# Immunology summary week no.8

**Lectures 13,14**

## Antigen presenting cells (APCs)

Present processed antigens for T-cells (helped CD4+ & cytotoxic CD8+) on MHC proteins.

1. *Dendritic cells* -> the most potent, activate naive T cells

   a.Classic (conventional): majorly present in the tissues, mainly secrete IL-6,12 &TNF, induce T cells response against most antigens.

   b.Plasmacytoid: majorly present in the blood, mainly secrete INF-1 (anti-viral), very involved in T cells response to viruses.

2. *Macrophages* -> activate CD4+ T (effector) cells which in turn reactivate macrophages (through cytokines) to kill microbes
3. *B lymphocyte* -> T-dependent humoral immunity (details in the previous lec)
4. *Thymic medullary epithelial cells* -> T cells maturation & selection
5. *Vascular endothelial cells*

***NOTE I** -> T cells recognise *the peptide (antigen)* **AND** *the receptor (MHC).*

***NOTE II** -> for an antigen to be presented for T cells it has to be a *linear peptide attached to either MHC-I* (Intracellular antigen, CD8+ T cells) or MHC-II (Extracellular antigen, CD4+ T cells).

***NOTE III** -> can recognise any type of antigens in their *native* (not processed) form.

***NOTE IV** -> the antigens are carried by APCs to where T cells reside, not the other way around.

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**Dendritic cells life:** capture at the site of entry -> migrate & mature -> process the antigen -> present it for T-cells.

**Sites of entry:**

Skin (Langerhans cells), GI tract, Respiratory Tract , Blood borne

In the T cells zone, chemokines called *CCL19,21 attract DCs* as they *express CCR7 receptors* which ***HOMES*** DCs to their receptors.

Dendritic cells are either MATURE [*capture &present & have longer half-life*] or IMMATURE [*capture only*]

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**MHC CLASS I&II**

| MHC I | MHC II |
|---|---|
| On the surfaces of almost all nucleated cells | Only on APCs |
| Present for CD8+ | Present for CD4+ |
| Cytosolic/intracellular antigens | Extracellular antigens |
| Close end (1-15 amino acids) | Open cleft (15-30 amino acids) |

**Pathways**

1.MHC-I Pathway (*ubiquitin-proteasome pathway*): The antigen is *tagged by ubiquitin* & *degraded by proteasome* -> then it's transported to the ER (where the MHC-I is synthesised) *by TAP* -> the antigen is loaded (Tapsin stabilise the transporter and the MHC-I during the loading) on MHC-I ***in the ER*** -> Golgi -> by a vesicle they're transported to the cell surface.

2.MHC-II Pathway: extracellular proteins/microbes internalised by phagosomes -> bind to lysosomes forming phagolysosome-> degrade the protein -> MHC-II synthesised in the ER then *transported to the phagolysosome where the loading occurs*.

**Invariant chain** -> *occupies the cleft of MHC-II to prevent binding of peptides in ER. It is converted into a **CLIP** in the phagolysosome*

**HLA-DM** -> *exchange the antigen for the invariant clip*

**Other types of T cells & cross presentation**

**Natural killer T cells* -> similar to those of the innate system but NOT THE SAME

**T cells γδ -> less specific*

> **These cells recognise various antigens, not necessarily proteins and don't require the involvement of MHCs .**

**Cross presentation* -> sometimes dendritic cells engulf *extracellular* antigens (in the form of a cell and a pathogen inside it for example) and it *presents it on MHC-I for CD8+ cells rather than MHC-II*.

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## Antigen receptors of lymphocytes

**B cells receptors:** they recognise a variety of antigens, can be bound or soluble & have an effector function (complement fixation or phagocyte binding)

**Antibodies** (we've talked about them 28801 times 🤦‍♀️ )

**Structure:**

Fab region (bind antigens) -> 2 heavy chains & 2 light chains , contain hypervariable regions (CDRs) determine the specificity of it. The epitope is the very specific part of the antigen that binds to the antibody. A monomer can bind 2 antigens or 2 epitopes

Fc region -> 2 heavy chains connected by a disulfied bond, bind to the lymphocyte.

