Generation of the Immune Response

Sheet 18 immunity

I only added extra notes that were explained in the lecture, refer back to the slides.

SLIDE 3:

In the generation of Immune response whether by B or T lymphocyte , T cells play a pivotal role as antigen-specific regulators and sometimes as effector cells, regulate and fine tune an immune response, T lymphocytes are almost always involved except in the response made by B lymphocytes for carbohydrates(T independent).

When we say humoral and cellular immune response these terms are misnomers, the immune response is always cellular because it involves T cells, even with the production of antibodies(humoral IR) T lymphocytes are involved, but when we say humoral and cellular we refer to the effector mechanism not to the mechanisms involved, to the effector arm of the immune system that's involved.

The nature of the T cell response to antigens is strongly influenced by the nature of the antigen presentation, that's the function of professional APC that interact with T lymphocytes and provide them with co stimulatory signals. Induction of most adaptive immune responses requires that T cells interact with APCs (antigen presenting cells), so the nature of presentation influence the type of immune response that result.
APCs also provide costimulatory signals for T cells in order for the response to take place.

SLIDE 4:

Bacteria are engulfed by Macrophages, it's fragmented in the macrophage by the phagocytic system(phagolysosome) and peptides from the antigen(bacteria) are presented on MHC class II in this case to the CD4 T lymphocytes. This antigen will be recognized by the T cell receptor, T cell becomes activated, the activation of T lymphocytes will be augmented by another signal(a costimulatory signal) provided by the macrophage(professional APC) that is production of IL-1,IL-1 acts to expand the activation of T lymphocytes which start producing the important cytokines

involved in the immune response and these are IL-2,TNF,and IFN- γ.One of the most important cytokines in the generation of the immune response is IL-2,IL-2 can act on many other cells, some of which are :-

1. T helper cell in an autocrine positive feedback loop, a feedback mechanism mediated by IL-2 acts on T lymphocytes causing more proliferation of these T cells
2. Cytotoxic T lymphocyte which will mediate attack of infected cell
3. B lymphocytes will proliferate under the influence of T lymphocytes into plasma cells (antibody producing b lymphocytes) with the mechanisms involved later like class switching and somatic hypermutation.

SLIDE 5:

- **Antigen Processing and Presentation**(few cells are capable of this such as Macrophages, dendritic cells, and B lymphocytes).
- **Antigen Recognition and Lymphocyte Activation** (this phase involves very complex interactions inside the T cell or the B cell, and this is also associated with the involvement of a large number of molecules)
- **Recruitment and Stimulation of Effector mechanisms**(responsible for destruction and elimination of invaders)**.**

SLIDE 6:

- **The innate immune system is the gateway to the adaptive immune responses**, without innate immunity system no adaptive immune response will be generated because it's initiated by cells of innate immunity such as macrophages and dendrites.

SLIDE 7:

The type of activation of T lymphocytes depends on the nature of the antigen

- Exogenous proteins are loaded into MHC class II molecules, whereas those synthesized within the cell's cytoplasm(endogenous proteins) load into class I MHC molecules. So that is the determinant, if it's an extracellular substance like a bacterium the presentation will take place in association with MHC class II molecules, if its an endogenous substance like protein produced by the body or a virus because the virus utilizes host cell machinery so it acts like a self protein and in this case it'll be presented in conjunction with class I MHC molecule.

SLIDE 8:

Whether it's a macrophage or a B cell, both have the capacity to process and present antigens to T lymphocytes. Macrophages engulf the bacterium while B lymphocyte binds to it via their BCR. Engulfment of the organism takes place and then loading of the antigen onto class II MHC molecule that's expressed on the surface in association with the antigen. Remember MHC molecules cannot be expressed on the surface of the cell without an antigen, they must carry an antigen so that's why in cases where no immune response is generated they carry self molecules and that's how T lymphocytes are MHC restricted in the thymus for example because the MHC molecule carries self antigens and that's how positive and negative selection processing are possible in the thymus.

SLIDE 9:

If it's a virus(intracellular antigen) , virus will uncoat ➔the genome of the virus is expressed by cellular mechanisms➔ peptides from the virus are loaded on MHC class I molecules,this will be expressed on the surface of the cell where CD8 can recognize these molecules.

SLIDE 10+11:

- Within the endoplasmic reticulum of the macrophage(Antigen processing cell), MHC class II molecules are synthesized and after the association of the alpha and beta chains together a peptide,an invariant (Ii) chain is loaded into the peptide binding site,into the groove created by the association of the alpha and beta chains of MHC class II.

- The purpose of the Ii chain is to keep the peptide-binding cleft of class II MHC molecules free of the cell's own peptide, until peptides of exogenous source are available,it occupies the site for a transient period of time waiting for a foreign peptide to be loaded on the peptide groove.

SLIDE 12:

Remember MHC class II binding site can accommodate up to 30 amino acids that's why its possible for CLIP(24 amino acids) to sit and fit on the antigen

binding site,if it was MHC class I it would be impossible because they only accommodate up to 10 amino acids.

