# Cells of the Immune System

- The immune system consists of many different organs and tissues that are found throughout the body. These organs can be classified functionally into **two main groups**.
- The ***primary lymphoid organs*** provide appropriate microenvironments for the development and maturation of lymphocytes.
- The ***secondary lymphoid organs*** trap antigen from defined tissues or vascular spaces and are sites where mature lymphocytes can interact effectively with that antigen.
- Blood vessels and lymphatic systems connect these organs, uniting them into a functional whole.
- Carried within the blood and lymph and populating the lymphoid organs are various white blood cells, or **leukocytes,** that participate in the immune response. Of these cells, only the lymphocytes possess the attributes of diversity, specificity, memory, and self/nonself recognition, the hallmarks of an adaptive immune response.
- All the other cells play accessory roles in adaptive immunity, serving to activate lymphocytes, to increase the effectiveness of antigen clearance by phagocytosis, or to secrete various immune-effector molecules.
- Some leukocytes, especially **T lymphocytes**, secrete various protein molecules called cytokines. These molecules act as immunoregulatory hormones and play important roles in the regulation of immune responses.

Lymphocytes are the central cells of the immune system, responsible for adaptive immunity and the immunologic attributes of diversity, specificity, memory, and self/nonself recognition. The other types of white blood cells play important roles, engulfing and destroying microorganisms, presenting antigens, and secreting cytokines.

## Lymphoid Cells

- Lymphocytes constitute 20 % – 40 % of the body's white blood cells and 99 % of the cells in the lymph. These lymphocytes continually circulate in the blood and lymph and are capable of migrating into the tissue spaces and lymphoid organs, thereby integrating the immune system to a high degree.
- The lymphocytes can be broadly subdivided into three populations—**B cells, T cells, and natural killer cells**—on the basis of function and cell-membrane components.
- **Natural killer cells (NK cells)** are large, granular lymphocytes that do not express the set of surface markers typical of B or T cells.
- **Resting B and T lymphocytes** are small, motile, nonphagocytic cells, which cannot be distinguished morphologically. B and T lymphocytes that have not interacted with antigen - referred to as **naive,** or unprimed—are resting cells in the $G_0$ phase of the cell cycle. Small lymphocytes have densely packed chromatin, few mitochondria, and a poorly developed endoplasmic reticulum and Golgi apparatus.
- The naive lymphocyte is generally thought to have a short life span. **Interaction of small lymphocytes with antigen, in the presence of certain cytokines**, induces these cells to enter the cell cycle by progressing from $G_0$ into $G_1$ and subsequently into S, $G_2$, and M.
- As they progress through the cell cycle, lymphocytes enlarge into 15 μm-diameter blast cells, called **lymphoblasts;** these cells have a higher cytoplasm: nucleus ratio and more organellar complexity than small lymphocytes. Lymphoblasts proliferate and eventually differentiate into

**effector cells** or into **memory cells.** Effector cells function in various ways to eliminate antigen. These cells have short life spans, generally ranging from a few days to a few weeks.

- **Plasma cells**—the antibody-secreting effector cells of the B cell lineage—have a characteristic cytoplasm that contains abundant endoplasmic reticulum (to support their high rate of protein synthesis) arranged in concentric layers and also many Golgi vesicles.
- The effector cells of the T-cell lineage include the cytokine-secreting T helper cell (Th cell) and the T cytotoxic lymphocyte (Tc cell).
- Some of the progeny of B and T lymphoblasts differentiate into memory cells. The persistence of this population of cells is responsible for life-long immunity to many pathogens.
- Memory cells look like small lymphocytes but can be distinguished from naive cells by the presence or absence of certain cell membrane molecules.
- Not, it is given a new CD designation reflecting a new membrane molecule. The homologous membrane molecules of other species, such as mice, are commonly referred to by the same CD designations. Lists some common CD molecules or ptotein markers) found on human lymphocytes. However, this is only a partial listing of the more than 200 CD markers that have been described. A complete list and description of known CD markers is in the appendix at the end of this book.

