

Understanding inverse correlation between the levels of class I major histocompatibility antigens on tumour cells and their susceptibility to lysis by natural killer cells: Evidence of competition experiments

Rajiv K. Saxena

School of Life Sciences, Jawaharlal Nehru University, New Delhi 110 067, India

Natural killer (NK) cells, a class of lymphocytes distinct from T or B lymphocytes, can spontaneously lyse a variety of tumour cells without the need for a prior sensitization. A specific immune response against tumour cells results in generation of another class of cytotoxic effector cells, i.e. cytotoxic T-lymphocytes. Tumour cells must share some class I MHC antigens with the cytotoxic T-cell in order to be recognized and lysed by the latter. There is no such requirement for NK cells. Target cell MHC I antigen expression is however still an important factor in regulating the susceptibility of target cells to NK cells. An inverse correlation between the expression levels of class I MHC antigens on target cells and their susceptibility to NK cells has been found. In this article, I have evaluated the existing hypotheses for explaining the basis of inverse correlation between target MHC I expression and NK susceptibility, in view of results of our recent experiments in which the effect of competing tumour cells with normal or augmented MHC I expression, on the lysis of target tumour cells has been studied.

UNLIKE cytotoxic T cells, natural killer (NK) cells kill targets in a MHC (major histocompatibility complex) non-restricted manner. Class I MHC antigens on target tumour cells may, however, play a role in determining their NK susceptibility. An inverse correlation between the levels of class I MHC antigens on target cells and their NK susceptibility has been demonstrated in many studies¹⁻⁴, though exceptions have also been noted⁵. Ljunggren and Karre¹ proposed two possible mechanisms by which target cell MHC class I antigens may influence the NK susceptibility. According to the first model, MHC class I antigens on target cell membrane may interfere with the recognition of target structure molecules by NK effector cells. Nature of the target structures on tumour target cells is not clearly understood, though recent evidence seems to indicate that

certain carbohydrate residues may act as target structures recognized by NK cells⁶. The second model for explaining the inverse correlation between the levels of class I MHC antigens on target cells and their NK susceptibility, proposes that class I MHC antigens on target cells, may send a down regulatory signal to effector NK cells.

If the activity of effector NK cells can be regulated by class I MHC antigens on the target cells, some receptor molecules on NK cells with target cell MHC class I molecules as their ligands, may be present. A family of type II integral membrane proteins, belonging to the superfamily of lectin-like molecules, has generated considerable interest in this regard. This family of molecules has, as its members, adhesion molecules of Selectin category (MEL 14/LAM 1, ELAM-1, etc.) which generally bind carbohydrate ligands in a calcium-dependent manner and are involved in directing the migration or homing patterns of leukocytes^{7,8}. Ly 49 molecule, which is a homodimer of 84 kDa, belongs to this superfamily, and is expressed on a subset of murine (C57Bl/6) NK cells⁹. Available evidence indicates that specific class I MHC molecules (H-2^d and H-2^k molecules) on tumour target cells, act as ligands for Ly 49 molecules and this interaction sends a down regulatory signal to the effector NK cell, resulting in sparing of the target cell from NK cell mediated lysis^{10,11}. In general, Ly 49⁺ class of NK cells fail to lyse H-2^d/H-2^k-bearing targets, whereas Ly 49⁻ subset of NK cells may efficiently lyse the same target cells. A prominent exception to this rule appears to be YAC tumour cells which express D^d antigens but are efficiently lysed by both Ly 49⁺ and Ly 49⁻ NK cells⁹. Since Ly 49 and/or related molecules may act as receptors for target cell MHC class I molecules, and send a down-regulatory signal to NK cells, it is tempting to hypothesize that this interaction may be responsible for the inverse correlation between the levels of class I MHC antigens expressed on