Autoimmunity and major histocompatibility complex

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Learning objectives

At the end of lecture students of 1st year MBBS should be able to

1. Define autoimmunity
2. Explain how immune reaction to self antigens is avoided
3. Define and classify major histocompatibility complex
4. Characterize the significance and functions of major histocompatibility complexes

Function of immune system

Protect the host from environmental agents such as microbes or chemicals, thereby preserving the integrity of the body. This is done by

1. **recognition of the self and**

2. **response to non-self.**

Autoimmunity(failure to recognition of self)

- The failure of an organism in recognizing its own constituent parts as *self, which allows an immune response against its own cells and tissues.*

- **Autoimmunity results from a failure or breakdown of the mechanisms normally responsible for maintaining self-tolerance in B cells, T cells, or both .**

Major Histocompatibility (MHC) proteins

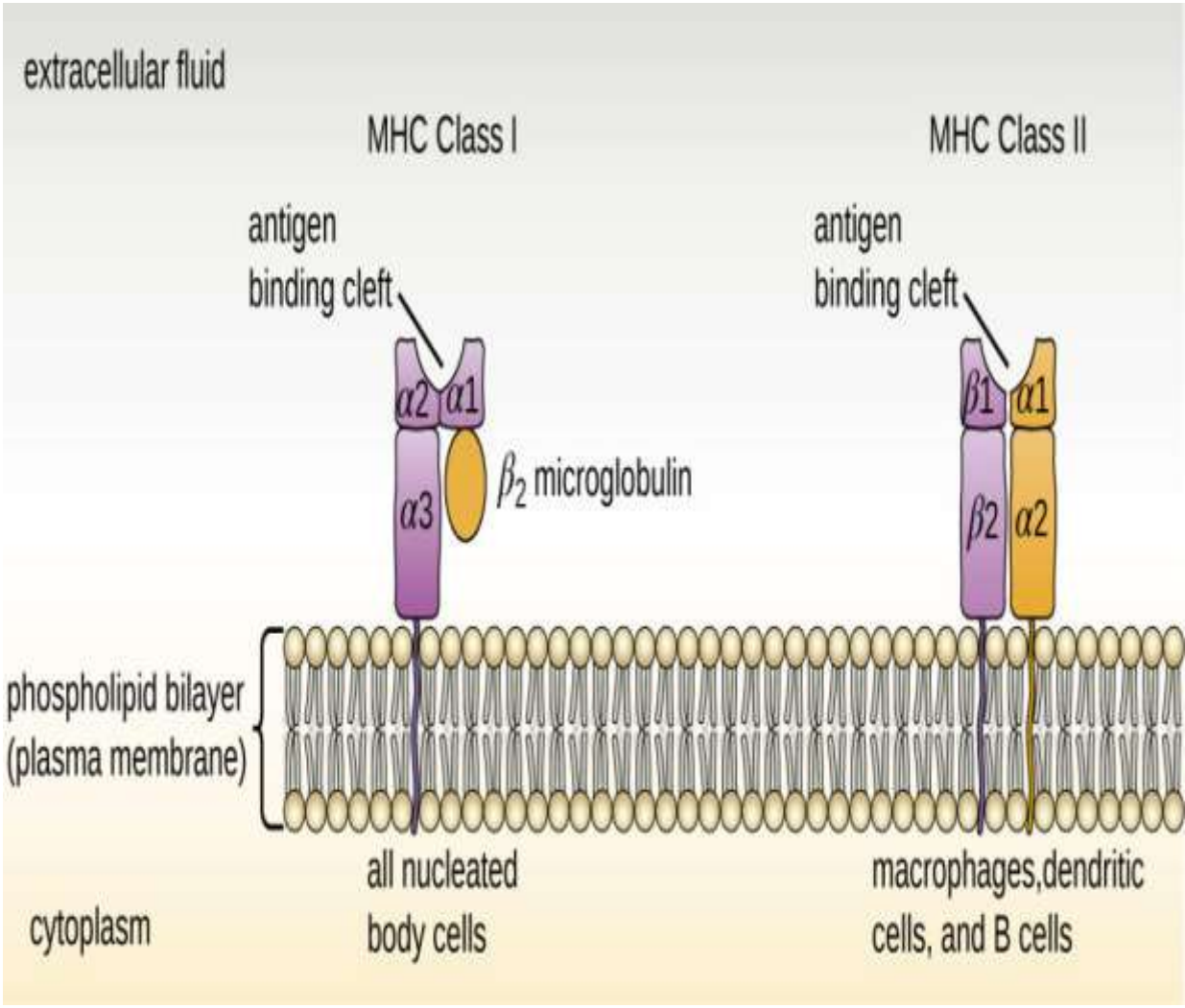
T cell receptor only recognize antigens combined with major histocompatibility (MHC) proteins on the surface of cells.

