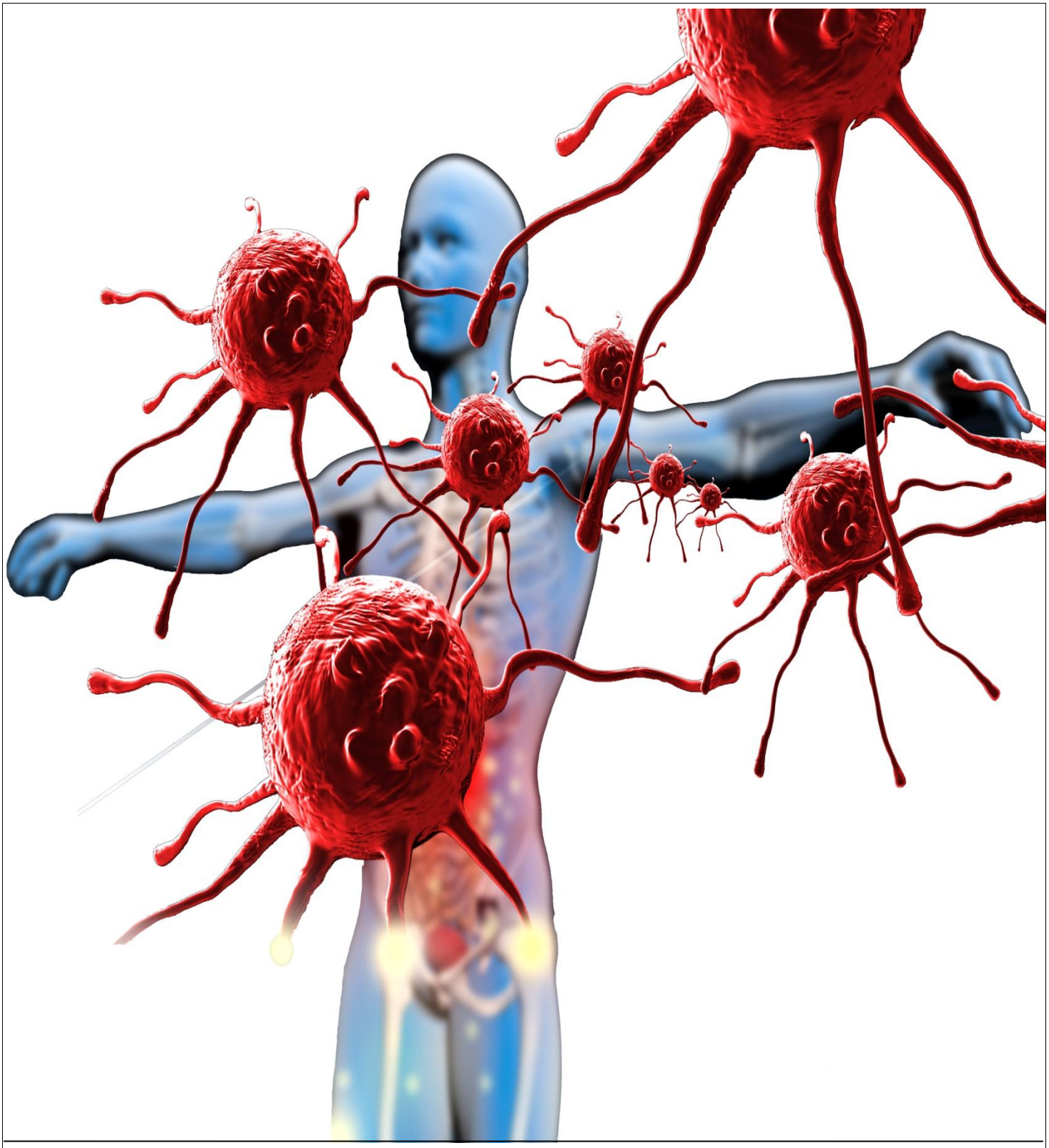

IMMUNOLOGY

Done By:

Handout # 1

Dr. Hassan Abu Al-Ragheb

By Mohammed Nawasreh

Structure and development of the immune system.

