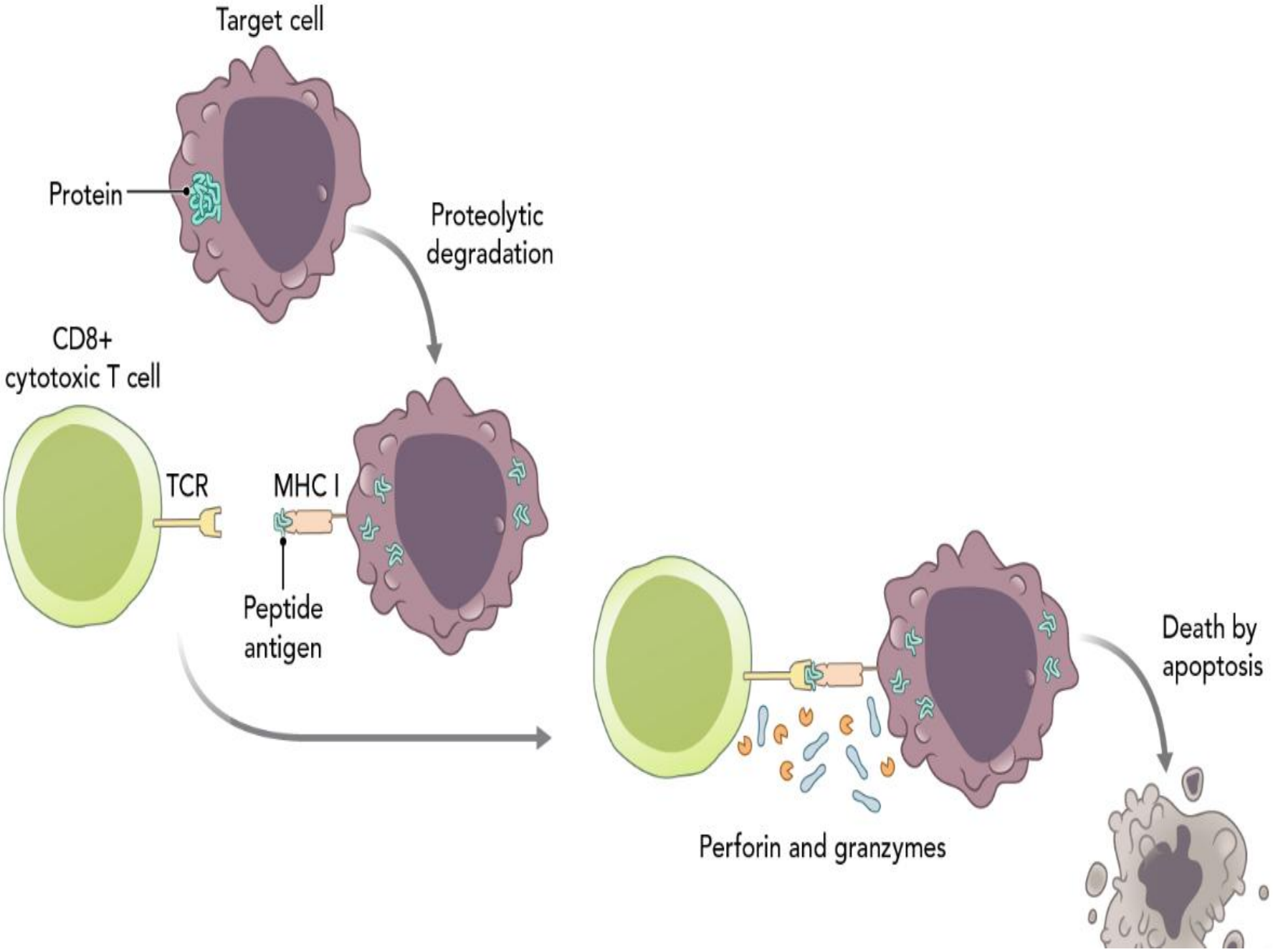
Major histocompatibility complex

Major histocompatibility complex, or MHC, molecules are transmembrane proteins that display antigens to T cells as part of the adaptive immune response. The antigens that MHC molecules are able to display consist of short, linear fragments of proteins, called peptides. To create these peptide antigens, proteins must be broken down inside the cell prior to being displayed on MHC. T cell receptors (TCRs) are highly specific for and only recognize a single peptide antigen in the context of a particular MHC variant. This is known as **MHC restriction**.

