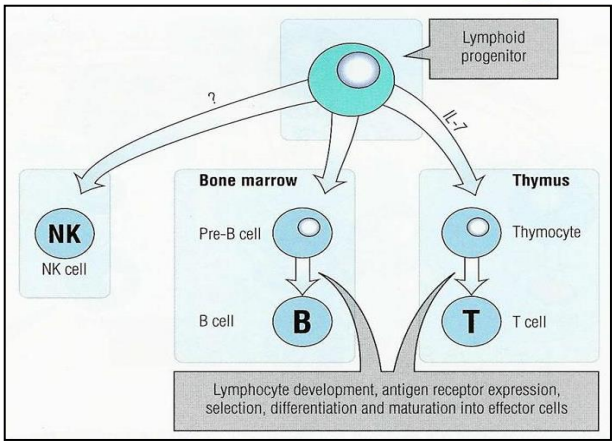
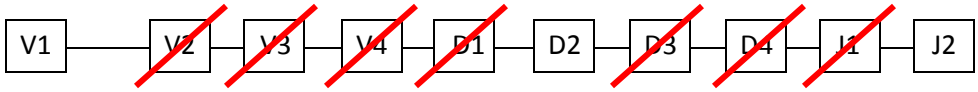
THYMIC DEVELOPMENT OF T-CELLS



- **Cell differentiation**: occurring throughout the life of lymphocytes (therefore different types of lymphocytes can be generated). Differentiation is derived by:
  - Differential gene expression.
  - Upregulation or downregulation of surface receptors.
  - Receptor-mediated cell-cell contact (an example on this is the interaction which is occurring between the receptors found on the surface of T-cells and those on the surface of antigen presenting cells APC).
  - Response to growth and differentiation factors.
  - Apoptosis (programmed cell death).
- **Events of T-cell maturation in the thymus:**
  - T-cell precursors migrate from the bone marrow to the thymus → in the thymus these precursor cells will be called thymocytes → in the second step there will be expression of T-cell receptor (TCR) → then, selection will take place:
    - ✓ Thymocytes with antigen receptors which will bind self antigens (presented on MHC molecules) too strongly will be induced to undergo apoptosis (negative selection: we don't want them or need them because they will attack the self antigens of the body and cause autoimmunity).
    - ✓ Thymocytes with antigen receptors which will recognize self antigens (presented on MHC molecules) but will bind with a low affinity will undergo (positive selection: these are the cells which we need them in our body).

    Note that a total of 95-99% of all T-cell precursors entering the thymus are destined to die there. Eventually those cells with positive selection will be converted to mature T-cells and released.
- **Generation of T-cell diversity:**
  - The human genome is composed of only 20,000-25,000 genes. Therefore, it is not possible that each gene will produce a T-cell receptor which will respond to a specific antigen because we have million of antigens that will be exposed to in the environment. A mechanism must exist to generate millions of idiotypes of antigen receptors necessary to meet this challenge.
  - **T-cell receptor:**
    - ✓ It is composed of 2 chains. Mostly these two chains are α & β but in some receptors they might be γ and δ → these are the constant regions.
    - ✓ The chains are also composed of variable regions which are responsible for binding of different antigens. Three gene segments (V, D and J) are combined to create the variable domain.



Note: V1, D2 and J2 segments were selected. They will be joined together while other segments will be removed. This process will generate diversity needed for TCRs to recognized many different antigens.

- ✓ The TCR is associated with CD3 (which will mediate intracellular signaling after the binding of the antigen to the TCR).

- **Precursor T-cells:**
  - They will be produced in the bone marrow and then migrate to the thymus for maturation.
  - When they reach the thymus they will be known as triple-negative cells which means that they don't have T-cell receptor, CD4 or CD8 on their surfaces.
  - In the beginning, TCR will be formed and expressed on the surface of these cells.
  - Then, both CD4 and CD8 will be formed and expressed on the surface of thymocytes.
  - The process of selection (positive or negative) will occur to chose those cells which can recognize foreign antigens without causing autoimmunity.

- **A process of differentiating T-cells will occur:**
  - ✓ *If TCR interacts with MHC-I* → this will result in production of CD8 cytotoxic T-cells.
  - ✓ *If TCR interacts with MHC-II* → this will result in production of CD4 helper T-cells.
- Finally, mature naïve (عديمة الخبرة) T-cells will pass through the medulla of the thymus and be released.

  Note: the thymus is supposed to present all self antigens of the body to the T-cells so they can develop tolerance and don't recognize them as foreign.

- **Self-reactivity:**
  - The process of generating variable T-cell receptors by gene rearrangement might generate receptors that can interacts with self antigens and cause damage to the body. The harmful effects of these cells can be avoided by the selection process occurring in the thymus.
- **Peripheral tolerance:**
  - Some of the self antigens of the body might not be presented to the developing T-cells in the thymus so these cells might cause autoimmunity because they will not be able to recognize some of the body antigens as self. To avoid the harmful effects a process of peripheral tolerance will take place:
    - ✓ Anergy (no signals).
    - ✓ Deletion/apoptosis (via increased pro-apoptotic proteins or expression of Fas and FasL).
    - ✓ Active suppression.
- **Regulatory T-cells:**
  - These are considered as CD4+/CD25+ cells.
  - When they are stimulated/activated they inhibit the activation of T-cells or their effector functions.
  - They suppress response to self antigens (so their absence will result in autoimmunity).
  - Found in peripheral blood with unknown antigenic specificity.
  - They produce IL-10 and TCGF.

AUTOIMMUNITY

- **Definition**: failure of self-tolerance.
- Autoimmunity must initially result from a failure of mechanisms of self-tolerance, as cells are educated in the bone marrow and thymus.
- Autoimmune diseases tend to be chronic and progressive.
- **What factor trigger autoimmunity?**
  - **Genetics**: among the strongest genetic associations with the development of autoimmune diseases are class II MHC genes.
  - **Infections may trigger autoimmune response by:**
    - ✓ *Bystander activation*: immune response may recruit leukocytes and increase expression of costimulators, which activate T-lymphocytes that are not specific for the infectious pathogen.
    - ✓ *Molecular mimicry*: antigens of a microbe cross-react with or mimic (يُشابِه) self-antigens.
    - ✓ *Inflammation*: and associated damage may expose self antigens that are normally concealed from immune cells.
- **Types of autoimmune diseases (figure).**
- **Manifestations of autoimmune disease:**
  - **Autoantibodies:**
    - ✓ Mediating direct cell damage via antigen-antibody-complement lysis of the cell.
    - ✓ Deposition of immune complexes.
    - ✓ Blockade or stimulation of receptors.
  - **Self-reactive T-cells:**
    - ✓ Direct damage by cytotoxic T-cells.
    - ✓ Infiltration of tissue by cytokines.