## *B Lymphocytes*

- The B lymphocyte derived its letter designation from its site of maturation, in the ***bursa of Fabricius*** in birds AND in the ***bone marrow*** in a number of mammalian species, including humans and mice. Mature B cells are definitively distinguished from other lymphocytes by their synthesis and display of membrane-bound immunoglobulin (antibody) molecules, which serve as receptors for antigen.
- Additionally, B cells present antigen (they are also classified as professional antigen-presenting cells or APCs) and secrete cytokines for propagating immune response.
- B cell activation occurs in the secondary lymphoid organs, such as the spleen and lymph nodes. After B cells mature in the bone marrow, they migrate through the blood to secondary lymphoid organs, which receive a constant supply of antigen through circulating lymph. At the secondary lymphoid organs, B cell activation begins when the B cell binds to an antigen via its B cell receptors.
- On interaction with antigen the B cells differentiates into ***Plasmoblasts*** first followed by ***Plasma cells*** and a separate set of ***Memory cells***.
- Plasmablast is short-lived, proliferating antibody-secreting cell arising from B cell differentiation. Plasmablasts are generated early in an infection and their antibodies tend to have a weaker affinity towards their target antigen compared to plasma cell.
- While Plasma cells are long-lived, non-proliferating antibody-secreting cell arising from B cell differentiation.
- The memory cells are dormant B cell arising from B cell differentiation. They circulate throughout the body and initiate a stronger, more rapid antibody response (known as secondary antibody response) if they detect the antigen that had activated their parent B cell.
- B-2 cell are mainly restricted to spleen and are further divided into ***Follicular (FO) B cells*** and ***Marginal zone (MZ) B cells***.
- **Follicular (FO) B cells** are the most common type of B cell, found mainly in the lymphoid follicles of secondary lymphoid organs. They are responsible for generating the majority of high-affinity antibodies during an infection.

- **Marginal zone (MZ) B cells** are found mainly in the marginal zone of the spleen and serves as a first line of defense against blood-borne pathogens, as the marginal zone receives large amounts of blood from the general circulation. They can undergo both T cell-independent and T cell-dependent activation, but preferentially undergo T cell-independent activation.
- B-1 cell arises from a developmental pathway different from FO B cells and MZ B cells. In mice, they predominantly populate the peritoneal cavity and pleural cavity, generate natural antibodies (antibodies produced without infection), defend against mucosal pathogens, and primarily exhibit T cell-independent activation.
- Regulatory B (Breg) cell are immunosuppressive B cell type that stops the expansion of pathogenic, pro-inflammatory lymphocytes.