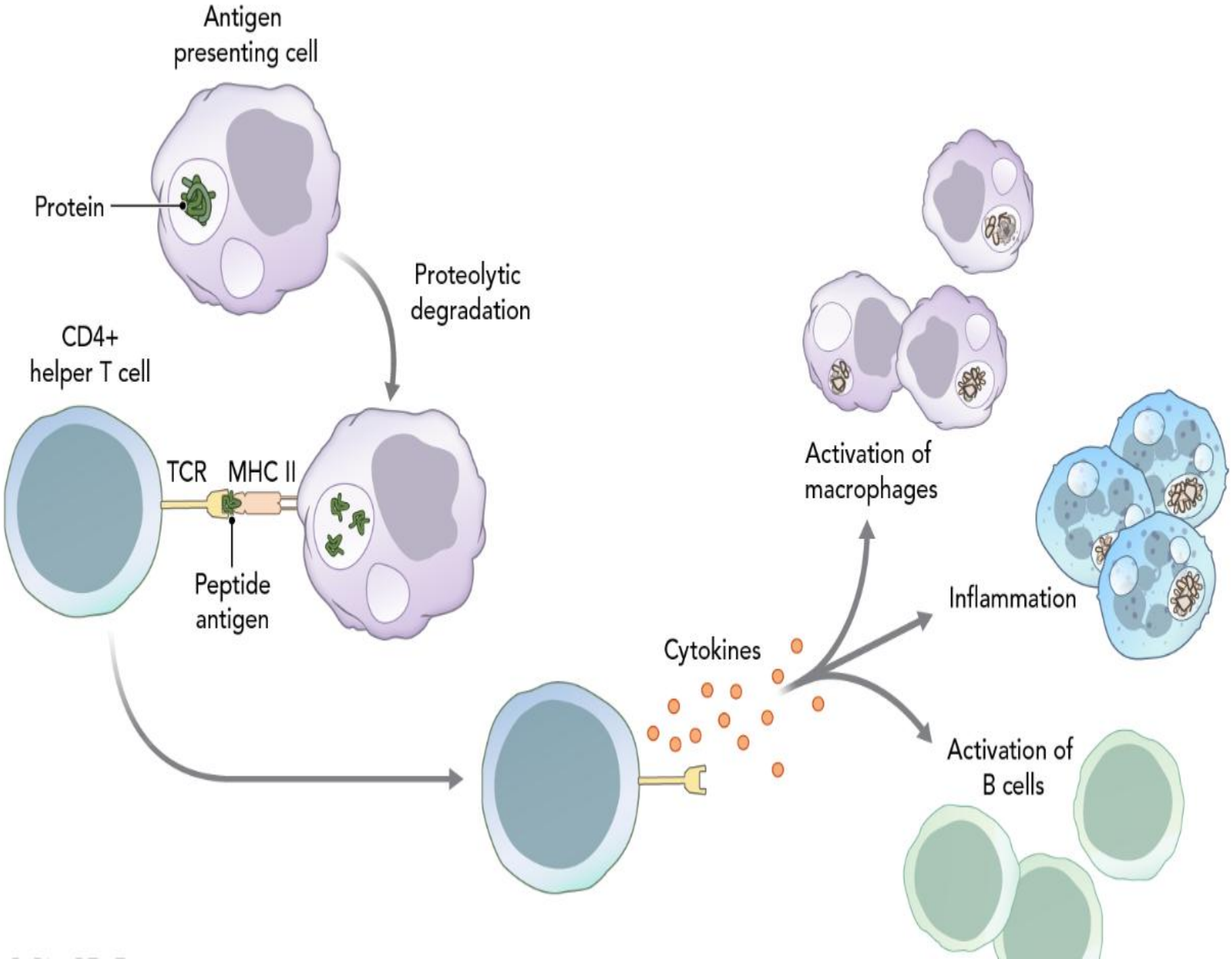
Types of MHC; MHC 1

There are two types of MHC: class I and class II. **MHC class I** is found on almost all nucleated cells and can be recognized by the T cell receptor of **$CD8^+$ cytotoxic T cells**. $CD8^+$ T cells are immune cells that recognize potentially hazardous cells and release signals that cause the target cells to die by apoptosis. Nucleated cells in the body proteolytically degrade proteins in the cytosol, and these proteins are then delivered to newly synthesized MHC I molecules. MHC I molecules with bound peptide are displayed on the cell surface for possible recognition by nearby $CD8^+$ T cells. When a cytotoxic T cell encounters a cell displaying the antigen it recognizes on MHC class I, the T cell releases perforin and granzymes (programmed cell death-inducing proteins) that initiate apoptosis in the presenting cell. Because cytotoxic T cells only recognize antigens when bound to MHC, any cells that do not display antigen on MHC class I, including red blood cells, are invisible to $CD8^+$ T cells. Many cells that are infected with viruses or that have become cancerous stop expressing MHC in order to evade detection and destruction by cytotoxic T cells.


Target cell
Protein
Proteolytic degradation
CD8+ cytotoxic T cell
TCR
MHC I
Peptide antigen
Perforin and granzymes
Death by apoptosis