The purpose of the immune system is to recognize self from non-self and to react accordingly, thus there is first a recognition phase (cells recognizing the foreign antigen) followed by a proliferative reaction and then an effector phase if necessary. This applies to adaptive or acquired immunity. The effector phase may follow the recognition phase immediately in the case of innate immunity.

The main elements of the immune sytem are : the cells that are involved in the production of the immune response, and the tissues where these cells develop and differentiate to mount their immune response.

Cells of the immune system are initially produced in the yolk sac and then in the liver in the foetus. In the adult they are formed in the bone marrow :

STEM CELL : myeloid : Granulocytes. Monocytes.
lymphoid : T-lymphocytes, B-lymphocytes. NK cells and dendritic cells also develop from lymphoid line. These cells migrate and populate various lymphoid tissues.

Lymphoid tissues :

Primary e.g. thymus and bone marrow, where lymphocytes mature into antigen recognizing cells.

Secondary e.g. spleen,, lymph glands and lymphoid patches, where these cells encounter antigen and undergo proliferation and differentiation.

Cells of the immune system generally possess surface molecules that enable them to carry out their functions, these molecules are referred to by names that denote their function in some cases while in others the **(C D)** nomenclature is applied.

These molecules serve various functions e.g. recognition of foreign proteins, signaling to the cell, cell-cell interaction. The presence or absence of these molecules serve to identify the cells of the immune system and the stage of their development and differentiation.

Neutrophils :

Phagocytic cell, response to inflammation - margination and adhesion to endothelial cells and diapedesis.

Life span a few days, fate is not really known.

Respond to chemotactic agents (chemotaxis) e.g. chemokines, C5a, bacterial products, metabolites of arachidonic acid.

Phagocytosis : non-specific receptors for non-mammalian molecules, specific receptors for complement and antibody (opsonins), hydrolytic enzymes kill bacteria (may cause tissue damage, pus formation), killing is enhanced by the respiratory burst through activation by C5a and cytokines e.g. interferon gama.

Eosinophils :

Allergy and parasitic infections (Helminths). ECF-A (eosinophil chemotactic factor) as chemotactic agent. Receptors for IgE, IgG and ? complement lead to release of basic proteins which are effective against helminths; these may also be responsible for tissue damage in allergic conditions.

The granules contain histaminase which may neutralize the effect of mast cells in allergic reactions.
IL-5 stimulates their growth and differentiation.

Mast cells (also Basophils in blood) :
Release inflammatory and repair mediators.
IgE receptor - degranulation leads to release of : histamine and arachidonic acid metabolites. ECF-A and NCF-A (neutrophil chemotactic factor).
Also release of granules through C5a and C3a.

Monocytes (Macrophages) :
Bone marrow to blood and then various tissues where the microenvironment leads to various tissue macrophages (Kupfer cells, microglia, osteoclasts etc.).
Phagocytosis, chemotaxis, CR1 and IgG receptors. They invade tissues after neutrophils and clear necrotic debris.
Antigen presentation to T-lymphocytes. B7 with CD28, LFA-3 with CD2, ICAM with LFA-1.
Produce inflammatory cytokines IL-1 and TNF. Ameliorating cytokines TGF-beta and IL-10.
Promote healing through growth factors.

Dendritic cells (Langerhans cells) :
Multiple thin membrane projections, found in spleen and lymph nodes. Excellent APC's (antigen presenting cells). Origin bone marrow.
Langerhans cells found in skin and squamous epithelia, migrate to lymph nodes with antigen (veiled cells).
Absent C3 and IgG receptors, high MHC II molecules for antigen presentation.

Follicular dendritic cells :
Origin ?, not bone marrow. Found in Germinal centres.
CR2 and Ig receptors, retains immune complexes for months, significant as APC for B cells and memory cell generation.

