SHEET NO. 13

IMMUNOLOGY

DOCTOR 2019 | MEDICINE | JU

DONE BY : Doctor 2018

SCIENTIFIC CORRECTION :

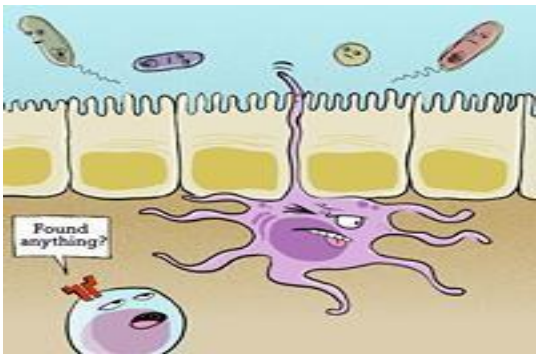
GRAMMATICAL CORRECTION :

DOCTOR : Dr.Nader

Topics Discussed in this sheet:

This sheet is our portal of entry to the adaptive immune response, and we'll start by talking about T lymphocytes and how they get activated by MHC molecules (which were discussed previously). Read with concentration, it'll be *a piece of cake*.

APCs (Professional Phagocytes):



*We already know, according to **MHC restriction phenomenon** (imp. rule), that T cells are quite selective. They only recognize **peptide** antigens, which are **linear** and **presented on the cleft of self MHC molecules "peptide antigen complex"** on **APCs** (Antigen Presenting Cells), so T-cells do not catch any antigen rather than peptides. Such cells include:

1) Dendritic cells: the most potent and the only ones that can activate naïve T cells.

2) Macrophages: they usually activate CD4+ve T cells which in turn re-activate macrophages and help in killing infectious agents.

3) B lymphocytes: have a role in T cell-dependent humoral immunity.

T-cells here are already differentiated

4) Thymic epithelial cells: have a role in lymphocytes' maturation, development and selection in thymus (also called nursery cells).

5) Vascular endothelial cells.

NOTE: There are two major populations of dendritic cells, called classical and plasmacytoid, which differ in their locations and responses. The following figure shows the differences that we need to know about them.

Feature	Classical dendritic cells	Plasmacytoid dendritic cells
Surface markers	CD11c high CD11b high	CD11c low CD11b negative B220 high
Major location	Tissues	Blood and tissue
Expression of Toll-like receptors	TLRs 4, 5, 8 high	TLRs 7, 9 high
Major cytokines produced	TNF, IL-6, IL-12	Type I interferons (Anti-viral)
Postulated major functions	Induction of T cell responses against most antigens	Antiviral innate immunity and induction of T cell responses against viruses

Unlike T cells, B lymphocytes, on the other hand, can recognize various molecules (either by membrane-bound or soluble antibodies). These molecules can be peptides, lipids, carbohydrates, small molecules, metal ions and others. also, they can be soluble and not bound to APCs.

- This figure emphasizes that both the peptide, and its presence on MHC molecule cleft are both required for the antigen to be recognized by T cell receptor. (Further details in the next lecture).

