

M.Sc ZOOLOGY
SEMESTER 3
PAPER CC 10
NK CELL MEDIATED IMMUNITY

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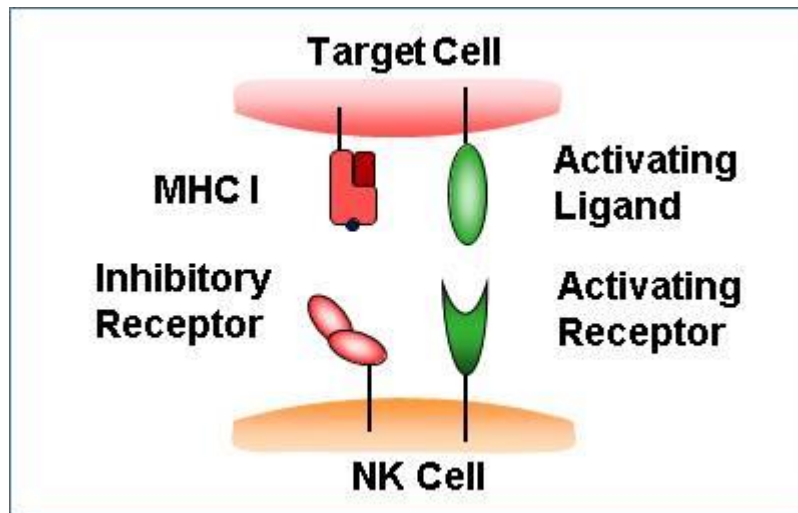
NK Cell-Mediated Cytotoxicity

Natural Killer (NK) Cells are lymphocytes in the same family as T and B cells, coming from a common progenitor. However, as cells of the innate immune system, NK cells are classified as group I Innate Lymphocytes (ILCs) and respond quickly to a wide variety of pathological challenges. NK cells are best known for killing virally infected cells, and detecting and controlling early signs of cancer. As well as protecting against disease, specialized NK cells are also found in the placenta and may play an important role in pregnancy.

NK cells were first noticed for their ability to kill tumour cells without any priming or prior activation (in contrast to cytotoxic T cells, which need priming by antigen presenting cells). They are named for this 'natural' killing. Additionally, NK cells secrete cytokines such as $IFN\gamma$ and $TNF\alpha$, which act on other immune cells like Macrophage and Dendritic cells to enhance the immune response.

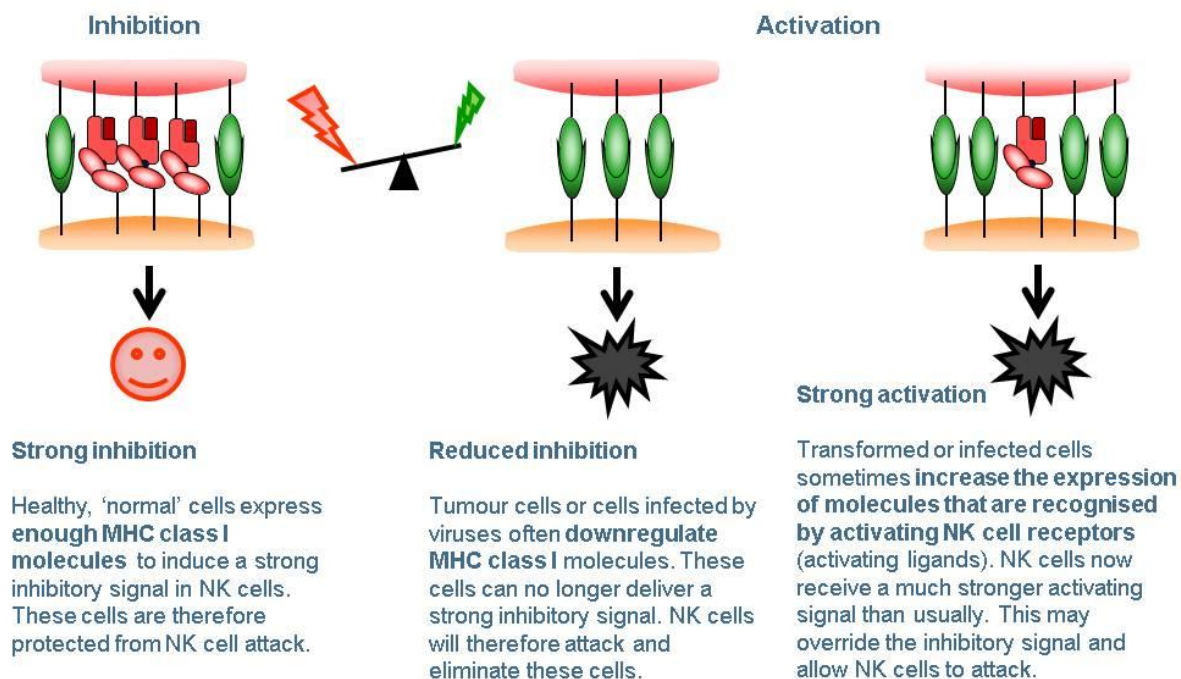
While on patrol NK cells constantly contact other cells. Whether or not the NK cell kills these cells depends on a balance of signals from activating receptors and inhibitory receptors on the NK cell surface. Activating receptors recognise molecules that are expressed on the surface of cancer cells and infected cells, and 'switch on' the NK cell. Inhibitory receptors act as a check on NK cell killing. Most normal healthy cells express MHC I receptors which mark these cells as 'self'. Inhibitory receptors on the surface of the NK cell recognise cognate MHC I, and this 'switches off' the NK cell, preventing it from killing. Cancer cells and infected cells often lose their MHC I, leaving them vulnerable to NK cell killing. Once the decision is made to kill, the NK cell releases cytotoxic granules containing perforin and granzymes, which leads to lysis of the target cell.