Response of B cells vs. T cells

- Whatever BCR bind to self proteins in bone marrow ,that B cell will be killed and not allowed to enter the circulation
- The rest of B cells that do not react with self will be released, settled in lymph nodes where they can attack bacteria etc

- T cell receptor only recognize antigens combined with major histocompatibility (MHC) proteins on the surface of cells.
- **MHC Class** I: Found on all cells and present antigens to Cytotoxic T cell
- **MHC Class II**: Found on phagocytes and present antigens to T helper cells

Self-antigens are cell membrane–bound glycoproteins known as MHC molecules because their synthesis is directed by a group of genes called the major histocompatibility complex, or MHC.



Class I MHC glycoproteins, which are found on the surface of all nucleated body cells

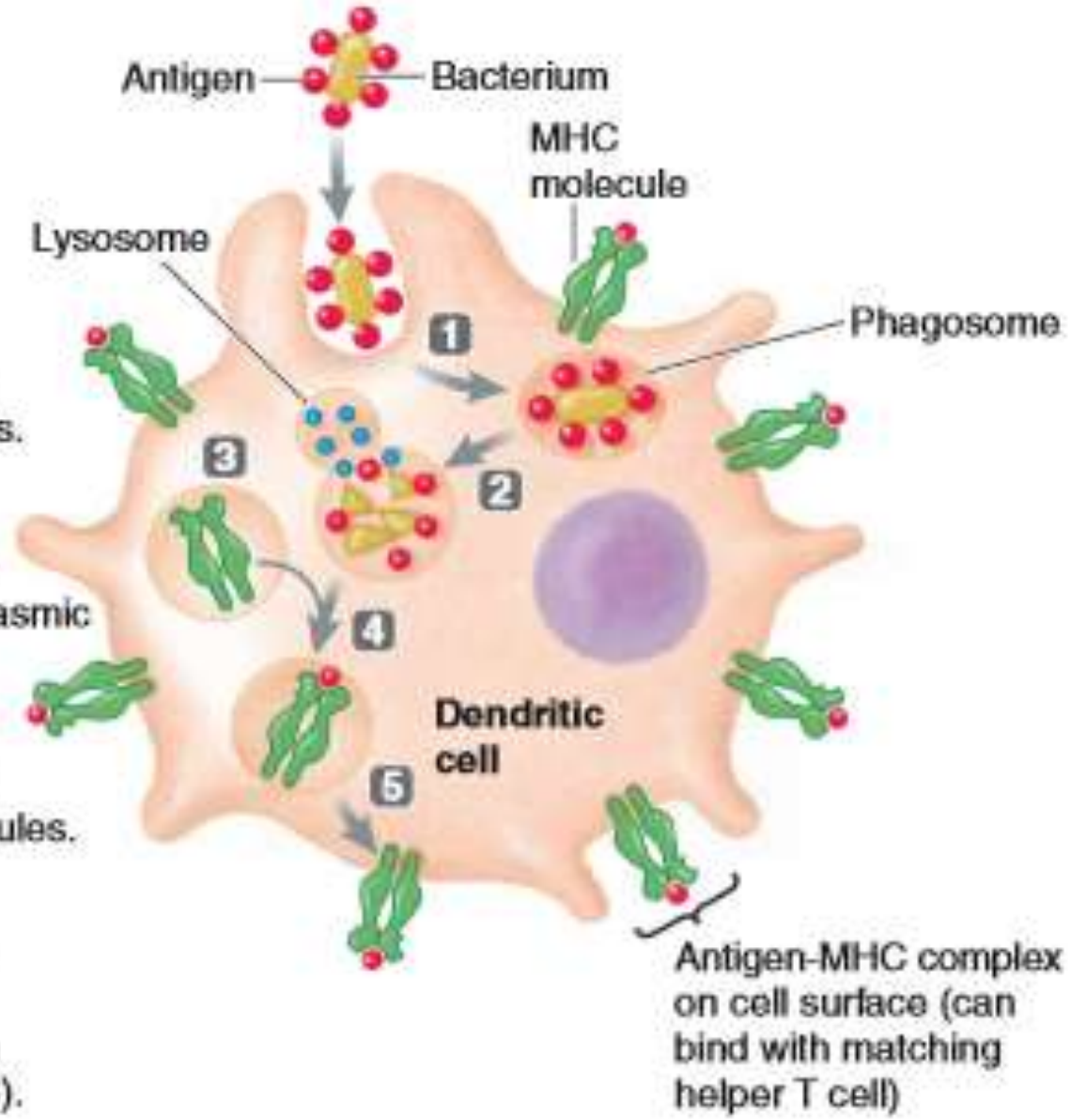
recognized by CD 8 cytotoxic T cell

Cass II MHC glycoproteins, which are, are restricted to the surface of a few special types of immune cells.

recognized by helper CD4 T cells

The natural function of MHC antigens lies in their ability to direct the responses of T cells,

T cells cannot perform their tasks without assistance from antigen-presenting cells. That is, relevant T cells cannot recognize “raw” foreign antigens entering the body; before reacting to it, a T-cell clone must be formally “introduced” to the antigen.



1 Dendritic cell engulfs a bacterium.

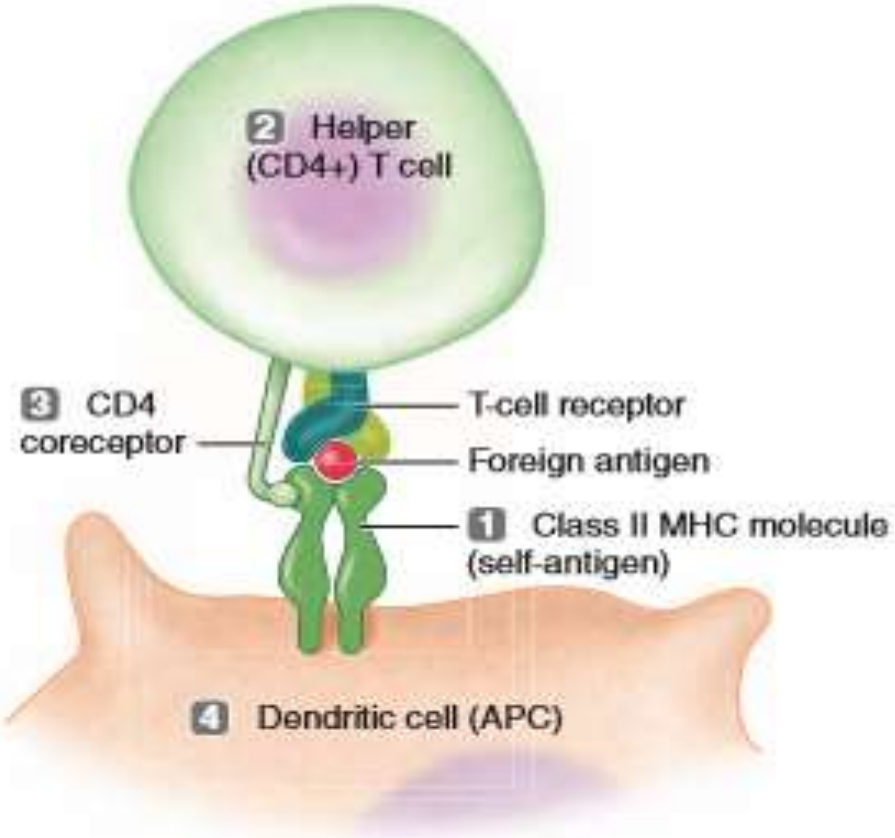
2 Large molecules of engulfed bacterium are broken down by lysosomes to produce antigenic peptides.

