11.3F: Natural Killer Cells (NK Cells) and Invariant Natural Killer T-Lymphocytes (iNKT Cells)

Skills to Develop

1. Describe how NK cells are able to recognize and kill infected cells and cancer cells lacking MHC-I molecules.
2. State two factors that can result in a nucleated human cell not producing MHC-I molecules.
3. State how iNKT cells recognize glycolipids in order to become activated.
4. Describe the overall function of iNKT cells in terms how they promote both innate and adaptive immunity and may also help to regulate the immune responses.

We will now take a closer look at natural killer (NK) cells and invariant natural killer T-lymphocytes (iNKT cells).

Natural Killer Cells (NK Cells)

NK cells are important in innate immunity because they are able to recognize infected cells, cancer cells, and stressed cells and kill them. In addition, they produce a variety of cytokines, including proinflammatory cytokines, chemokines, colony-stimulating factors, and other cytokines that function as regulators of body defenses. For example, through cytokine production NK cells also suppress and/or activate macrophages, suppress and/or activate the antigen-presenting capabilities of dendritic cells, and suppress and/or activate T-lymphocyte responses.

NK cells use a dual receptor system in determining whether to kill or not kill human cells. When cells are either under stress, are turning into tumors, or are infected, various stress-induced molecules such as MHC class I polypeptide-related sequence A (MICA) and MHC class I polypeptide-related sequence B (MICB) are produced and are put on the surface of that cell.
The first receptor, called the killer-activating receptor, can bind to these stress-induced molecules, and this sends a positive signal that enables the NK cell to kill the cell to which it has bound unless the second receptor cancels that signal.

This second receptor, called the killer-inhibitory receptor, recognizes MHC-I molecules that are usually present on all nucleated human cells. MHC-I molecules, produced by all nucleated cells in the body, possess a deep groove that can bind peptides from proteins found within the cytosol of human cells, transport them to the surface of that cell, and display the MHC-I/peptide complex to receptors on cytotoxic T-lymphocytes or CTLs. If the MHC-I molecules have peptides from the body's own proteins bound to them, CTLs do not recognize those cells as foreign and the cell is not killed. If, on the other hand, the MHC-I molecules have peptides from viral, bacterial, or mutant proteins bound to them, CTLs recognize that cell as foreign and kill that cell. (CTLs will be discussed in greater detail in Unit 6.)

If MHC-I molecules/self peptide complexes are expressed on the cell, the killer-inhibitory receptors on the NK cell recognize this MHC-I/peptide complex and sends a negative signal that overrides the original kill signal and prevents the NK cell from killing the cell to which it has bound (see Figure 3).

Viruses, stress, and malignant transformation, however, can often interfere with the ability of the infected cell or tumor cell to express MHC-I molecules. Without the signal from the killer-inhibitory receptor, the kill signal from the killer-activating signal is not overridden and the NK cell kills the cell to which it has bound (see Figure 4).

The NK cell then releases pore-forming proteins called perforins, proteolytic enzymes called granzymes, and chemokines. Granzymes pass through the pores and activate the enzymes that lead to apoptosis of the infected cell by means of destruction of its structural cytoskeleton proteins and by chromosomal degradation. As a result, the cell breaks into fragments that are subsequently removed by phagocytes (see Figure 5). Perforins can also sometimes result in cell lysis.

Cytokines such as interleukin-2 (IL-2) and interferon-gamma (IFN-gamma) produced by TH1 lymphocytes activate NK
NK cells also play a role in adaptive immune responses. As will be seen in Unit 6, NK cells are also capable of antibody-dependent cellular cytotoxicity or ADCC where they kill cells to which antibody molecules have bound.

For More Information: ADCC from Unit 6

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**Invariant Natural Killer T-Lymphocytes (iNKT Cells)**

iNKT cells are a subset of lymphocytes that bridge the gap between innate and adaptive immunity. They have T-cell receptors (TCRs) on their surface for glycolipid antigen recognition. They also have natural killer (NK) cell receptors.

Through the cytokines they produce once activated, iNKT cells are essential in both innate and adaptive immune protection against pathogens and tumors. They also play a regulatory role in the development of autoimmune diseases, asthma, and transplantation tolerance. It has been shown that iNKT cell deficiency or disfunction can lead to the development of autoimmune diseases, human asthma, and cancers.

