12.3D: T8-Lymphocytes (T8-Cells)

Skills to Develop

1. Describe the overall function of T8-lymphocytes and their activation in terms of the following:
   a. the role of their TCRs and CD8 molecules
   b. how they are activated by antigen-presenting dendritic cells
   c. the type of effector cells into which activated T8-lymphocytes differentiate
   d. what CTLs recognize on infected cells and tumor cells
   e. how CTLs kill infected cells and tumor cells
2. State the overall function of T8-lymphocytes in adaptive immunity.

The primary role of T8-lymphocytes (T8-Cells; CD8+ Cells; Cytotoxic T-Lymphocytes) is to kill infected cells and tumor cells by inducing apoptosis of those cells. Once naive T8-lymphocytes are activated by dendritic cells, they proliferate and differentiate into T8-effector lymphocytes called cytotoxic T-lymphocytes (CTLs) that bind to and kill infected cells and tumor cells.

T8-lymphocytes are T-lymphocytes displaying a surface molecule called CD8. T8-lymphocytes also have on their surface, T-cell receptors or TCRs similar to those on T4-lymphocytes. The TCR on T8-lymphocytes, in cooperation with CD8, bind peptides from endogenous antigens bound to MHC-I molecules.

During its development, each T8-lymphocyte becomes genetically programmed, by gene-splicing reactions similar to those in B-lymphocytes and T4-lymphocytes, to produce a TCR with a unique shape capable of binding epitope/MHC-I complex with a corresponding shape. It is estimated that the human body has the ability to recognize 10^7 or more different epitopes. In order to recognize this immense number of different epitopes, the body produces 10^7 or more distinct clones of T-lymphocytes, each with a unique T-cell receptor. In this variety of T-cell receptors there is bound to
be at least one that has an epitope-binding site able to fit, at least to some degree, peptides of any antigen the immune system eventually encounters.

**Activation of a naive T8-lymphocyte by a dendritic cell**

One of the body's major defenses against viruses, intracellular bacteria, and cancers is the destruction of infected cells and tumor cells by cytotoxic T-lymphocytes or CTLs. These CTLs are effector cells derived from naive T8-lymphocytes during cell-mediated immunity. However, in order to become CTLs, naive T8-lymphocytes must become activated by dendritic cells as shown in Figure 1 and Figure 2.

To view an electron micrograph of a dendritic cell presenting antigen to T-lymphocytes, see the Web page for the University of Illinois College of Medicine.

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Certain dendritic cells are capable of cross-presentation of exogenous antigens to naive T8-lymphocytes. In this way, T8-lymphocytes can play a role in defending against both exogenous and endogenous antigens.

Naive T-lymphocytes circulate in the blood. In response to chemokines produced by lymphoid tissues, they leave the vascular endothelium in regions called high endothelial venules and enter lymph nodes (see Figure 3) or other lymphoid tissues, a process called diapedesis.

As naive T8-lymphocytes migrate through the cortical region of lymph nodes, they use surface cell adhesion molecules such as LFA-1 and CD2 to bind transiently to corresponding receptors such as ICAM-1, ICAM-2 and CD58 on the surface of dendritic cells. This transient binding allows time for the TCRs on the T8-lymphocyte to sample large numbers of MHC-I/peptide complexes on the antigen-presenting dendritic cells (see Figure 4).

Those naive T8-lymphocytes not activated by epitopes of antigens on the dendritic cells exit the lymph node (or other lymphoid tissue) and eventually re-enter the bloodstream. However, if a TCR and CD8 molecule of the naive T8-lymphocyte detects a corresponding MHC-I/peptide complex on a mature dendritic cell, this will send a first signal for the activation of that naive T-lymphocyte. Next, a second signal that promotes survival of that T-lymphocyte is sent when
co-stimulatory molecules such as B7.1 and B7.2 on the dendritic cell bind to CD28 molecules on the T8-lymphocyte. Finally, the dendritic cell produces cytokines such as interleukin-6 (IL-6), IL-4, IL-12, and T-cell growth factor-beta (TGF-ß) that contribute to proliferation of the T8-lymphocytes and their differentiation into effector T8-lymphocytes called cytotoxic T-lymphocytes (CTLs) that are able to bind to and kill infected cells and tumor cells displaying the same peptide/MHC-I complex on their surface. (Activated T8-lymphocytes remain in the lymph node as they proliferate (clonal expansion) and only leave the lymphoid tissues and re-enter the bloodstream after they have differentiated into CTLs.)