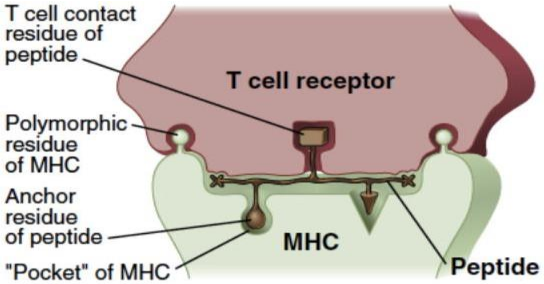


TABLE 6–1 Features of Antigens Recognized by T Lymphocytes

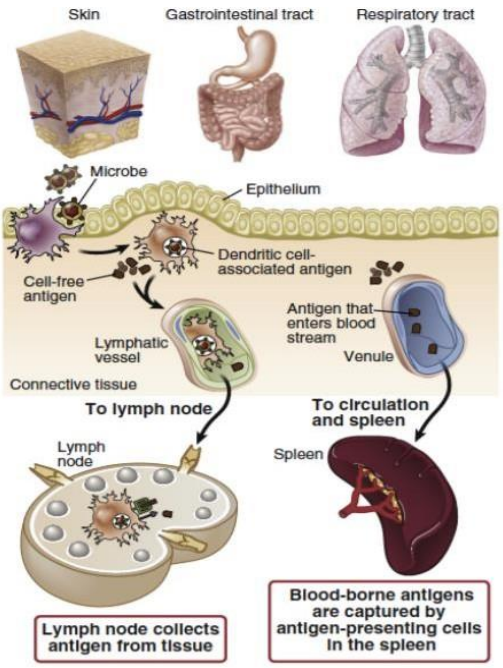
Features of Antigens Recognized by T Cells	Explanation
Most T cells recognize peptides and no other molecules.	Only peptides bind to MHC molecules.
T cells recognize linear peptides and not conformational determinants of protein antigens.	Linear peptides bind to clefts of MHC molecules, and protein conformation is lost during the generation of these peptides.
T cells recognize cell-associated and not soluble antigens.	T cell receptors recognize only MHC-like shapes, and MHC molecules are membrane proteins that display stably bound peptides on cell surfaces.
$CD4^+$ and $CD8^+$ T cells preferentially recognize antigens sampled from the extracellular and cytosolic pools, respectively.	Pathways of assembly of MHC molecules ensure that class II molecules display peptides that are derived from extracellular proteins and taken up into vesicles in APCs and that class I molecules present peptides from cytosolic proteins; CD4 and CD8 bind to nonpolymorphic regions of class II and class I MHC molecules, respectively.

- APCs display peptideMHC complexes for recognition by T cells and also provide additional stimuli to the T cells that are required for the full responses of the T cells.

CAPTURE OF PROTEIN ANTIGENS BY DENDRITIC CELLS:

-There are about 1-5000 lymphocytes/µL of blood, which is clearly not enough to patrol all sites of microbe entry. In fact, T lymphocytes do not go looking for antigens, it's the opposite that takes place in our body. Antigens are phagocytosed and captured by APCs and taken to secondary lymphoid organs, such as lymph nodes and spleen, where T lymphocytes are abundant.

- Protein antigens of microbes that enter the body are captured mainly by dendritic cells and concent-rated in the peripheral lymphoid organs, where im -mune responses are initiated .



LIFE OF DENDRITIC CELLS: They capture antigens from sites of entry ➔ they migrate (if they originally located in tissue, they migrate to lymph nodes. If in blood they migrate to spleen) ➔ they become mature (activated) upon stimulation by antigenic agent and are now able to present the antigen in the form of peptide-MHC. Complex.

*This figure shows common microbial sites of entry:

- Skin (Dendritic cells called Langerhans cells).
- GI tract (by ingestion).
- Respiratory tract (through inhalation).
- Blood-borne (They are sampled in the spleen.)

•Some insectborne microbes may be injected into the bloodstream as a result of insect bites, and some infections are acquired through the genitourinary tract

•Microbial antigens can also be Produced in any infected tissue

What makes a dendritic cell migrate?

- The activated DCs (also called mature DCs) lose their adhesiveness for epithelia or tissues and migrate into lymph nodes. The DCs also begin to express a chemokine receptor called CCR7 that is specific for two chemokines, CCL19 and CCL21, that are produced in the T cell zones of lymph nodes. CCR7 is also called "homing receptor" because it HOMES dendritic cells toward their targets.

Remember: APCs capture antigens that bind to innate immune receptors (PRRs) such as rig-like receptors, TLRs, RIGs, etc.

NOTE: Phagocytes' action is not limited to phagocytosis, they can perform pinocytosis (engulfing fluid containing antigen) and receptor-mediated endocytosis.