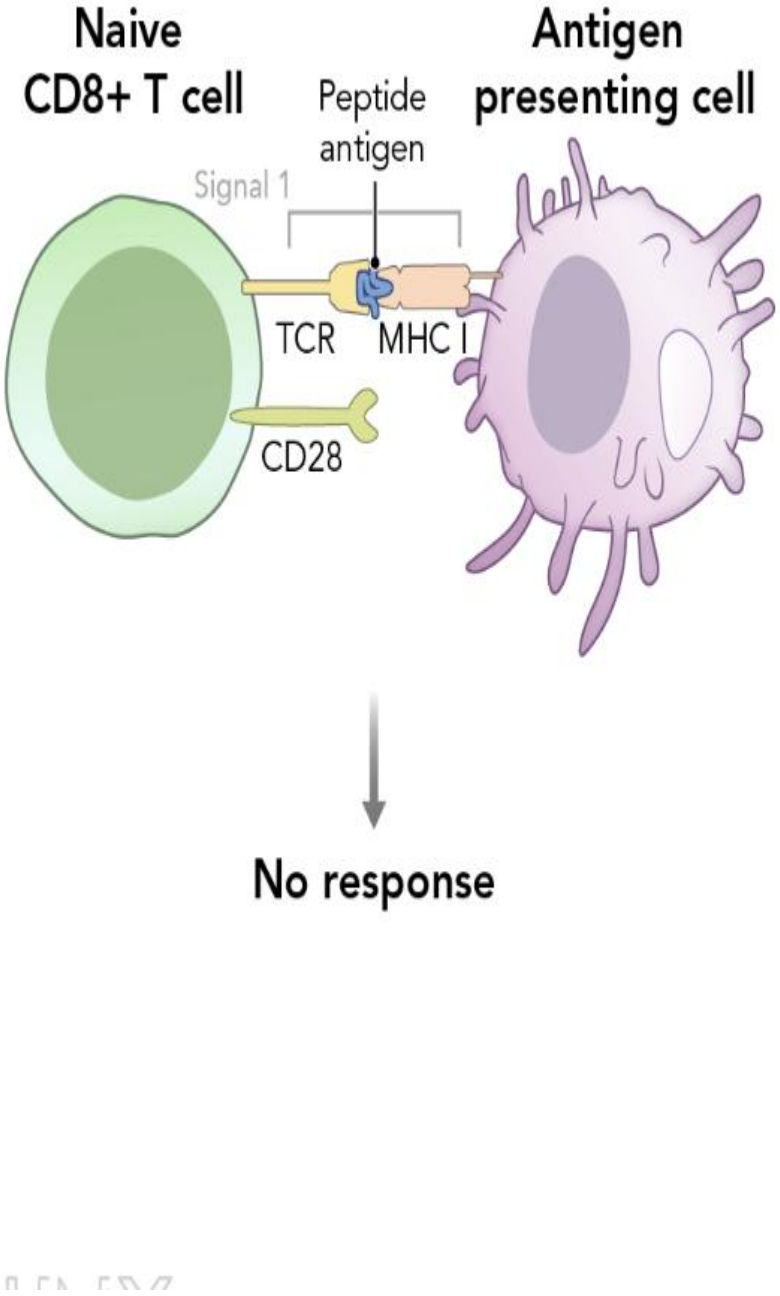
MHC 2

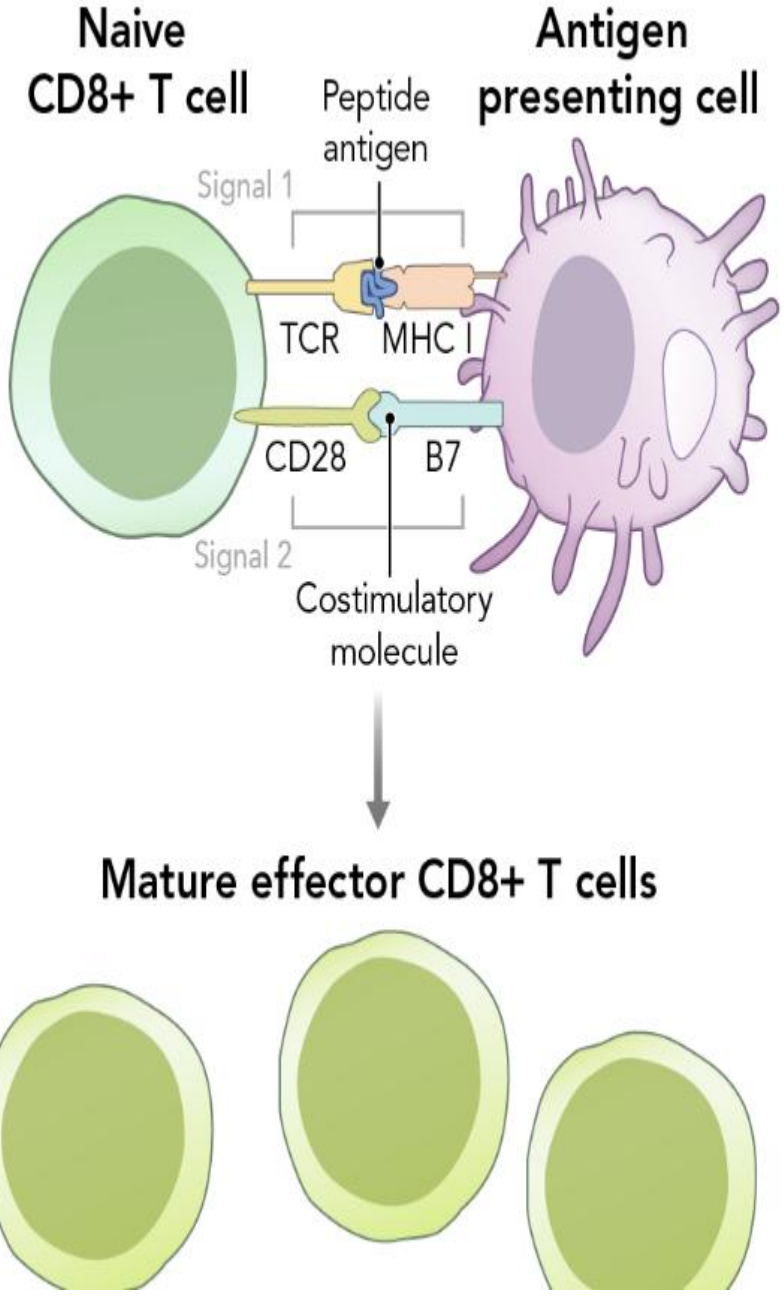
In contrast, **MHC class II** is only found on a few types of antigen-presenting cells, including dendritic cells, B cells, and macrophages, and is recognized by the T cell receptor of **$CD4^+$ helper T cells**. $CD4^+$ helper T cells are immune cells that act indirectly to protect us from threats to our health by increasing the activity of other immune cells. Antigen-presenting cells internalize proteins from the extracellular space or other cells through phagocytosis and degrade them into peptides in endosomes or lysosomes. The peptides then bind to and are presented by MHC class II. When a $CD4^+$ helper T cell recognizes a peptide-MHC complex on an antigen-presenting cell, it expresses secreted and membrane-bound proteins that increase the activation of nearby immune cells. These signals aid in the activity of many immune cells, including $CD8^+$ T cells, B cells, and innate immune cells.