Hinge region -> the part between Fab & Fc, gives the antibody flexibility to bind to different epitopes.

Isotypes -> different types of the heavy chains (IgG,IgM,IgD,IgA,IgE), naive B cells have membrane bound receptors (mainly IgM & IgD). The heavy chain might change during the B cells life but the light chains (κ kappa, λ lambda) don't. [refer to the table , page 6 sheet 14]

Affinity -> the strength of binding ***one*** epitope by ***one*** antibody

Avidity -> the ***total*** strength of the antigen-antibody binding which is much greater than affinity.

**Monoclonal antibodies** -> each antigen causes the generation of a very specific antibody we call it monoclonal &it has multiple medical and therapeutic uses.

*Antigen injected into a mouse, we remove the spleen which contains the b cells and fuse these cells with immortal tumour cells that are unable to produce its own antibodies then we extract the produced antibodies.*

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**T cells receptors**: bound receptors that recognise processed peptides presented on MHC molecules and they don't have an effector function.

It's a heterodimer of two polypeptide chains (α&β mostly) with a disulfied bridge between them. They have variable & constant domains & ofc hypervariable regions & they have a transmembrane sequence (bound).

***T cells receptor complex -> TCR + signalling molecules for signal transduction.***

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**The immune repertoire:** *Cells that cannot recognise antigens or have the potential to cause harm must be eliminated*, this is needed because the *adaptive immunity must be specific* and distinguish between foreign bodies and chemicals.

**Lymphocytes development:**

Lymphoid progenitor cell -> B or T -> proliferation and antigen receptor gene rearrangement (important) -> +ve or -ve selection.

**Diverse antigen receptors**

We achieve this by *somatic recombination* or *rearrangement* of the genes that code for the variable regions. -> ***diversity***

Lymphoid progenitors contain genes for Ig (heavy & light chains) and for TCR ( α&β chains) both contain codes for *variable (v)* and *constant (c)* regions. In addition to a code called *diversity (D)* and *joining (J)*. ***All present on all chains except D gene, only present on the Ig heavy chain & TCR β chain.***

**Antigen receptor gene rearrangement**

Mediated by *Lymphoid-specific enzymes* and *additional enzymes, sometimes not lymphocytes specific* involved in the repair of dsDNA .

**Types** : 1. Combinatorial-> *rearrange* V,D&J to give different combinations, *limited and the nucleotides number doesn't change*.

2. Junctional-> *endonucleases* either *add or remove nucleotides* at the junctions between V,D&J . *Larger diversity*.

**B cells maturation**

1. In the bone marrow-> progenitors give pro-B cells (*no receptors*)
2. They start to express BCRs. Ig rearranges and cells that are able to express Igμ survive & *pro-B cells -> pre B-cells* (*immature*)
3. Mature B cells express IgM & IgD
4. Selection-> positive (*intact functional receptors*), negative (*react strongly to self-antigens*)

**T cells maturation**

1. From the bone marrow to the thymus, the least developed progenitors called pro T-cells (double-ve don't express CD4+ nor CD8+)
2. Express β chain first (pre T-cell)

a.TCR β gene recombination is mediated by VDJ recombinase (two alleles for the gene)

b.if recombination is successful in one of the two, TCR β is synthesised and expressed on the surface with a protein called pre- Tα forming pre -TCR complex of pre-TCR. If it's nit successful in one of them, recombination takes place on the other one. If it fails in the two the cell dies. *Pre TCR sends signals that promote survival and inhibits the expression of another β chain (allele exclusion)*

c.*after the expression of β chain, the expression of α takes place* , if it failed the cell dies.

3. When the α&β chains are expressed, *the cell expresses BOTH CD4+&CD8+* (double +ve)
4. Selection:
    a. Interaction with self-antigens (double +ve)
    1.Interact with *low affinity*-> *survive* (+ve selection)
    2.Interact with very *high affinity*-> *eliminate* (-ve selection)
    ***In cases of autoimmune diseases, the -ve selection is defected.***
    b. Selection (single +ve) when the cell changes from having both CD4&8+ to having one
    1.*React with MHC I -> CD8+*
    2.*React with MHC II -> CD4+*