer inhibitory receptor; NK, natural killer

The immune system is clearly an important regulator of tumor development.1 In contrast to the antigen-specific regulation of adaptive immunity, natural killer (NK) cell-mediated responses are controlled by receptors that convey activating or inhibitory signals. Early studies of NK cell inhibition demonstrated that the absence of MHC Class I molecules on the surface of cancer cells resulted in their clearance, leading to the “missing self” hypothesis.2 Molecular data in support of this model was provided with the identification of MHC Class I recognition by the inhibitory receptor Ly49A. The “missing self” theory proposed that the absence of MHC Class I molecules should render cells more susceptible to NK cell-mediated killing. An extension of this model was the “at least one” proposal, suggesting that—for missing self to be active—each NK cell must express an inhibitory receptor that recognizes self MHC molecules.3 However, neither of these models can completely explain NK-cell tolerance, since not all Ly49 molecules have been shown to bind to host MHC molecules and NK cells from MHC Class I-deficient mice do not acquire full effector function. These facts raised some doubt about the fidelity of NK-cell inhibitory receptor interactions with MHC Class I molecules.

Members of the non-classical MHC Class Ib family, most significantly Rae/ULBP (NKG2D) and HLA-E/Qa-1b (NKG2ACE), also regulate the functions of NK cells. Given the importance of these non-classical MHC molecules in NK-cell function, it is surprising to note that whether other members of this family actively regulate NK cell biology has not been intensively investigated. H2-M3 is a relatively non-polymorphic MHC Class Ib molecule from the same non-classical region as Qa-1b, and was first identified as a minor histocompatibility antigen. The mRNA encoding H2-M3 can be found in most tissues of all strains of mice at a lower level than that coding for classical MHC Class I molecules. However, in contrast to classical MHC molecules, most cells do not express H2-M3 on their surface, B cells being a notable exception. H2-M3 specifically binds \(^{\text{\textsuperscript{N}-formylated peptides}}\) that contain hydrophobic residues with an affinity 100–1000 times greater than that for standard peptides. Given that prokaryotes and mitochondria are the only sources of \(^{\text{\textsuperscript{N}-formylated peptides}}\), H2-M3 appears to have evolved to present peptides of bacterial (or mitochondrial) origin.4 Indeed, in the past 20 years attention has been focused on the role H2-M3 in the biology of a subset of CD8\(^+\) T cells. Intriguingly, the first description of H2-M3-deficient mice reported an impaired capacity of lymphocytes from these mice to kill NK cell-sensitive targets.5

Our recent findings demonstrate that H2-M3 can be recognized by Ly49A, the prototypic NK-cell inhibitory receptor.6 This existence of non-classical MHC Class Ib molecule-binding receptors specific for allotypic classical Class I indicates that there may be a previously unrecognized crossover between these receptor-ligand families. Potentially, this result provides further support to the “at least one” hypothesis and suggests that ligands for Ly49 (and potentially KIR) may exist outside the classical MHC family. From a functional standpoint, the absence of H2-M3 results in NK-cell hyporesponsiveness (due to the ineffective licensing of the Ly49A` NK-cell subset) and missing-self rejection (H2-M3 acts a self molecule recognized by NK cells) (Fig. 1). Consequently, H2-M3-deficient mice display increased sensitivity to oncogenesis, tumor progression and metastatic spread, the latter in a Ly49A-dependent fashion. Distinct genetic and phenotypic
alterations of tumor cells allow for their escape from the control of the immune system, representing a critical step in cancer progression. The ability of inhibitory Ly49A to bind H2-M3, which is constitutively expressed by some malignant cells, suggests that tumors may potentially use this interaction to escape both NK and Ly49A-expressing T cells.

Although there is not a direct human homolog of H2-M3, it is possible that a functional homolog exists. Indeed, T-cell responses to N-formylated peptides derived from self (mitochondrial) and foreign (microbial) antigens have been described in humans. HLA-F is physiologically expressed by cell types similar to those that express H2-M3, and has been shown to bind inhibitory ILT-2 and ILT-4 receptors. Still, HLA-F lacks an obvious consensus sequence for the binding of N-formylated peptides. HLA-E and HLA-G are the best studied non-classical MHC-like molecules, but a better characterization of the functions of MHC-linked genes to CD8+ T cells is a fundamental premise for most modern cancer immunotherapies, the role of non-classical MHC Class Ib molecules in regulating the immune response to cancer deserves greater attention.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

References
1. Schreiber RD, Old LJ, Smyth MJ. Cancer immunoeediting: integrating immunity's roles in cancer suppression and promotion. Science 2011; 331:1565-70; PMID:21436444; http://dx.doi.org/10.1126/science.1210386.
2. Kärre K. How to recognize a foreign submarine. Immunol Rev 1997; 155:5-9; PMID:9059878; http://dx.doi.org/10.1111/j.1600-065X.1997.tb00935.x.
3. Raulet DH, Vance RE. Self-tolerance of natural killer cells. Nat Rev Immunol 2006; 6:520-31; PMID:16799477; http://dx.doi.org/10.1038/nri1863.
4. Colome A, Wang CR. H2-M3-restricted T cell response to infection. Microbes Infect 2006; 8:2277-83; PMID:16824777; http://dx.doi.org/10.1016/j.micinf.2006.03.020.
5. Xu H, Chun T, Choi HJ, Wang B, Wang CR. Impaired response to Listeria in H2-M3-deficient mice reveals a nonredundant role of MHC class Ib-specific T cells in host defense. J Exp Med 2006; 203:449-59; PMID:16476767; http://dx.doi.org/10.1084/jem.20051866.
6. Andrews DM, Sullivan LC, Baschuk N, Chan CJ, Berry R, Cotterell CL, et al. Recognition of the nonclassical MHC class I molecule H2-M3 by the receptor Ly49A regulates the licensing and activation of NK cells. Nat Immunol 2012; 13:1171-7; PMID:23142773; http://dx.doi.org/10.1038/ni.2468.
7. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011; 144:646-74; PMID:21376230; http://dx.doi.org/10.1016/j.cell.2011.02.013.
8. Ristori G, Montesperelli C, Fosillio MT, Battistini L, Cherri A, Sorrentino R, et al. T cell response to N-formylated peptides in humans. Eur J Immunol 2001; 31:2762-70; PMID:11536175; http://dx.doi.org/10.1002/1521-4141(200109)31:9<2762::AID-IMMU2762>3.0.CO;2-X.
9. Bukur J, Jasinski S, Seliger B. The role of classical and non-classical HLA class I antigens in human tumors. Semin Cancer Biol 2012; 22:358-8; PMID:22465194; http://dx.doi.org/10.1016/j.semcancer.2012.03.003.
10. Gasser S, Ozallic S, Brown EJ, Raulet DH. The DNA damage pathway regulates innate immune system ligands of the NKG2D receptor. Nature 2005; 436:1186-90; PMID:15995699; http://dx.doi.org/10.1038/nature03884.