3 New MHC molecule has been synthesized by endoplasmic reticulum–Golgi complex.

4 Antigenic peptides bind to newly formed MHC molecules.

5 Antigen is displayed on cell surface bound to MHC molecule—the cell is now an antigen-presenting cell (APC).

Generation of an antigen-presenting cell when a dendritic cell engulfs a bacterium.

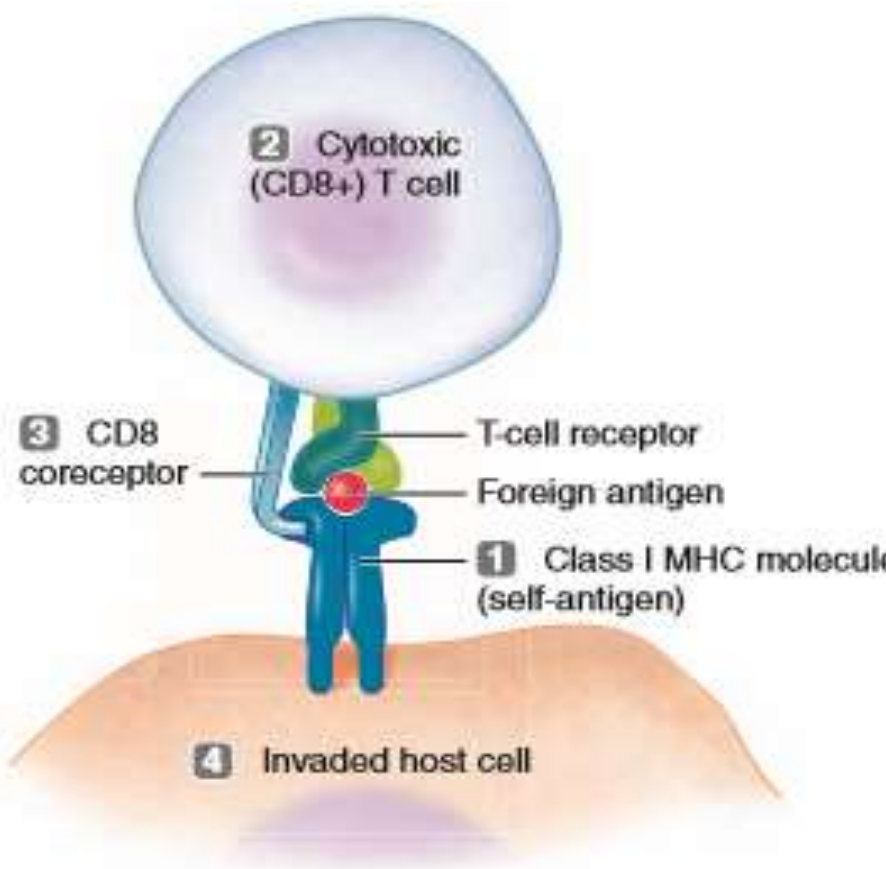


1 Class II MHC molecules are found on the surface of immune cells with which helper T cells interact: dendritic cells, macrophages, and B cells.

2 They are recognized only by helper (CD4+) T cells.

3 CD4 coreceptor links the two cells together.

4 To be activated, helper T cells must bind with a class II MHC-bearing APC (dendritic cell or macrophage). To activate B cells, helper T cell must bind with a class II MHC-bearing B cell with displayed foreign antigen.