Antigen presenting cell
Protein
Proteolytic degradation
CD4+ helper T cell
TCR
MHC II
Peptide antigen
Cytokines
Activation of macrophages
Inflammation
Activation of B cells

Activation of CD4 and CD8 cells

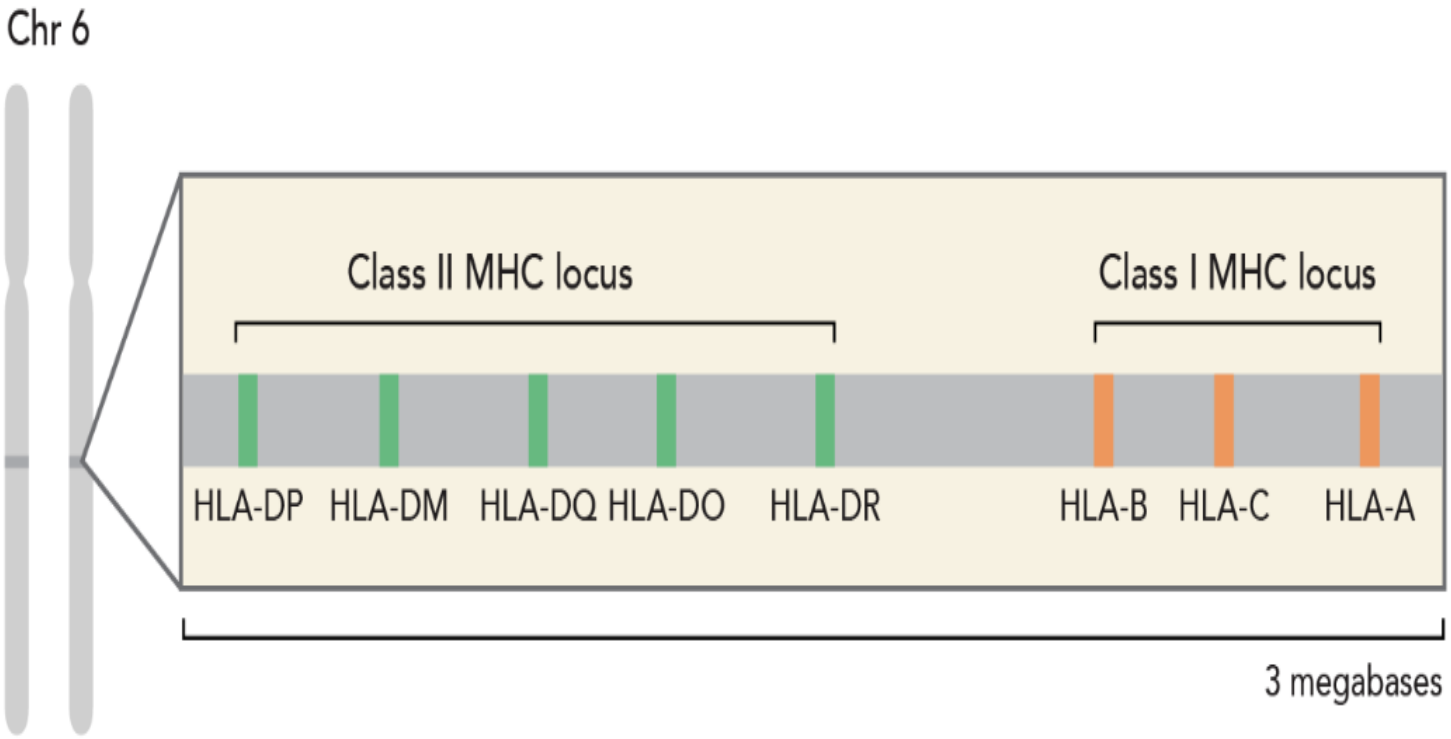
Presentation of antigen on MHC by specific antigen-presenting cells in the lymph node is also required to activate both naive $CD4^+$ and naive $CD8^+$ T cells and enable them to become effector cells. This activation requires two signals. The first signal is provided by the interaction of the T cell receptor with the peptide-MHC complex on an antigen-presenting cell. The second signal consists of interactions between **costimulatory molecules** on antigen-presenting cells with receptors on the naive T cells. Expression of costimulatory molecules, such as B7, on antigen-presenting cells is induced in response to damage associated molecular patterns or cytokines. These costimulatory molecules bind to receptors, such as CD28, on the T cells, providing the second signal. When a naive T cell receives the first signal without costimulation, no response will be generated and the T cell may become unresponsive or die. While the figure in the next slide shows the molecular interactions required for activation of $CD8^+$ T cells, the same interactions occur during $CD4^+$ T cell activation during which the T cell receptor binds to a peptide/MHC II complex.