NOTE: Mature dendritic cells are able to phagocyte and present antigens (they have MHC molecules), while immature ones can only phagocyte (capture) antigens.

NOTE: Expression of MCH is increased by INTERFERON-γ. (as part of T-cell maturation)

•DCs can ingest infected cells and present antigens from these cells to CD8+ T lymphocytes , crosspresentation, or cross-priming.

T cell zone

	Immature dendritic cell	Mature dendritic cell
Principal function	Antigen capture	Antigen presentation to T cells
Expression of Fc receptors, mannose receptors	++	–
Expression of molecules involved in T cell activation: B7, ICAM-1, IL-12	– or low	++
Class II MHC molecules		
Half-life	~10 hr	>100 hr
Number of surface molecules	~10^6	~7×10^6

Different types of APC serve distinct functions in T cell dependent immune responses:

*Dendritic cells are the principal inducers of such responses, because these cells are located at sites of microbe entry and are the most potent APCs for activating naive T lymphocytes

*One important type of APC for effector T cellsis the macrophage, which is abundant in all tissues. In cellmediated immune reactions, macrophages phagocyte microbes and display the antigens of these microbes to effector T cells, which activate the macrophages to kill the microbes

*B lymphocytes ingest protein antigens and display them to helper T cells within lymphoid tissues; this process is important for the development of humoral immune responses.

*All nucleated cells (MHCI) can present antigens derived from microbes in the cytoplasm to CD8+ T cells.

Cell type	Expression of		Principal function
	Class II MHC	Costimulators	
Dendritic cells	Constitutive; increases with maturation; increased by IFN-γ	Constitutive; increases with maturation; increased by TLR ligands, IFN-γ, and T cells (CD40-CD40L interactions)	Antigen presentation to naive T cells in the initiation of T cell responses to protein antigens (priming)
Macrophages	Low or negative; inducible by IFN-γ	Low, inducible by TLR ligands, IFN-γ, and T cells (CD40-CD40L interactions)	Antigen presentation to CD4+ effector T cells in the effector phase of cell-mediated immune responses
B lymphocytes	Constitutive; increased by cytokines (e.g., IL-4)	Induced by T cells (CD40-CD40L interactions), antigen receptor cross-linking	Antigen presentation to CD4+ helper T cells in humoral immune responses (T cell–B cell interactions)

MHC Class I and II:

-There are some major differences between the two molecules, which are mentioned briefly in the following table.

MHC I	MHC II
Found in all nucleated cells	Found only in APCs
With a peptide bound to it, it activates CD8+ T lymphocytes	With a peptide bound to it, it activates CD4+ T lymphocytes
Cytosolic antigens are presented here	Extracellular antigens are presented here
Closed ends ⟶ Binds peptides with 1-15 amino acids	Open cleft ⟶ Binds peptides with 15-30 amino acids

NOW we can conclude the 2 golden rules that you should never forget.

GOLDEN RULES:
-Rule of 8: MHC I activates CD8+ T cells, while MHC II activate CD4+ T cells.
(+ means this CD is present on its surface)

-Extracellular antigens go through MHC II pathway, while intracellular antigens go through MHC I pathway.