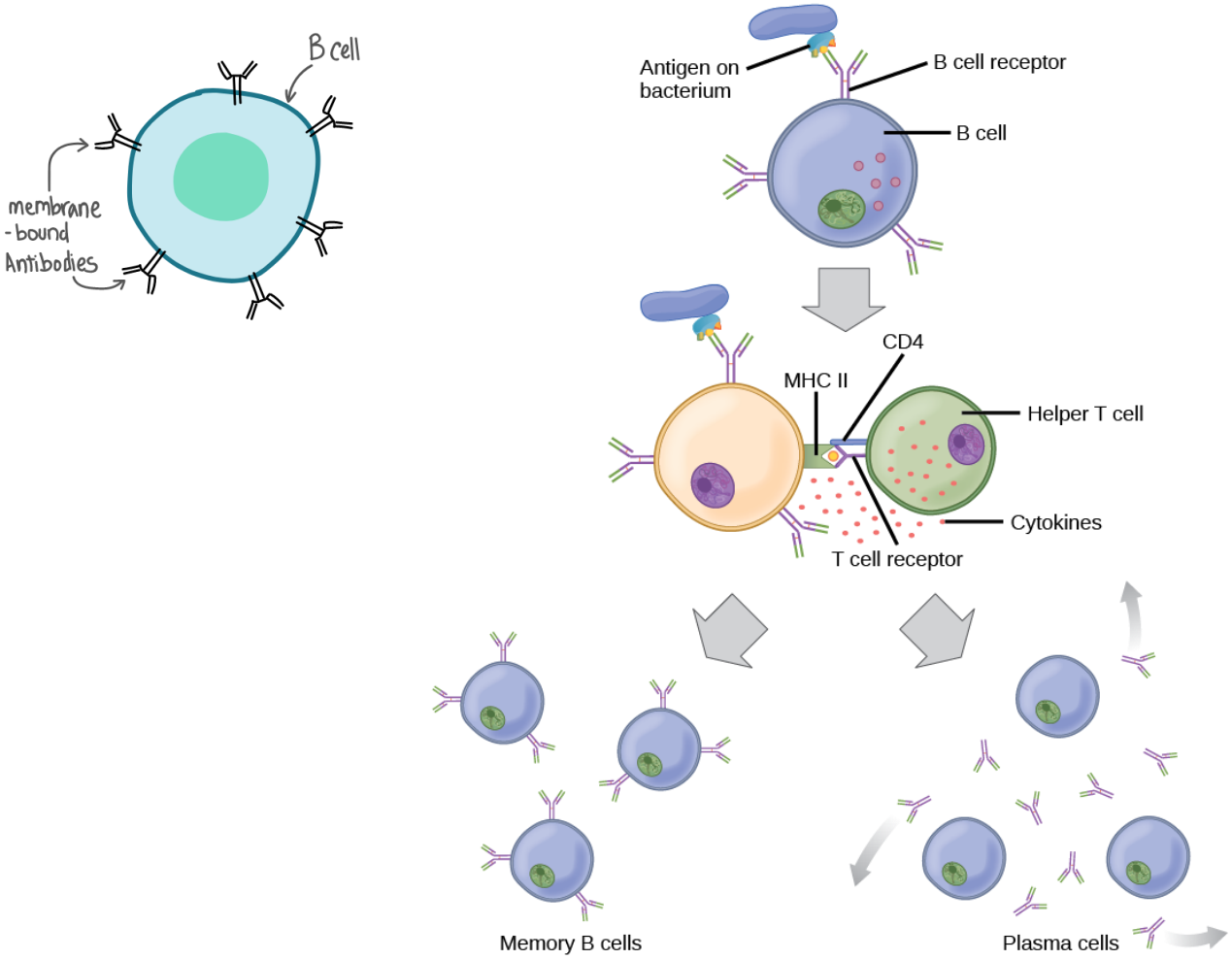



**Figure: B cell and T cell dependent B cell differentiation**

## *T Lymphocytes*

T lymphocytes derive their name from their site of maturation in the ***thymus***. Like B lymphocytes, these cells have membrane receptors for antigen. Although the antigen binding T-cell receptor is structurally distinct from immunoglobulin, it does share some common structural features with the immunoglobulin molecule, most notably in the structure of its antigen-binding site.

Unlike the membrane-bound antibody on B cells, though, the T-cell receptor (TCR) does not recognize free antigen. Instead the TCR recognizes only antigen that is bound to particular classes of self-molecules. Most T cells recognize antigen only when it is bound to a self-molecule encoded by genes within the major histocompatibility complex (MHC).

Fundamental difference between the humoral and cell-mediated branches of the immune system is that the B cell is capable of binding soluble free antigen, whereas the T cell is restricted to binding antigen displayed on self- cells.

To be recognized by most T cells, this antigen must be displayed together with MHC molecules on the surface of antigen-presenting cells or on virus-infected cells, cancer cells, and grafts.

The T-cell system has developed to eliminate these altered self-cells, which pose a threat to the normal functioning of the body.