Naive
CD8+ T cell
Peptide
antigen
Antigen
presenting cell
Signal 1
TCR
MHC I
CD28
No response


Naive
CD8+ T cell
Peptide
antigen
Antigen
presenting cell
Signal 1
TCR
MHC I
CD28
B7
Signal 2
Costimulatory
molecule
Mature effector CD8+ T cells

MHC haplotype inheritance

In humans, the MHC proteins are also known as human leukocyte antigen, or HLA. The HLA genes are highly polymorphic, meaning that in the population, there are many different **alleles**, or versions of the gene that differ in sequence. Because the genome contains multiple HLA genes and individuals inherit copies of the HLA genes from each of their parents, a person's cells can display many different HLA variants. The genes that encode class I MHC proteins in humans include HLA-A, HLA-B, and HLA-C, while those that encode class II MHC proteins in humans include HLA-DP, HLA-DM, HLA-DO, HLA-DQ, and HLA-DR. These genes are all located in the same region of chromosome 6, which means that the full set of HLA alleles found on one parental chromosome tend to be inherited together. This set of linked alleles found on one chromosome is referred to as a **haplotype**. Genomic studies have indicated that certain HLA alleles are associated with numerous diseases and conditions including diabetes, psoriasis, multiple sclerosis, several types of cancer, and certain severe, life-threatening reactions to medications. Because T cells and other immune cells recognize antigen in the context of specific MHC allelic variants, the immune system sees cells with different MHC alleles as foreign and attacks them. This plays a role in transplantation, as the immune system will reject any cells with MHC alleles that they do not recognize.


Chr 6
Class II MHC locus
Class I MHC locus
HLA-DP
HLA-DM
HLA-DQ
HLA-DO
HLA-DR
HLA-B
HLA-C
HLA-A
3 megabases