***But for every rule, there is an exception. We are going to talk about this exception shortly.**

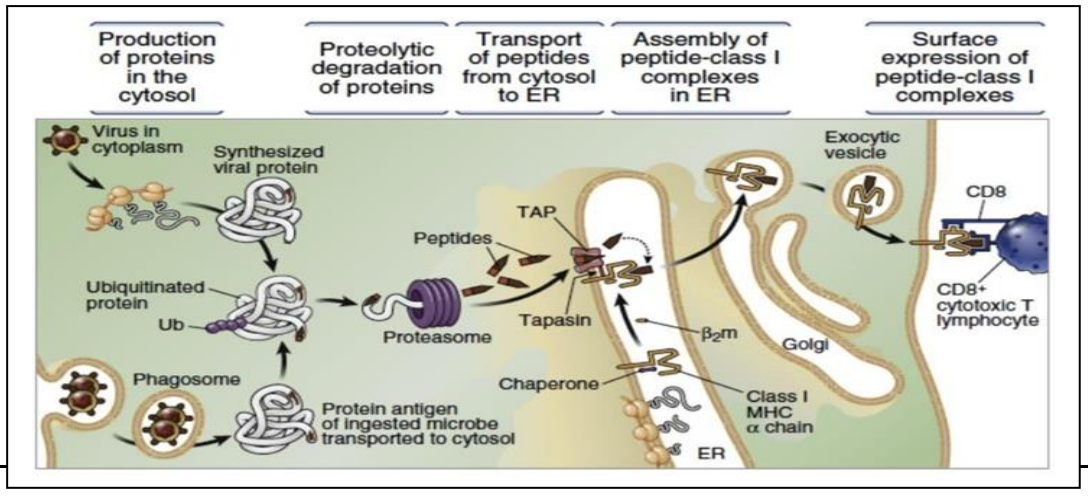
Since cells pick up antigens in their original forms (3D proteins), there must be a way for them to process them, and that's called a **processing pathway.**

-Now let's talk about each pathway in detail, shall we?

1) MHC I Pathway:

We have cytosolic foreign antigens. These antigens, themselves, can be microbes, mutated proteins like in tumor cells, or even extracellular antigens that could escape from their endosomes once they got inside the cell. This antigen **gets tagged** with a molecule called 'ubiquitin' and **degraded** by a proteasome (a proteolytic machinery), giving the pathway a unique name of **ubiquitin-proteasome (UPS**) pathway. **MHC I** is synthesized in the ER. Peptides generated in the cytosol are translocated by a specialized transporter -called **TAP**(transporter associated with antigen processing) - into the ER, where newly synthesized MHC I molecules are available to bind the peptides. Now that MHC cleft is loaded with a peptide, they go through a vesicle into the golgi apparatus and finally reach the cell's outer surface. Our cell is now ready to be recognized by a CD8+ T cell :)

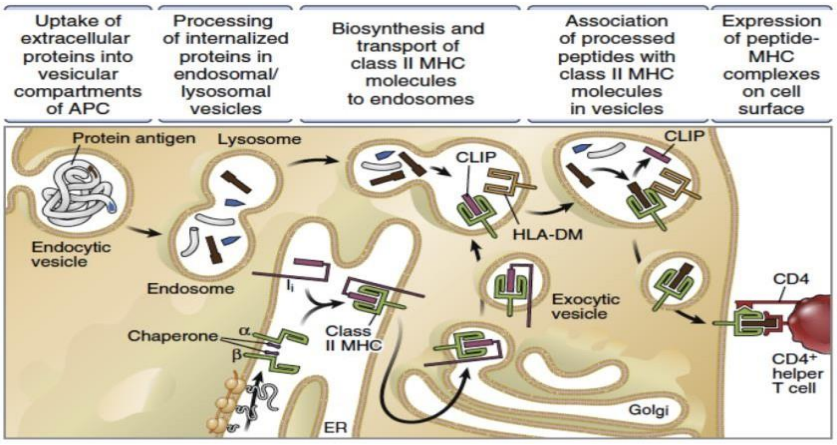
NOTE: A protein called **Tapasin** has high affinity towards TAP transporter, so it binds it (and binds to newly synthesized MHC I) **stabilizing them** during the MHC cleft loading step.