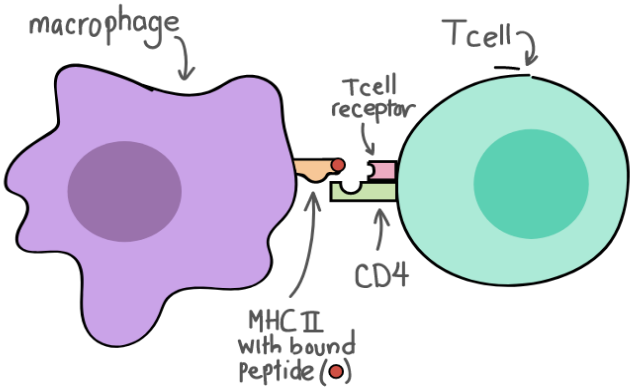
Like B cells, T cells express distinctive membrane molecules.

All T-cell subpopulations express the T-cell receptor, a complex of polypeptides that includes CD3; and most can be distinguished by the presence of one or the other of two membrane molecules, CD4 and CD8. In addition, most mature T cells express the following membrane molecules:

- **CD28,** a receptor for the co-stimulatory B7 family of molecules present on B cells and other antigen presenting cells.
- **CD45,** a signal-transduction molecule.

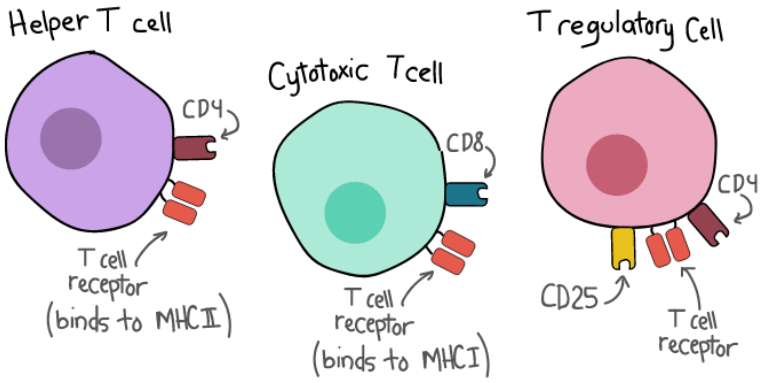
## *Classification of T Lymphocytes*

- In general, expression of CD4 and of CD8 also defines two major functional subpopulations of T lymphocytes. T cells that express the CD4 cell surface receptor are restricted to antigen bound to class II MHC molecules are called **T helper ($T_H$) cells**, whereas T cells expressing CD8, are restricted to antigen bound to class I MHC molecules are called **T cytotoxic ($T_c$) cells**.
- Thus the ratio of $T_H$ to $T_C$ cells in a sample can be approximated by assaying the number of $CD4^+$ and $CD8^+$ T cells.
- This ratio is approximately 2:1 in normal human peripheral blood, but it may be significantly altered by immunodeficiency diseases, autoimmune diseases, and other disorders.
- The $T_H$ cells secrete various cytokines, which play a central role in the activation of B cells, T cells, and other cells that participate in the immune response.
- Another subpopulation of T lymphocytes; **Tregs or Regulatory T cells**. Immunosuppressive in action and generally suppress or downregulate induction and proliferation of effector T cells; also known as **T suppressor (Ts) cells**. Tregs express the biomarkers CD4, FOXP3, and CD25 and are thought to be derived from the same lineage as naïve CD4 cells.




## *What are TH1 and TH2 subpopulation?*

Changes in the pattern of cytokines produced by $T_H$ cells can change the type of immune response. The **$T_H$1 response** produces a cytokine profile that supports inflammation and activates mainly certain T cells and macrophages, whereas the **$T_H$2 response** activates mainly B cells and immune responses that depend upon antibodies.