B-lymphocytes :
Earliest cell the pro-B cell, has CD10 and CD19 and appearance of RAG 1 and 2 (recombination activation genes), D and J segments join and then V to produce a μ heavy chain which combines with surrogate chains and then displayed transiently at the surface, this probably transmits a signal to the cell to continue maturation.
The next stage is the pre-B cell which has only μ in cytoplasm, light chains are now produced leading to association with the heavy chain.
Immature B-cell has IgM (now the RAG1 and 2 are shut off). Cross linking of the receptor with its specific antigen at this stage leads to death.
IgM is only expressed at the surface in conjunction with Igα and Igβ chains and all together constitute the B cell receptor.
The immature cell remains in the bone marrow for 1-3 days, expresses IgD becoming a mature B cell and then is released to the periphery.
Resting B cells are IgM + and IgD ++. These cells die within a few days or weeks unless they are exposed to their respective antigen.
They also express complement receptors CR2, CR1 and Fc receptor for IgG.

On activation IgD is lost : leads to plasma cells or memory cells. Isotype switching. They are also APC (antigen presenting cells).
CD5 B cells are a separate lineage (5% of B cells), producing IgM molecules only, many of which are auto-antibodies; they are long lived, abundant in peritoneum and are probably connected with T-independent antigens. These antibodies are reactive with self antigens and polysaccharides and are called natural antibodies.

Maturation of B cells :

1)- Earliest committed cell is the pro-B cell in bone marrow. This has CD19 and CD10 markers.

2)- Pre-B cell is the next stage, cytoplasmic μ chains, some of these chains associate with the surrogate (invariant) chain and are expressed on the surface as the pre-B cell receptor (in association with Igα and Igβ), this receptor is necessary for further development of the B cells, but the ligand and type of signal are not known..

3)- Immature B cell : light chains are synthesized and IgM is expressed on the surface, negative selection occurs at this stage.

4)- Mature B cell : expresses IgM and IgD. Mature B cells leave the bone marrow and enter the blood

T-lymphocytes :
Precursors migrate to thymus ? special adhesion molecule.
In the Cortex they develop TcR (T cell receptor), CD3, CD4, CD8.
Cortex : 85% of thymocytes are found, double +ve, +ve selection (epithelial cells) .
Medulla : 15% of thymocytes, single +ve, -ve selection (epithelial cells, dendritic cells and macrophages).
Helper, cytotoxic and suppressor. Long lived usually.
10% of T lymphocytes in LN are memory cells.
Circulation of lymphocytes.
Maturation of T lymphocytes : precursors to thymus, TcR is acquired through gene rearrangement, expression of TCR occurs with the expression of CD3, CD4 and CD8 (double positive).
NB. γδ TCR cells develop earlier and do not express CD4 and CD8.
Rearrangement of the beta chain occurs in double -ve, while rearrangement of alpha chain occurs in the double +ve.
Positive selection occurs at the double +ve stage in cortex.
Negative selection occurs in the single +ve stage in medulla.

Maturation of T cells :

1)- Pro-T cell : lack TCR, CD4 and CD8, they are known as double negative.

2)- Pre-T cell : express β chains of the TCR, these combine with surrogate invariant chain and are expressed on the surface in conjunction with CD3, this pre-Tcell receptor is essential for further development of the cell.

3)- Next CD4 and CD8 are expressed (double positive stage), the αβ receptor is expressed. Positive selection occurs at this stage.

4)- Single positive stage either CD4 or CD8 expressed (negative selection).

NK cells :
Found in blood (5-10% of WBC) and in lymphoid tissues specially spleen. Also called LGL. They are also called Null cells because they do not have surface receptors like Ig or TcR. They are part of innate immunity.
Have ability to non-specifically kill tumour and virally infected cells , no TcR and not MHC restricted. Not thymus dependent. They are also involved in graft versus host reactions.
Express CD2 and Fc receptor (NK cells are a principal mediator of ADCC). Can be activated by cytokines INF gamma, TNF. IL-2 in particular gives rise to LAK cells.
They are involved in GVHD, they kill epithelial cells. Graft rejection.
Cell killing is similar to CTL, perforin and toxic molecules (granzymes).
NK markers CD 16, CD 56.
They possess receptors that when engaged to ligand lead to activation or suppression : MICA and MICB on cells (stress related) engage NKG2D receptors which induce killing of cells by NK cells. Absence of MHCI leads to killing by NK cells. Presence of MHCI and MHCG prevent killing by NK cells.