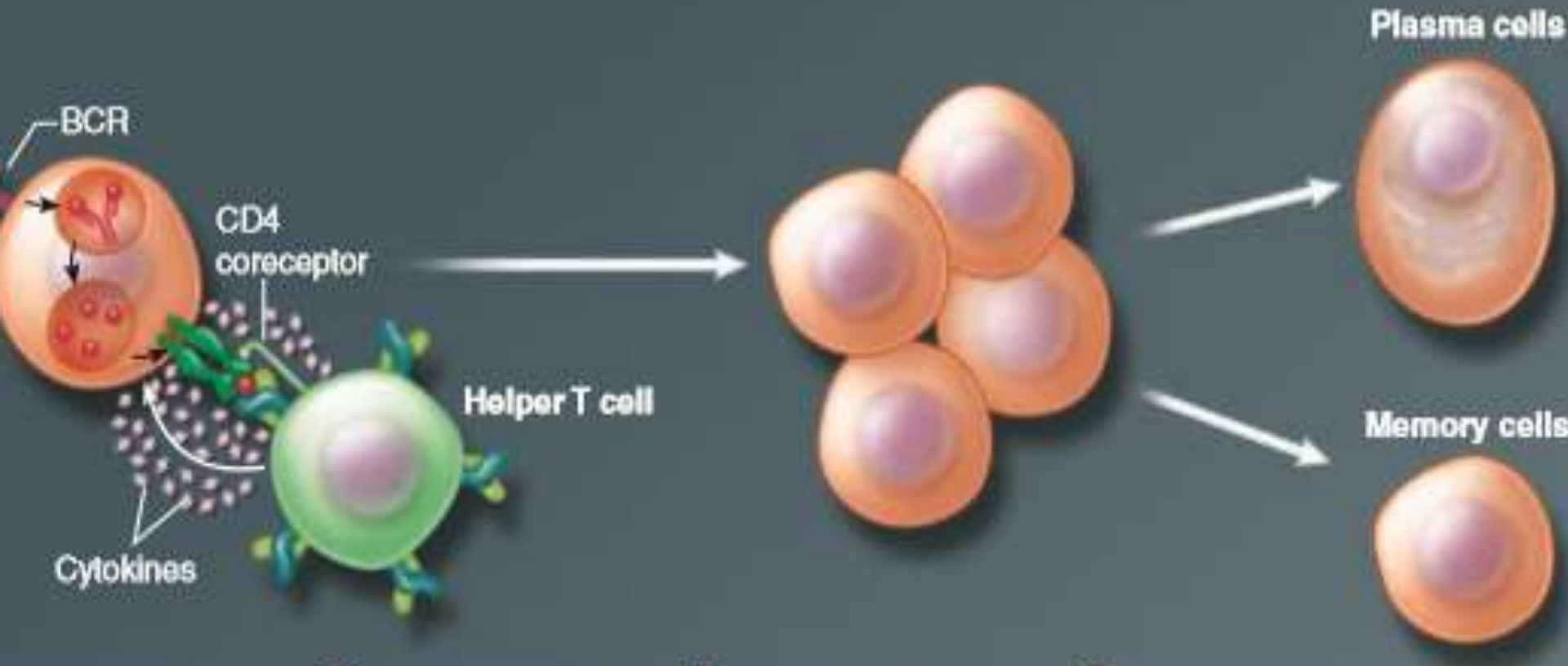
1 Class I MHC molecules are found on the surface of all cells.

2 They are recognized only by cytotoxic (CD8+) T cells.

3 CD8 coreceptor links the two cells together.

4 Linked in this way, cytotoxic T cells can destroy body cells if invaded by foreign (viral) antigen.

f B cells responsive to T-dependent antigen



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7 TCR of a helper T cell recognizes specific antigen on B cell, and CD4 coreceptor links the two cells together.

8 Helper T cell secretes cytokines that stimulate B cell proliferation to produce clone of selected cells.

9 Some cloned B cells differentiate into plasma cells, which secrete antibodies specific for the antigen, while a few differentiate into memory B cells.