## *Natural killer cells (NK cells)*

- **Natural killer cells,** or **NK cells,** are a type of large granular lymphocyte cytotoxic in action, critical to the innate immune system. The role NK cells play is analogous to that of $T_c$ cells in the vertebrate adaptive immune response.
- NK cells provide rapid responses to virus-infected cells and tumors.
- Typically, immune cells detect the major histocompatibility complex (MHC) presented on infected cell surfaces, triggering cytokine release, causing lysis or apoptosis.
- NK cells are unique, however, as they have the ability to recognize stressed cells in the **absence of antibodies and MHC**, allowing for a much faster immune reaction.
- They were named "natural killers" because of the initial notion that they do not require activation to kill cells that are missing "self" markers of MHC class 1. This role is especially important because harmful cells that are missing MHC I markers cannot be detected and destroyed by other immune cells, such as T lymphocyte cells.
- NK cell receptors are of two types - inhibitory, and activating members; few examples to follow:

### *Activating receptors*

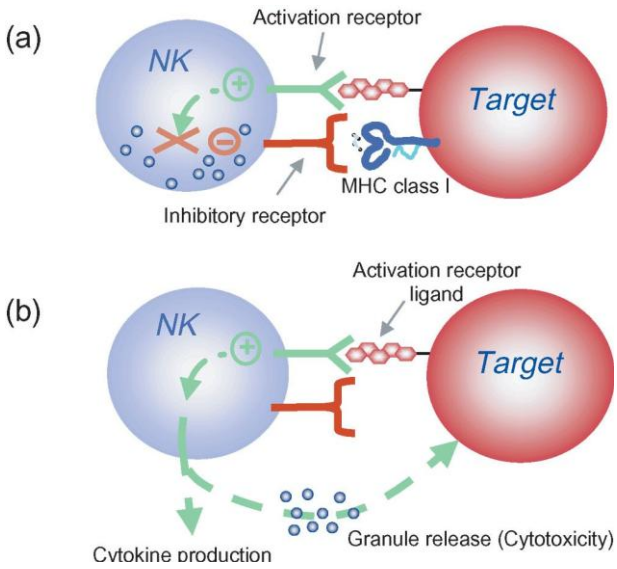
- **NCR** (natural cytotoxicity receptors), a type of type 1 transmembrane proteins of the immunoglobulin superfamily, upon stimulation, mediate NK killing and release of IFNγ.
- **CD16 (FcγIIIA)** plays a role in antibody-dependent cell-mediated cytotoxicity; in particular, they bind IgG.
- **Ly49**, - C-type lectin family receptors. Have both activating and inhibitory isoforms.

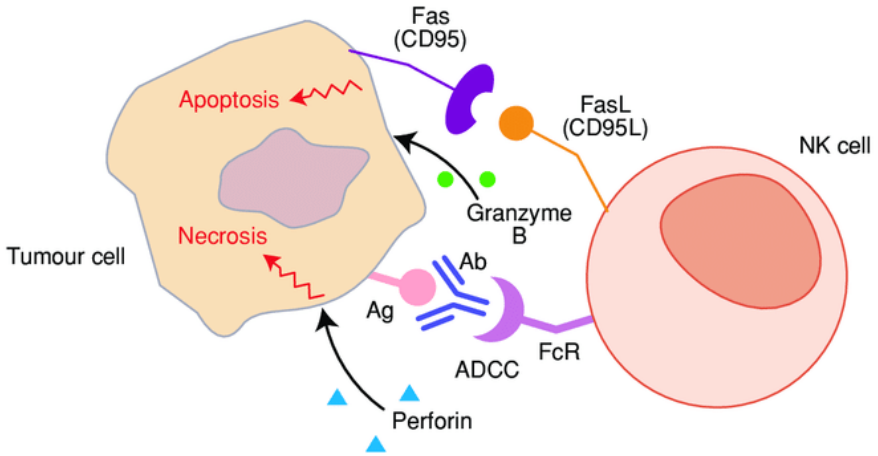
### *Inhibitory receptors*

- Killer-cell immunoglobulin-like receptors (KIRs)
- **CD94/NKG2**, a C-type lectin family receptor.
- **ILT** or **LIR** (immunoglobulin-like receptor).