While activated T8-lymphocytes produce interleukin-2 (IL-2) as well as a high-affinity IL-2 receptor themselves, in most cases it is the IL-2 produced by effector T4-lymphocytes that enables cell proliferation and formation of a clone of thousands of identical T8-lymphocytes after several days. IL-2 also contributes to survival of those activated T8-lymphocytes and their differentiation into T8-effector cells called a cytotoxic T-lymphocytes or CTLs .

CTLs leave the secondary lymphoid organs and enter the bloodstream where they can be delivered anywhere in the body via the circulatory system and the inflammatory response. In addition, some of the T8-lymphocytes differentiate into circulating T8-memory cells . Circulating T8-memory cells allow for a more rapid and greater production of CTLs upon subsequent exposure to the same antigen.

**Marking an infected cell or tumor cell for destruction by cytotoxic T-lymphocytes (CTLs)**

During the replication of viruses and intracellular bacteria within their host cell, as well as during the replication of tumor cells, viral, bacterial, or tumor proteins in the cytosol of that cell are degraded into a variety of peptide epitopes by cylindrical organelles called proteasomes . Other endogenous antigens such as proteins released into the cytosol from the phagosomes of antigen-presenting cells, such as macrophages and dendritic cells as well, as a variety of the human cell's own proteins (self-proteins) are also degraded by proteasomes. As these various endogenous antigens pass through proteasomes, proteases and peptidases chop the protein up into a series of peptides, typically 8-11 amino acids long (see Figure 5).

A transporter protein called TAP located in the membrane of the cell's endoplasmic reticulum then transports these peptide epitopes into the endoplasmic reticulum where they bind to the grooves of various newly made MHC-I molecules. The MHC-I molecules with bound peptides are then transported to the Golgi complex and placed in exocytic vesicles. The exocytic vesicles carry the MHC-I/peptide complexes to the cytoplasmic membrane of the cell where they become anchored to its surface (see Figure 6). A single cell may have up to 250,000 molecules of MHC-I with bound epitope on its surface.

Flash animation of MHC-I molecules binding epitopes from endogenous antigens in an infected cell.

html5 version of animation for iPad showing MHC-I molecules binding epitopes from endogenous antigens in an infected cell.
CTLs binding to infected cells or tumor cells and inducing apoptosis

CTLs are, by way of their TCRs and CD8 molecules, able to recognize infected cells and tumor cells displaying MHC-I molecules with bound peptides on their surface (see Figure 7) and destroy them through apoptosis, a programmed cell suicide.

Apoptosis involves a complex of intracellular granules. This complex of granules in a protected state including:

1. Pore-forming proteins called perforins;
2. Proteolytic enzymes called granzymes; and
3. A proteoglycan called granulysin.

When the TCR and CD8 of the CTL binds to the MHC-I/epitope on the surface of the virus-infected cell or tumor cell (see Figure 7), this sends a signal through a CD3 molecule which triggers the release of the perforins/granzymes/granulysin complexes from the CTL.

The exact mechanism of entry of the granzymes into the infected cell or tumor cell is still debated. It is, however, dependent on perforins. Possibilities include:

- The perforins/granzymes/granulysin complex may be taken into the target cell by receptor-mediated endocytosis. The perforin molecules may then act on the endosomal membrane allowing granzymes to enter the cytosol.
- The perforin molecules may put pores in the membrane of the target cell allowing the granzymes to directly enter the cytosol (see Figure 7).

