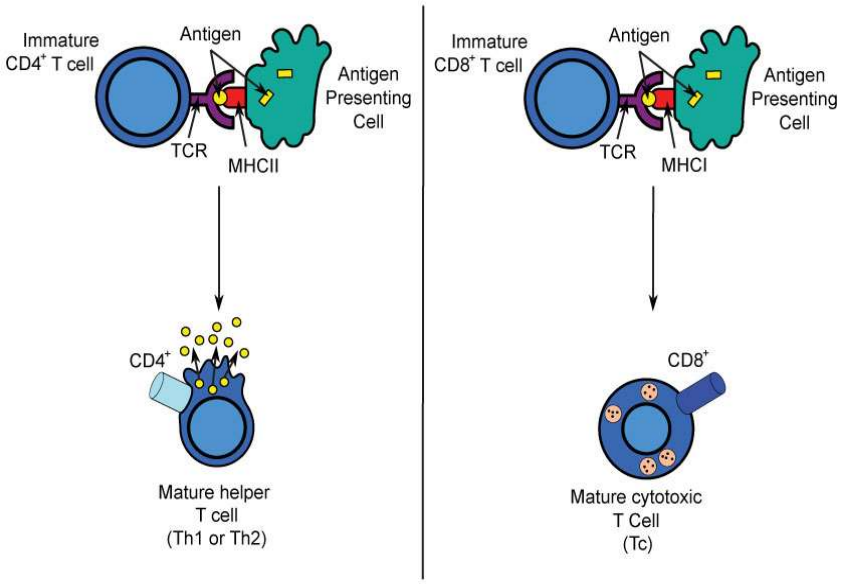
Cytotoxic T cell

From Wikipedia, the free encyclopedia



Antigen presentation stimulates T cells to become either "cytotoxic" CD8+ cells or "helper" CD4+ cells.

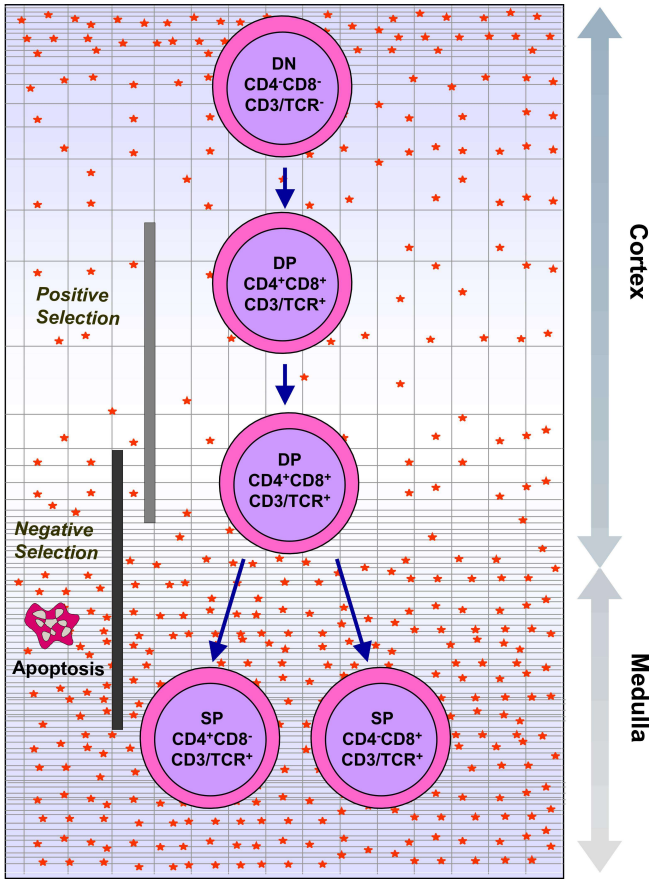
A **cytotoxic T cell** (also known as **T_C**, **cytotoxic T lymphocyte**, **CTL**, **T-killer cell**, **cytolytic T cell**, **CD8+ T-cell** or **killer T cell**) is a T lymphocyte (a type of white blood cell) that kills cancer cells, cells that are infected (particularly with viruses), or cells that are damaged in other ways.

Most cytotoxic T cells express T-cell receptors (TCRs) that can recognize a specific antigen. An antigen is a molecule capable of stimulating an immune response, and is often produced by cancer cells or viruses. Antigens inside a cell are bound to class I MHC molecules, and brought to the surface of the cell by the class I MHC molecule, where they can be recognized by the T cell. If the TCR is specific for that antigen, it binds to the complex of the class I MHC molecule and the antigen, and the T cell destroys the cell.