The thymus : this develops from the 3rd and 4th pharyngeal pouches, max. at birth and then involutes in the adult (about puberty).
Cortex : mainly immature T-lymphocytes (thymocytes) . Epithelial cells some are known as nurse cells. Some macrophages and dendritic cells of Langerhans type.
Medulla : more mature T-lymphocytes to blood. Dendritic cells and macrophages. Only 5-10% of thymocytes reach maturation.
Scattered in between are epithelial cells and bone marrow derived dendritic cells and macrophages.
Hassal ' s corpuscles are medullary thymic epithelial cells (similarity to skin keratinocytes). ? negative selection

Spleen : the major site of antibody production. lymphocytes are found in the white pulp. PALS (periarteriolar lymphoid sheath) is T-cell area, Germinal centre is B-cell area. DENDRITIC cells. FDC's.
Follicles are found within the PALS.
Marginal zone surrounding the mantle of the follicles and PALS, is site of entry of lymphocytes into the white pulp through venous capillaries. Blood flows from the central arterioles through small follicular arterioles into the marginal sinus and then to the red pulp.
The arteries end as they leave the sheath giving rise to penicillar arteries (paintbrush like). There are follicular arterioles that branch from the central arterioles to the marginal sinus that lies between the PALS and the marginal zone (importance for antigen passage). The marginal zone contains B and T cells and it is believed that interaction with antigen from the blood occurs there.

The marginal sinus and zone are the area of entry of lymphocytes to the spleen as no HEV are present as in lymoh nodes.

Lymph nodes : B-cells in germinal centres (follicles). T-cells in deep cortex (paracortex). Follicular Dendritic cells are important in antigen presentation in B cell areas. Interdigitating dendritic cells are abundant in T-cell areas are important in antigen presentation to naive T-cells.
Plasma cells in secondary follicles, after antigen stimulation.
Medulla contains many plasma cells.

MALT : importance as sites for IgA production, also T cells, may have a role after involution of the thymus.
Strategic sites GIT and RT, breast, salivary glands.
M cells serve as antigen presenting cells.

Circulation of lymphocytes :
Naive T and B lymphocytes enter lymph nodes through HEV (special receptors, selectins and addressins), they tend to leave the LN through efferents, back to the circulation and eventually back to the same lymphoid tssues. Once activated they develop adhesive molecules that allow them to stay in the LN where they proliferate into effector and memory cells, which leave LN to blood and enter tissues, they return to LN through afferents rather than HEV. Immunological Surveillance.
Selective receptor molecules on H.Endothelium and hence HOMING.

In a naive animal the chance of a lymphocyte capable of recognizing a typical antigen is 10^3 to 10^5. Also B and T lymphocytes specific to the same antigen have to interact with the antigen to produce an immune response. To overcome this difficulty the immune tissues trap antigen and present on the surface of fixed cells where it comes in contact with B and T cells. Thus there is a concentration mechanism for all these cells.

The cells of the immune system :

W.B.C. : 4000-11000 cells/cu.mm. of blood.
60% granulocytes (55% PMN, 3% eosinophils, 0.5% basophils)
7% monocytes.
35% lymphocytes (B-cells 10-15%, T_h-cells 50-60%, T_c-cells 20-25%, NK cells 10% from total T-cells).

Activation of T-cells --- increase in cytoplasm. Cytokines .
Activation of B-cells --- plasma cells.
Memory cells resemble resting cells, differ in CD45 the common leukocyte antigen. Long lived 20 years. Both B and T-cells.
Various T-cells are differentiated according to surface molecules CD cluster of differentiation. Helper, cytotoxic etc. B-cells have surface immunoglobulins .