Specific binding requirements for the two types of T cells ensure that these cells bind only with the target cells with which they can interact.

Helper (CD4) T cells, which are activated by or enhance the activities of dendritic cells, macrophages, and B cells, can recognize and bind with foreign antigen only when it is in association with class II MHC glycoproteins, which are found only on the surface of these other immune cells.

CD4 T-cell's coreceptor

Cytotoxic (CD8) T cells can recognize and bind with foreign antigen only when the antigen is in association with class I MHC glycoproteins, which are found on the surface of all body cells. This requirement is met when a virus invades a body cell, whereupon the cell is destroyed by the cytotoxic T cells

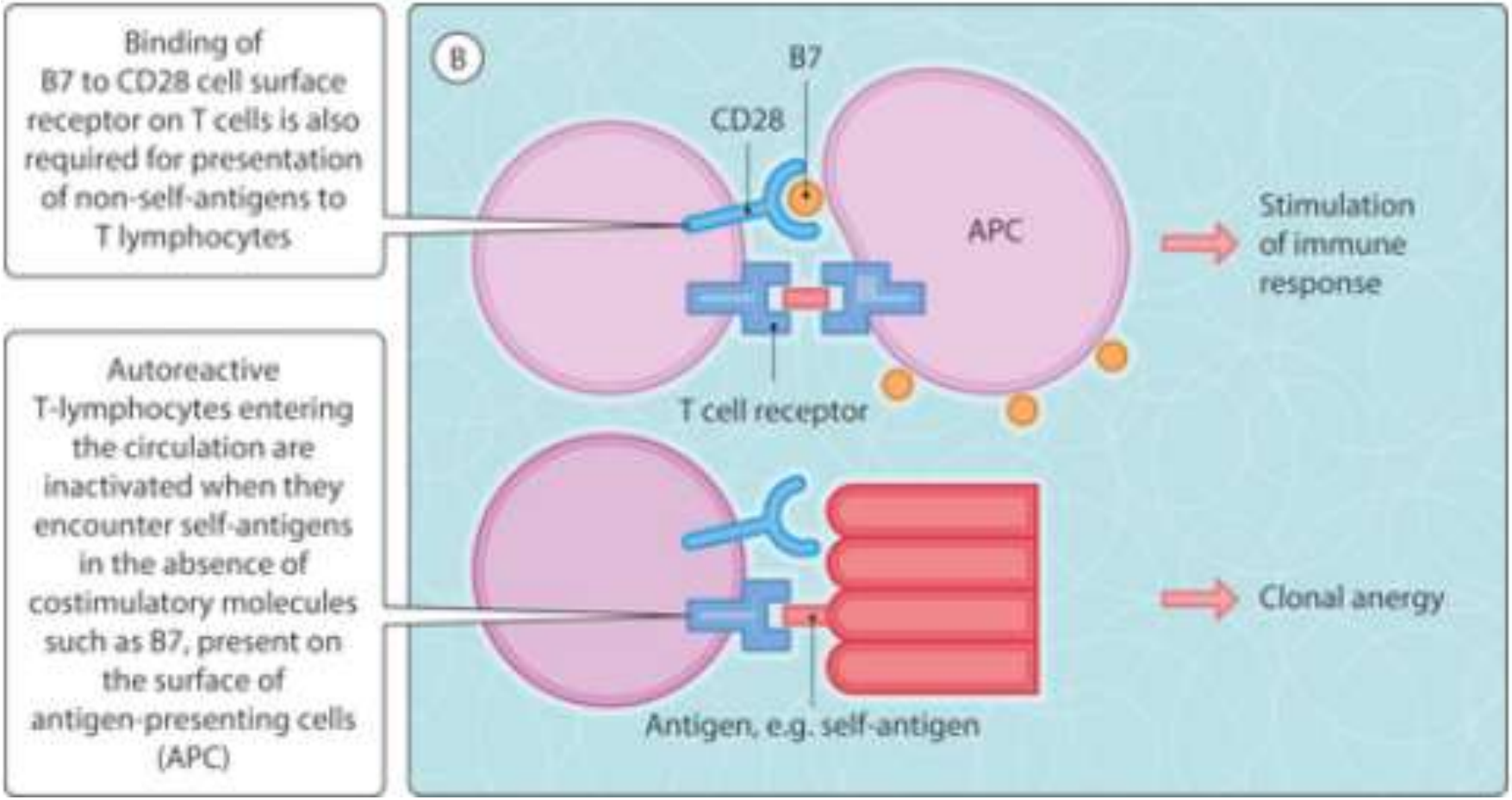
CD8 – T cell coreceptor

Mechanisms of tolerance

1) **Clonal deletion**. In response to continuous exposure to body antigens early in development, B and T lymphocyte clones specifically capable of attacking these self-antigens in most cases are permanently destroyed within the thymus. This clonal deletion is accomplished by triggering apoptosis of immature cells that would react with the body's proteins.

2. Anergy

- The first exposure to a single signal from a self-antigen “turns off” the compatible T cell, rendering the cell unresponsive to further exposure to the antigen. This reaction is referred to as clonal anergy (anergy means “lack of energy”) because T cells are inactivated (that is, “become lazy”) rather than activated by their antigens. Anergized T lymphocyte clones survive, but they cannot function


Binding of B7 to CD28 cell surface receptor on T cells is also required for presentation of non-self-antigens to T lymphocytes
Autoreactive T-lymphocytes entering the circulation are inactivated when they encounter self-antigens in the absence of costimulatory molecules such as B7, present on the surface of antigen-presenting cells (APC)
B
B7
CD28
APC
T cell receptor
Stimulation of immune response
Clonal anergy
Antigen, e.g. self-antigen

3. Active suppression by regulatory cells