In order for the TCR to bind to the class I MHC molecule, the former must be accompanied by a glycoprotein called CD8, which binds to the constant portion of the class I MHC molecule. Therefore, these T cells are called **CD8+ T cells**.

The affinity between CD8 and the MHC molecule keeps the T_C cell and the target cell bound closely together during antigen-specific activation. CD8+ T cells are recognized as T_C cells once they become activated and are generally classified as having a pre-defined cytotoxic role within the immune system. However, CD8+ T cells also have the ability to make some cytokines.

Development



Development of single positive T cells in the thymus

The immune system must recognize millions of potential antigens. There are fewer than 30,000 genes in the human body, so it is impossible to have one gene for every antigen. Instead, the DNA in millions of white blood cells in the bone marrow is shuffled to create cells with unique receptors, each of which can bind to a different antigen. Some receptors bind to tissues in the human body itself, so to prevent the body from attacking itself, those self-reactive white blood cells are destroyed during further development in the thymus.

TCRs have two parts, usually an alpha and a beta chain. (Some TCRs have a gamma and a delta chain.) Hematopoietic stem cells in the bone marrow migrate into the thymus, where they undergo VDJ recombination of their beta-chain TCR DNA to form a developmental form of the TCR protein, known as pre-TCR. If that rearrangement is successful, the cells then rearrange their alpha-chain TCR DNA to create a functional alpha-beta TCR complex. This highly-variable genetic rearrangement product in the TCR genes helps create millions of different T cells with different TCRs, helping the body's immune system respond to virtually any protein of an invader. The vast majority of T cells express alpha-beta TCRs (αβ T cells), but some T cells in epithelial tissues (like the gut) express gamma-delta TCRs (γδ T cells), which recognize non-protein antigens.

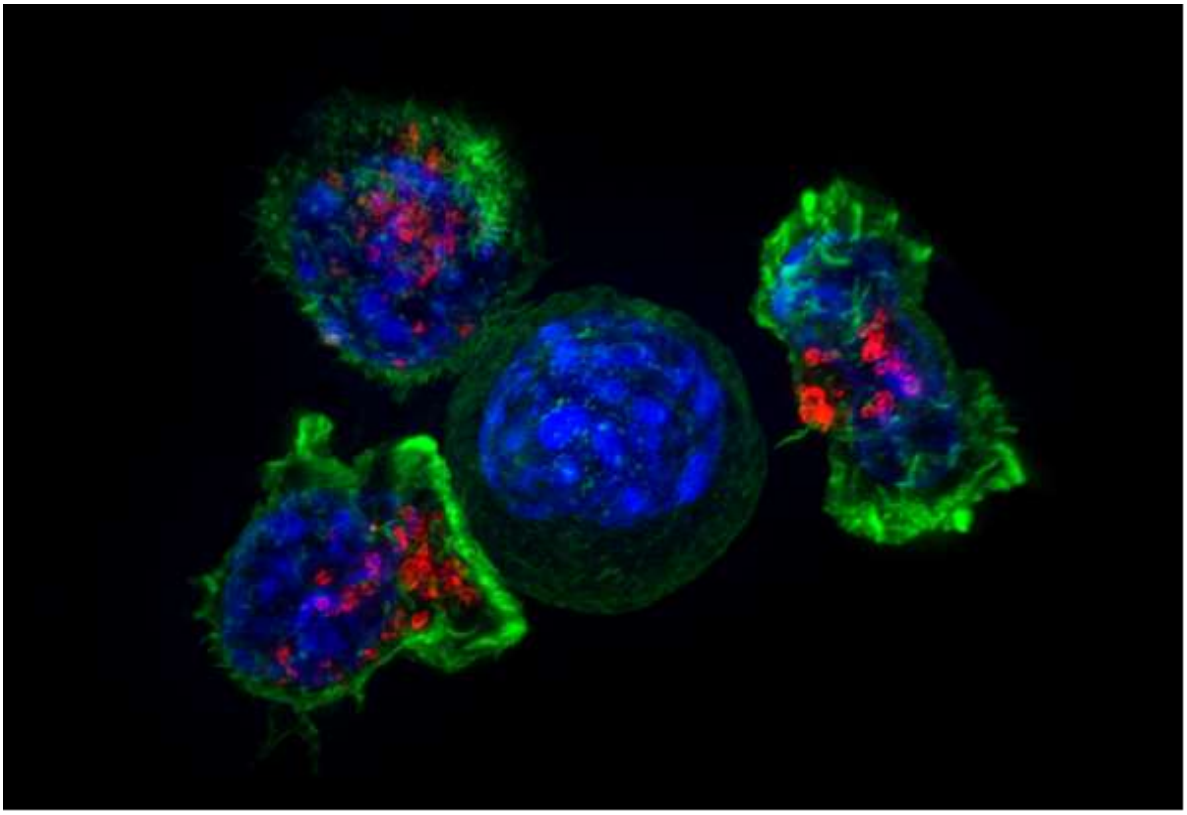
T cells with functionally stable TCRs express both the CD4 and CD8 co-receptors and are therefore termed "double-positive" (DP) T cells (CD4+CD8+). The double-positive T cells are exposed to a wide variety of self-antigens in the thymus and undergo two selection criteria:

