**11.4C: Natural Killer Cells**

**LEARNING OBJECTIVES**

- Describe natural killer cells

Natural killer cells (or NK cells) are a type of cytotoxic lymphocyte critical to the innate immune system. The role NK cells play is similar to that of cytotoxic T cells in the vertebrate adaptive immune response. NK cells provide rapid responses to virally infected cells and to tumor formation, beginning around three days after infection. Typically immune cells detect MHC that is present on infected cell surfaces, triggering cytokine release and causing lysis or apoptosis. NK cells are unique, however, as they have the ability to recognize stressed cells in the absence of antibodies and MHC, allowing for a much faster immune reaction. They were named “natural killers” because of the initial notion that they do not require activation in order to kill cells that are missing “self” markers of major histocompatibility complex (MHC) class 1.

NK cells are defined as large granular lymphocytes (LGL) and constitute the third kind of cell differentiated from the common lymphoid progenitor generating B and T lymphocytes. NK cells are known to differentiate and mature in the bone marrow, lymph node, spleen, tonsils, and thymus, where they then enter into the circulation. NK cells differ from Natural Killer T cells (NKT) phenotypically, by origin, and by respective effector functions. Often NKT cell activity promotes NK cell activity by secreting IFNγ. In contrast to NKT cells, NK cells do not express T-cell antigen receptors (TCR) or Pan T marker CD3 or surface immunoglobulins (Ig) B cell receptors, but they usually express the surface markers CD16 (FcγRIII) and CD56 in humans, NK1.1 or NK1.2 in C57BL/6 mice. Up to 80% of human NK cells also express CD8.
Mechanism

NK cells paralyze target cells using the cytolytic protein perforin and a variety of protease enzymes. An NK cell will first use perforin to create pores in a target cell, allowing it to inject granzymes through an aqueous channel. The granzymes then break down the target cell, inducing death by either apoptosis or osmotic cell lysis.

NK cells also alert the greater immune system by secreting chemicals that are taken as a message that a threat has arrived.

Natural Killer Cells Play Other Roles

Natural killer cells are not only effectors of innate immunity; recent research has also uncovered information on both activating and inhibitory NK cell receptors, which play roles in maintaining self-tolerance and sustaining NK cell activity. NK cells also play a role in the adaptive immune response. Numerous experiments have demonstrated their ability to adjust to the immediate environment and formulate antigen-specific immunological memory, which is fundamental for responding to secondary infections with the same antigen. The ability for NK cells to act in both innate and adaptive immune response is becoming increasingly important in research utilizing NK cell activity in potential cancer therapies.

NK cell receptors can also be differentiated based on function. Natural cytotoxicity receptors directly induce apoptosis after binding to ligands that directly indicate infection of a cell. The MHC dependent receptors (described above) use an alternate pathway to induce apoptosis in infected cells. Natural killer cell activation is determined by the balance of inhibitory and activating receptor stimulation—for example, if the inhibitory receptor signaling is more prominent, then NK cell activity will be inhibited. Similarly, if the activating signal is dominant, then NK cell activation will result.
Functions of NK cells include: Cytolytic Granule Mediated Cell Apoptosis; Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC); Cytokine induced NK and CTL activation; Missing 'self' hypothesis; Tumor cell surveillance; NK cell function in adaptive response; NK cell function in pregnancy; and NK cell evasion by tumor cells.

**Key Points**

- NK cells are defined as large granular lymphocytes (LGL).
- NK cells constitute the third kind of cells differentiated from the common lymphoid progenitor generating B and T lymphocytes.
- NK cells provide rapid responses to virally infected cells and respond to tumor formation, acting at around 3 days after infection.

**Key Terms**

- **Natural killer cells (or NK cells):** Natural killer cells (or NK cells) are a type of cytotoxic lymphocyte critical to the innate immune system. The role NK cells play is analogous to that of cytotoxic T cells in the vertebrate adaptive immune response.
- **lymphocyte:** A type of white blood cell or leukocyte that is divided into two principal groups and a null group: B-lymphocytes, which produce antibodies in the humoral immune response, T-lymphocytes, which participate in the cell-mediated immune response, and the null group, which contains natural killer cells, cytotoxic cells that participate in the innate immune response.
- **innate immune system:** This is the initial line of defense that entails a cascade of cells and mechanisms that protect the host from infection by different organisms in an indeterminate pattern.