2) MHC II Pathway:

We have **extracellular antigens** that are internalized and put inside membrane-bound vesicles called endosomes. They are called phagosomes then phagolysosomes (after fusing with a lysosome -low pH environment-). **Proteins** inside phagolysosomes are **degraded** enzymatically (mainly by cathepsins) to generate **smaller peptides**. Meanwhile, MHC II is synthesized in ER and bound with a molecule called '**invariant chain**' which occupies the cleft and prevents the binding to MHCII by any peptide found in the ER. This whole complex(MHCII) travels to the endosome, and with the help of proteolytic enzymes, the invariant chain is converted (trimmed) into another molecule called **CLIP**(class II associated protein). A protein called **HLA-DM** (Human Leukocyte antigen) is also found in the endosome and works as a peptide exchanger. Basically, its job is to take CLIP from the MHC_{II} cleft and give it the **antigenic peptide** in return. The MHC_{II}-peptide complex travels through an exocytic vesicle to the outer surface of the cell, ready to get recognized by CD4+ T cells.

BE CAREFUL:
*The loading of peptides occurs in the **ER** in the first pathway, while it occurs in an **endosome** in the second pathway.*



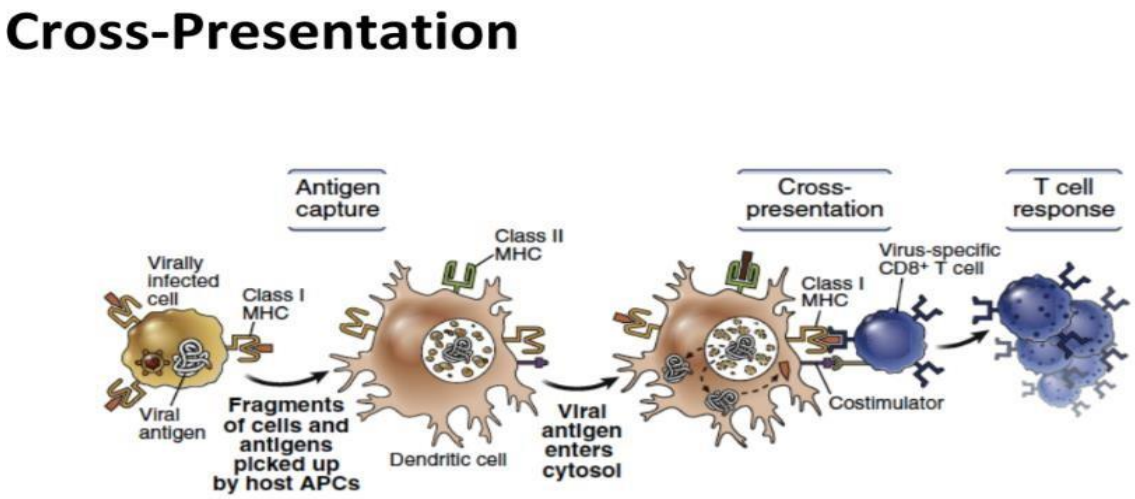
Remember the exceptions we mentioned previously? We'll talk about them now.

-The first violation is regarding the first golden rule. T cells, generally, follow the MHC restriction phenomenon. However, some small populations of T cells are able to recognize nonprotein antigens (like lipids, glycolipids, phosphorylated molecules and alkyl amines) without the involvement of class I or class II MHC molecules, these two populations are NKT (Natural Killer) T cells and γδ (gamma-delta) T cells.

NOTE: Natural Killer T cells are called so because they share properties of both T cells and NK cells. They've got surface proteins called 'markers' from both cells.

BE CAREFUL:
Natural Killer T cells are different from Natural killer cells of innate immunity

-The second violation is regarding the second Golden rule. Let's take parvovirus as an example. These viruses affect immature RBCs specifically (progenitors). In some cases, the whole RBC gets phagocytosed by some types of dendritic cells. Surprisingly, the antigen gets transported into the cytosol, processed by proteasomes, and goes through the rest of **MHC I pathway**. Although it is an **extracellular antigen** to dendritic cells, it got presented to CD8+ (cytotoxic) T cell through MHC I pathway. This phenomenon is called **cross-presentation** or **cross-priming.**



GOOD LUCK