Pathogens may not directly activate iNKT cells. The TCR of iNKT cells recognize exogenous glycolipid antigens, as well as endogenous self glycolipid antigens presented by MHC-I-like CD1d molecules on antigen presenting dendritic cells. iNKT cells can also be activated by the cytokine interleukin-12 (IL-12) produced by dendritic cells that have themselves become activated by pathogen-associated molecular patterns (PAMPs) of microbes binding to the pattern-recognition receptors (PRRs) of the dendritic cell.

Once activated, the iNKT cells rapidly produce large quantities of cytokines, including interferon-gamma (IFN-?), interleukin-4 (IL-4), interleukin-2 (IL-2), interleukin-10 (IL-10), tumor necrosis factor-alpha (TNF-a), interleukin-13 (IL-13), and chemokines. Through the rapid productions of such cytokines, iNKT cells are able to promote and suppress different innate and adaptive immune responses. For example, large amounts of IFN-? are produced by activated iNKT cells. IFN-? activates NK cells and macrophages as a part of innate immunity.

It has been proposed that if the iNKT cell is repeatedly stimulated by the body's own glycolipids in the absence of microbes that this might stimulate the iNKT cell/dendritic cell interaction to produce tolerizing signals that inhibit the Th1 cell response and possibly stimulate the production of regulatory T-lymphocytes (Treg cells). In this way it might suppress autoimmune responses and prevent tissue damage.

There is also growing evidence that early childhood exposure to microbes is associated with protection against allergic diseases, asthma, and inflammatory diseases such as ulcerative colitis. It has been found that germ-free mice have large accumulations of mucosal iNKT cells in the lungs and intestines and increased morbidity from allergic asthma and inflammatory bowel disease. However, colonization of neonatal germ-free mice with normal microbiota resulted in mucosal iNKT cell tolerance to these diseases. It has been proposed that microbes the human body has been traditionally exposed to from early childhood throughout most of human history might play a role in developing normal iNKT cell numbers and iNKT cell responses.

iNKT cells will be discussed in further detail in Unit 6.
Summary

1. Natural Killer (NK) cells are able to recognize infected cells, cancer cells, and stressed cells and kill them. In addition, they produce a variety of cytokines, including proinflammatory cytokines, chemokines, colony-stimulating factors, and other cytokines that function as regulators of body defenses.

2. When body cells are either under stress, are turning into tumors, or are infected, various stress-induced molecules are produced and are put on the surface of that cell.

3. NK cells use a dual receptor system in determining whether to kill or not kill human cells.

4. The first receptor, called the killer-activating receptor, can bind to these stress-induced molecules, and this sends a positive signal that enables the NK cell to kill the cell to which it has bound unless the second receptor cancels that signal.

5. The second receptor, called the killer-inhibitory receptor, recognizes MHC-I molecules that are usually present on all nucleated human cells. If MHC-I molecules/self peptide complexes are expressed on the cell, the killer-inhibitory receptors on the NK cell recognize this MHC-I/peptide complex and sends a negative signal that overrides the original kill signal and prevents the NK cell from killing the cell to which it has bound.

6. Viruses, stress, and malignant transformation can often interfere with the ability of the infected cell or tumor cell to express MHC-I molecules. Without the signal from the killer-inhibitory receptor, the kill signal from the killer-activating signal is not overridden and the NK cell kills the cell to which it has bound.

7. NK cells kill their target cells by inducing apoptosis, a programmed cell suicide.

8. NK cells also play a role in adaptive immune responses by way of antibody-dependent cellular cytotoxicity or ADCC where they bind to and kill cells to which antibody molecules have bound.

9. Invariant natural killer T-lymphocytes (iNKT cells) are a subset of lymphocytes that have T-cell receptors on their surface for glycolipid antigen recognition. They also have natural killer (NK) cell receptors.

10. Through the cytokines they produce, iNKT cells are able to promote and suppress different innate and adaptive immune responses. They also play a regulatory role in the development of autoimmune diseases, asthma, and transplantation tolerance. iNKT cell deficiency or disfunction can lead to the development of autoimmune diseases, human asthma, and cancers.

Contributors

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