Natural killer (NK) cells are defined as large granular lymphocytes and play a critical role in the innate immune system. They often lack antigen-specific cell surface receptors. Instead of acting via antigen-specific receptors, like T-cells, lysis of tumour cells by NK cells involves exocytosis of cytoplasmic granules from the NK cell towards cancer cells; this process can directly occur in the proximity of cancer cells or after engagement of alternative receptor members of the TNF superfamily (FasL/TNF) and their corresponding ligands (Fas/TNFR).

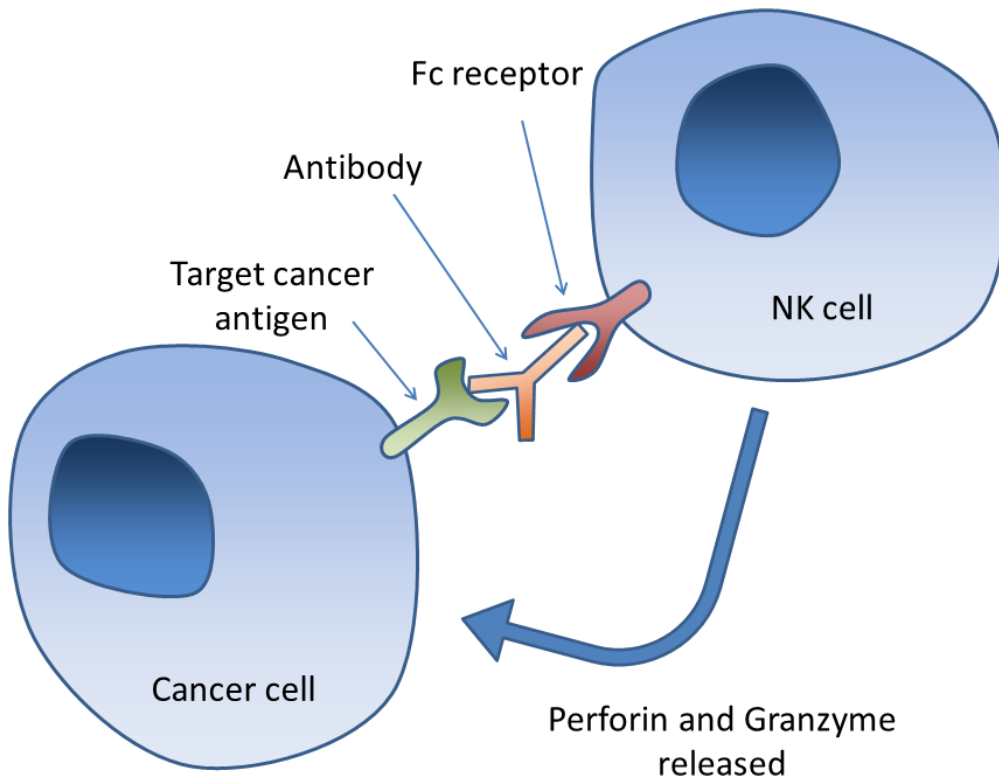


The genes for both MHC I and the NK cell **inhibitory receptors** which recognise them vary a lot between individuals. The versions (or **alleles**) of these genes a person carries have been linked to their ability to fight HIV infection and their risk of some autoimmune diseases. NK cell varieties also change with age and are affected by chronic viral infections such as cytomegalovirus (CMV).

Because of their ability to kill tumour cells, NK cells are an attractive target for cancer immunotherapy. Some therapeutic monoclonal antibodies rely on NK cell killing. Researchers are also developing treatments to activate NK cells using small molecules or cytokines, and even testing genetically modified living NK cells as therapies.



NK cell mediated lysis of cancer cells



NK cells can mediate cancer cell killing through the release of granules/granzymes. This occurs:

1. In a direct manner or after activation of receptors on the NK cell's surface that bind ligands on the cancer cell's surface.
2. Upon this activation, the cytotoxic granules released by the NK cells are vectorially secreted into the intercellular space formed during conjugation of the NK cell and the cancer cell.
3. The granules contain a number of proteins, including perforin, which induce the formation of membrane lesions on the cancer cell, resulting in NK cell mediated lysis of cancer cells.