1. **positive selection**, in which those double-positive T cells that bind *too weakly* to MHC-

presented *self antigens* undergo apoptosis because of their inability to recognize MHC-protein complexes.
2. **negative selection**, in which those double-positive T cells that bind *too strongly* to MHC-presented *self antigens* undergo apoptosis because they could otherwise become autoreactive, leading to autoimmunity.

Only those T cells that bind to the MHC-self-antigen complexes weakly are positively selected. Those *cells that survive positive and negative selection differentiate into single-positive T cells (either CD4+ or CD8+), depending on whether their TCR recognizes an MHC class I-presented antigen (CD8) or an MHC class II-presented antigen (CD4).* It is the CD8+ T-cells that will mature and go on to become **cytotoxic T cells** following their activation with a class I-restricted antigen.

Activation



In this immunofluorescence image, a group of killer T cells (outer three) is engaging a cancer cell (centered one). A patch of signaling molecules (pink) that gathers at the site of cell-cell contact indicates that the CTL has identified a target. Lytic granules (red) that contain cytotoxic components then travel along the microtubule cytoskeleton (green) to the contact site and are secreted, thus killing the target.

With an exception of some cell types, such as non-nucleated cells (including erythrocytes), Class I MHC is expressed by all host cells. When these cells are infected with a virus (or another intracellular pathogen), the cells degrade foreign proteins via antigen processing. These result in peptide fragments, some of which are presented by MHC Class I to the T cell antigen receptor (TCR) on CD8+ T cells.

The activation of cytotoxic T cells is dependent on several simultaneous interactions between molecules expressed on the surface of the T cell and molecules on the surface of the antigen-presenting

cell (APC). For instance, consider the ***two signal model*** for T_C cell activation.

Signal	T cell	APC	Description
First Signal	TCR	peptide-bound MHC class I molecule	There is a second interaction between the CD8 coreceptor and the class I MHC molecule to stabilize this signal.
Second Signal	CD28 molecule on the T cell	either CD80 or CD86 (also called B7-1 and B7-2)	CD80 and CD86 are known as *costimulators* for T cell activation. This second signal can be assisted (or replaced) by stimulating the T_C cell with cytokines released from helper T cells.

A simple activation of naive $CD8^+$ T cells requires the interaction with professional antigen-presenting cells, mainly with matured dendritic cells. To generate longlasting memory T cells and to allow repetitive stimulation of cytotoxic T cells, dendritic cells have to interact with both, activated $CD4^+$ helper T cells and $CD8^+$ T cells.[1][2] During this process, the $CD4^+$ helper T cells "license" the dendritic cells to give a potent activating signal to the naive $CD8^+$ T cells.

While in most cases activation is dependent on TCR recognition of antigen, alternative pathways for activation have been described. For example, cytotoxic T cells have been shown to become activated when targeted by other CD8 T cells leading to tolerization of the latter.[3]

Once activated, the T_C cell undergoes clonal expansion with the help of the cytokine Interleukin-2 (IL-2), which is a growth and differentiation factor for T cells. This increases the number of cells specific for the target antigen that can then travel throughout the body in search of antigen-positive somatic cells.

Effector functions

When exposed to infected/dysfunctional somatic cells, T_C cells release the cytotoxins perforin, granzymes, and granulysin. Through the action of perforin, granzymes enter the cytoplasm of the target cell and their serine protease function triggers the caspase cascade, which is a series of cysteine proteases that eventually lead to apoptosis (programmed cell death).