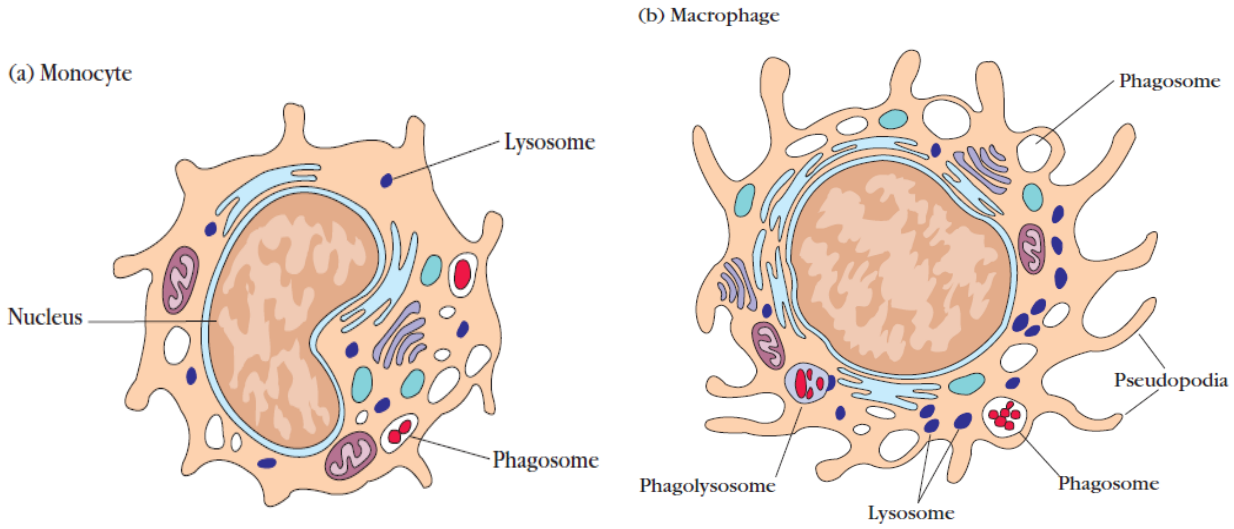
### *Functions*

- **NK cells are cytotoxic;** small granules in their cytoplasm contain proteins such as **perforin** and proteases known as **granzymes.**
- Upon release in close proximity to a cell slated for killing, perforin forms pores in the cell membrane of the target cell, creating an aqueous channel through which the granzymes and associated molecules can enter, inducing either apoptosis or osmotic cell lysis.
- **Antibody-dependent cell-mediated cytotoxicity:** Infected cells are routinely opsonized with antibodies for detection by immune cells. Antibodies that bind to antigens can be recognized by FcϒRIII (CD16) receptors expressed on NK cells, resulting in NK activation, release of cytolytic granules and consequent cell apoptosis.
- NK cells to defend the body against viruses and other pathogens.
- NK cells preferentially kill cells that possess low levels of MHC class I molecules.
- Natural killer cells often lack antigen-specific cell surface receptors, so are part of innate immunity.
- NKs play a role in tumor immunosurveillance by directly inducing the death of tumor cells.