Killing of the infected cell or tumor cell by apoptosis involves a variety of mechanisms:

- Certain granzymes can activate the caspase enzymes that lead to apoptosis of the infected cell. The caspases are proteases that destroy the protein structural scaffolding of the cell - the cytoskeleton - and nucleases that degrade both the target cell's nucleoprotein and any microbial DNA within the cell (see Figure 8).
- Granzymes cleave a variety of other cellular substrates that contribute to cell death.
- The perforin molecules may also polymerize and form pores in the membrane of the infected cell, similar to those produced by MAC. This can increase the permeability of the infected cell and contribute to cell death. If enough perforin pores form, the cell might not be able to exclude ions and water and may undergo cytolysis.
- Granulysin has antimicrobial actions and can also induce apoptosis.
  - Electron micrograph of a CTL binding to a tumor cell.
  - Electron micrograph showing a killed tumor cell.

Flash animation of a CTL triggering apoptosis by way of perforins and granzymes.

html5 version of animation for iPad showing a CTL triggering apoptosis by way of perforins and granzymes.

Flash animation of CTL-induced apoptosis of a virus-infected cell.

https://bio.libretexts.org/Bookshelves/Microbiology/Book%3A_Microbiology_(Kaiser)/Unit_6%3A_Adaptive_Immunity/12%3A__...
Summary

1. T-lymphocytes refer to lymphocytes that are produced in the bone marrow but require interaction with the thymus for their maturation.
2. The primary role of T8-lymphocytes is to kill infected cells and tumor cells by inducing apoptosis of those cells.
3. Once naive T8-lymphocytes are activated by dendritic cells, they proliferate and differentiate into T8-effector lymphocytes called cytotoxic T-lymphocytes (CTLs) that bind to and kill infected cells and tumor cells.
4. T8-lymphocytes display CD8 molecules and T-cell receptors (TCRs) on their surface.
5. The TCR on T8-lymphocytes, in cooperation with CD8, typically bind peptides from endogenous antigens bound to MHC-I molecules.
6. During its development, each T8-lymphocyte becomes genetically programmed, by gene-splicing reactions similar to those in B-lymphocytes and T4-lymphocytes, to produce a TCR with a unique shape capable of binding epitope/MHC-I complex with a corresponding shape.
7. To become activated, naive T8-lymphocytes migrate through lymph nodes where the TCRs on the T8-lymphocyte are able to sample large numbers of MHC-I/peptide complexes on the antigen-presenting dendritic cells for ones that “fit”, thus enabling activation of that naïve T8-lymphocyte.
8. After activation, the dendritic cell produces cytokines that contribute to proliferation of the T8-lymphocytes and their differentiation into effector T4-lymphocytes called cytotoxic T-lymphocytes (CTLs) that are able to bind to and kill infected cells and tumor cells displaying the same peptide/MHC-I complex on their surface.
9. Some of the T8-lymphocytes differentiate into circulating T8-memory cells that enable a more rapid and greater production of CTLs upon subsequent exposure to the same antigen.
10. During the replication of viruses and intracellular bacteria within their host cell, as well as during the replication of tumor cells, viral, bacterial, or tumor proteins in the cytosol of that cell are degraded into a variety of peptide epitopes by cylindrical organelles called proteasomes.
11. As these various endogenous antigens pass through proteasomes, proteases and peptidases chop the protein up into a series of peptides that are transported into the endoplasmic reticulum where they bind to newly made MHC-I
molecules.

12. The MHC-I molecules with bound peptides are then transported to the Golgi complex and placed in exocytic vesicles that carry the MHC-I/peptide complexes to the cytoplasmic membrane of the cell where they become anchored to its surface.

13. CTLs are, by way of their TCRs and CD8 molecules, are then able to recognize infected cells and tumor cells displaying MHC-I molecules with bound peptides on their surface. This sends a signal that triggers the release of the perforins/granzymes/granulysin complexes from the CTL to destroy the infected cell or tumor cell through apoptosis.

14. The perforin molecules may put pores in the membrane of the target cell allowing the granzymes to directly enter the cytosol, and certain granzymes activate the caspase enzymes that lead to apoptosis of the infected cell or tumor cell by destroying the cytoskeleton of the cell and degrading both the target cell's nucleoprotein and any microbial DNA within the cell.

Contributors

• Dr. Gary Kaiser (COMMUNITY COLLEGE OF BALTIMORE COUNTY, CATONSVILLE CAMPUS)