A second way to induce apoptosis is via cell-surface interaction between the T_C and the infected cell. When a T_C is activated it starts to express the surface protein FAS ligand (FasL)(Apo1L)(CD95L), which can bind to *Fas* (Apo1)(CD95) molecules expressed on the target cell. However, this Fas-Fas ligand interaction is thought to be more important to the disposal of unwanted T lymphocytes during their development or to the lytic activity of certain T_H cells than it is to the cytolytic activity of T_C effector cells. Engagement of Fas with FasL allows for recruitment of the death-induced signaling complex (DISC).[4] The Fas-associated death domain (FADD) translocates with the DISC, allowing recruitment of procaspases 8 and 10.[5] These caspases then activate the effector caspases 3, 6, and 7, leading to cleavage of death substrates such as lamin A, lamin B1, lamin B2, PARP (poly ADP ribose polymerase), and DNAPK (DNA-activated protein kinase). The final result is apoptosis of the cell that expressed Fas.

Role in disease pathogenesis

See also: Hepatitis B virus

During hepatitis B virus (HBV) infection cytotoxic T cells play an important pathogenetic role. They contribute to nearly all of the liver injury associated with HBV infection and, by killing infected cells and by producing antiviral cytokines capable of purging HBV from viable hepatocytes, cytotoxic T cells also eliminate the virus.[6] Platelets have been shown to facilitate the accumulation of virus-specific cytotoxic T cells into the infected liver.[7]

Cytotoxic T cells have been implicated in the progression of arthritis: depletion of knee joint cartilage macromolecules such as glycosaminoglycans by cytotoxic T cells and macrophages has been observed in a rat model of the disease.[8]

References

- Claire Hivroz, Karine Chemin, Marie Tourret, Armelle Bohineust: *Crosstalk between T Lymphocytes and Dendritic Cells.* In: *Critical Reviews™ in Immunology.* 32, 2012, S. 139, doi:10.1615/CritRevImmunol.v32.i2.30.
- Stefanie Hoyer, Sabrina Prommersberger, Isabell A. Pfeiffer, Beatrice Schuler-Thurner, Gerold Schuler, Jan Dörrie, Niels Schaft: *Concurrent interaction of DCs with CD4 and CD8 T cells improves secondary CTL expansion: It takes three to tango* . In: *European Journal of Immunology.* 44, 2014, S. 3543, doi:10.1002/eji.201444477.
- Milstein, O., Hagin, D., Lask, A., Reich-Zeliger, S., Shezan E., Ophir E., Eidelshtein Y., Afik R., Antebi YE., Dustin ML. and Reisner Y. (2011) CTLs respond with activation and granule secretion when serving target for T cell recognition. Blood 117,1042-1052
- *Bakshi, Rakesh K.; Cox, Maureen A.; Zajac, Allan J. (2014). Mackay, Ian R.; Rose, Noel R.; Diamond, Betty; Davidson, Anne, eds. Encyclopedia of Medical Immunology. Springer New York. pp. 332–342. ISBN 9780387848273. doi:10.1007/978-0-387-84828-0_36.*
- *Bakshi, Rakesh K.; Cox, Maureen A.; Zajac, Allan J. (2014). Mackay, Ian R.; Rose, Noel R.; Diamond, Betty; Davidson, Anne, eds. Encyclopedia of Medical Immunology. Springer New York. pp. 332–342. ISBN 9780387848273. doi:10.1007/978-0-387-84828-0_36.*
- *Iannacone, Matteo; Sitia, Giovanni; Guidotti, Luca G (2006). "Pathogenetic and antiviral immune responses against hepatitis B virus". Future Virology. **1** (2): 189–96. doi:10.2217/17460794.1.2.189.*
- *Iannacone, Matteo; Sitia, Giovanni; Isogawa, Masanori; Marchese, Patrizia; Castro, Maria G; Lowenstein, Pedro R; Chisari, Francis V; Ruggeri, Zaverio M; Guidotti, Luca G (2005). "Platelets mediate cytotoxic T lymphocyte–induced liver damage". Nature Medicine. **11** (11): 1167–9. PMC 2908083. PMID 16258538. doi:10.1038/nm1317.*
- *Subramanian S and Ramalingam K (2005). "Electron microscopic evidence on the participation Cytotoxic T Lymphocytes and Macrophages in Mtb adjuvant induced connective tissue inflammation and arthritogenesis in Rattus norvegicus". Asian Journal of Microbiology, Biotechnology and Environmental Sciences. 7 (2): 227–233. ISSN 0972-3005.*