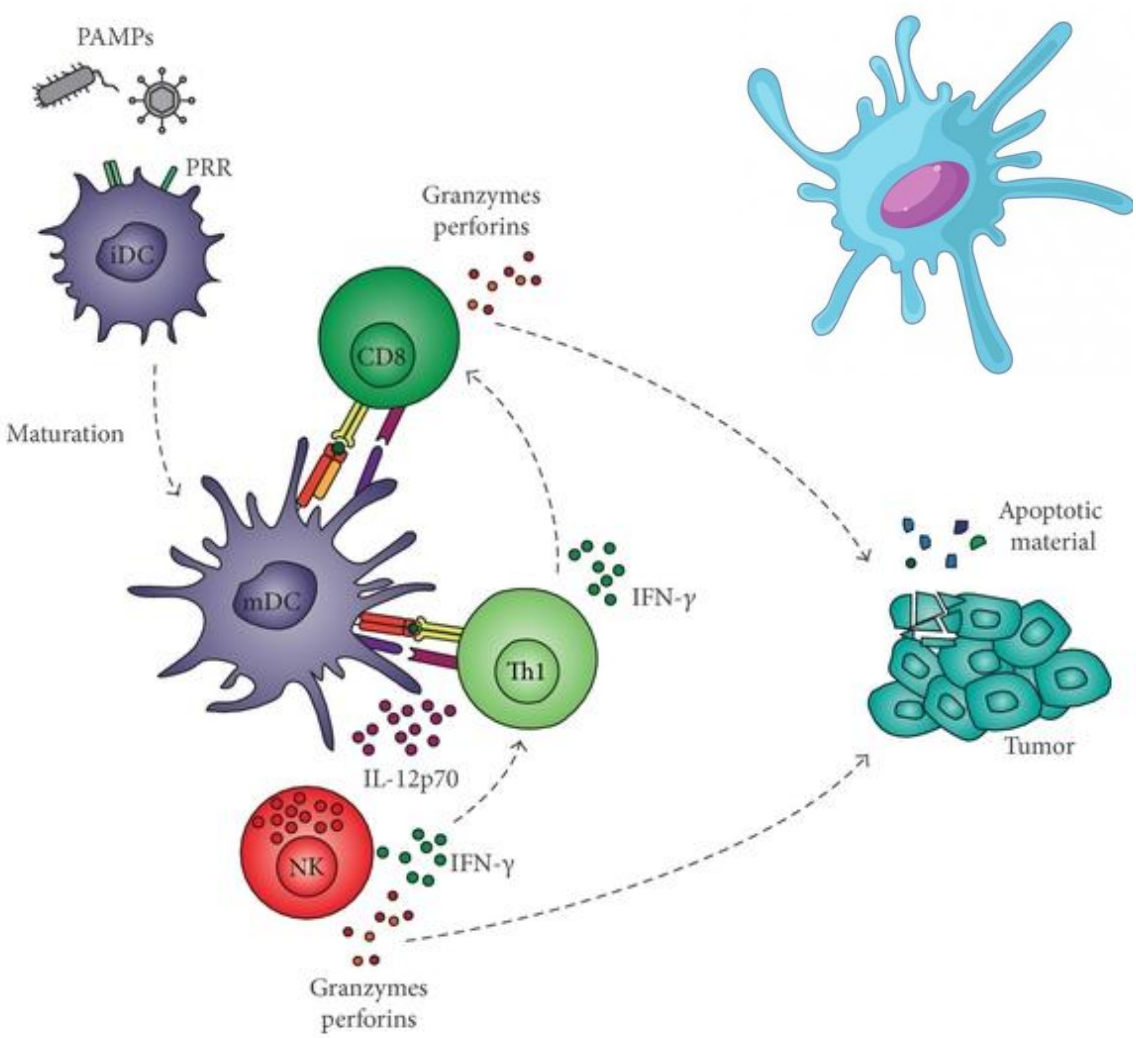

The natural killer (NK)-cell response to tumour cells




## *Mononuclear Phagocytes: Dendritic cells*

The **dendritic cell (DC)** acquired its name because it is covered with long membrane extensions that resemble the dendrites of nerve cells.

There are many types of dendritic cells, although most mature dendritic cells have the same major function, the presentation of antigen to $T_H$ cells. Four types of dendritic cells are known: Langerhans cells, interstitial dendritic cells, myeloid cells, and lymphoid dendritic cells. Each arises from hematopoietic stem cells via different pathways and in different locations.


PAMPs
PRR
iDC
Granzymes
perforins
CD8
Maturation
mDC
IFN-γ
Th1
Apoptotic
material
Tumor
IL-12p70
NK
IFN-γ
Granzymes
perforins