play a role in self-tolerance by inhibiting throughout life some lymphocyte clones specific for the body's tissues

4. Receptor editing

With receptor editing, once a B cell that bears a receptor for one of the body's antigens encounters the self-antigen, the B cell escapes death by swiftly changing its antigen receptor to a non self version. In this way, an originally self-reactive B cell survives but is "rehabilitated" so that it never targets the body's tissues again.

5. Immunological ignorance

Alternatively known as antigen sequestering. Some self-molecules are normally hidden from the immune system because they never come into direct contact with the ECF in which the immune cells and their products circulate. An example is thyroglobulin, a complex protein sequestered within the hormone-secreting structures of the thyroid gland

Autoimmunity

1. Escape of auto-reactive clones

   The negative selection in the thymus may not be fully functional to eliminate self reactive cells.

2. Not all self antigens may be represented in the thymus

3. Certain antigens may not be properly processed and

presented.

4.Cross reactive antigens(molecular mimicry)

Antigens on certain pathogens may have determinants which cross react with self antigens and an immune response against these determinants may lead to formation of antibodies against tissue antigens.

Post streptococcal arthritis and carditis,

Table 1. Spectrum of autoimmune diseases, target organs and diagnostic tests

	Disease	Organ	Antibody to
Organ specific	Hashimoto's thyroiditis	Thyroid	Thyroglobulin, thyroid peroxidase
	Primary Myxedema	Thyroid	Cytoplasmic TSH receptor
	Pernicious anemia	Red cells	Intrinsic factor, Gastric parietal cell
	Addison's disease	Adrenal	Adrenal cells
	Male infertility	Sperm	Spermatozoa
	Insulin dependent juvenile diabetes	Pancreas	Pancreatic islet beta cells
	Insulin resistant diabetic	Systemic	Insulin receptor
	Myasthenia graves	Muscle	Muscle, acetyl choline receptor
	Vitiligo	Skin Joints	Melanocytes
Non-organ specific	Rheumatoid arthritis	Skin, kidney, joints	IgG
	Systemic lupus erythematosus	Joints, etc.	DNA, RNA, nucleoproteins

THANKS