- HLA-DM replaces CLIP with the foreign peptide.

SLIDE 15:

- Cytoplasmic proteins are constantly degraded in all nucleated cells into peptides , the degradation is achieved by the proteasome, which is a product of class I MHC.
- TAP serves as a gatekeeper to the endoplasmic reticulum, TAP with the help of other molecules is responsible for loading of the peptide derived from endogenous antigens into MHC class I molecules, so a TAP in this case is similar to HLA-DM.

SLIDE 16:

- On the formation of the Iα:β2 complex, calnexin is replaced with calreticulin and tapasin proteins, making the complex stable.

SLIDE 18:

Ubiquitin carries proteins that are destined to be degraded and proteasome will degrade these into small peptides, and within the endoplasmic reticulum the newly synthesized MHC class I with the help of calnexin associated with β 2 microglobulin will result in a complex and this complex will associate with calreticulin and tapasin and now the peptide is loaded with the help of TAP.

SLIDE 19:

The first step is the synthesis of the MHC class I that is composed of the alpha chain which associates with calnexin, calnexin will enable the binding of β2

microglobulin so we'll have now calnexin β2 microglobulin with MHC class I. Calreteculin and tapasin will replace calnexin and they will enable tap to add a peptide from those being created by the proteasome to the antigen binding site on the MHC.

SLIDE 21:

Antigen is ready and is being presented by a dendritic cell to T lymphocyte,this will provide the first signal(antigen binding), the second signal is provided by production of il 1 which activates t lymphocytes.activated t lymphocytes secrete cytokines that will activate b lymphocytes and cytotoxic t cells with the generation of memory cells.

SLIDE 22:

Now the antigen is presented, the role of the T lymphocyte is to recognize the antigen and to initiate a cascade of events that culminates in the expression of many nuclear factors to produce these cytokines that will activate T or B lymphocytes.

SLIDE 23+24:

There are many sources for the costimulatory signal, one of the most important molecules involved in the generation of the second signal is the CD45(Common Leukocyte Antigen),the CD45 activates kinases such as fyn, fyn is essential to activate inositol triphosphate kinase in association with CD28,remember CD28 is a molecule that is specific for t lymphocytes so CD28 and fyn activate the guanine nucleotide exchange factor (Ras)
Ras activates the Mitogen Activated Protein (MAP) kinase cascade, ultimately leading to the activation of AP-1(Activation Protein 1),which are a family of factors that initiate transcription of a number of proteins.

The costimulatory signal here will be provided by binding between CD28 and b7-1 or b7-2.

Slide 25:

So T cell receptor recognition of an antigen that is presented in conjunction with MHC class II will activate CD45 and CD28 and the activation of these enzymes result in the activation of phosphorylases like fyn and fyn with IP3K will activate ras, ras activates MAP(Mitogen Activation Protein) that will activate AP(Activation Protein),and this is a nuclear factor that activates the expression of several genes that code for cytokines, so cytokine production is the end result of the antigen recognition and involvement of these antigens.

Slide 26:

LFA-1(Leukocyte Function Antigen-1),and now an immunological synapse which provides a very strong signal to T lymphocytes is in place which is responsible for the full activation of T lymphocytes. MHC class II with an antigen is recognized by the TCR in conjunction with CD4, binding of the CD40 to the CD40 ligand will activate the expression of the CD80/CD86, binds to CD28.CD2 on the surface of T lymphocytes binds to LFA-3, ICAM-1 binds to LFA-1,this causes a strong interaction between an antigen presenting cell and T lymphocyte which will activate T cells. Now the activation of T lymphocytes creates a signal, this signal must be transduced to activate gene expression.

SLIDE 28:

ITAMs are present on CD3, ITAMs are essential for transduction of T cell signal and B cell signal as you will see later on.

SLIDE 30:

ZAP-70 is a critical molecule in the activation of T lymphocytes, this is a specific T cell molecule, there is an equivalent of this enzyme in B lymphocytes but it's

not the same molecule. Phospholipase c-γ and the linker of activation of T cells represent two pathways of T cell activation, T cell activation follows either the PLC-**γ** OR the LAT, and they can't be activated simultaneously.

Slide 33:

MAP: Mitogen Activation Protein

Slide 35:

CD4 activation will activate Lck as a consequence of antigen recognition by TCR in association with MHC class II,CD4 will become active, Lck will activate phosphorylation of ITAMs,ITAM phosphorylation will activate ZAP 70 which activates either PLC-**γ** OR the LAT. PLC-γ will act on PIP2 to generate two molecules(DAG or IP3),in the presence of calneurin IP3 will activate NFAT whereas DAG will activate PKC which will activate NF-κB and that will activate transcription of certain genes.
The other pathway which is also acted upon by ZAP70 is the LAT pathway which will activate a number of phosphorylases like Ras or Rac that can activate MAP or SAP, and this'll activate AP-1 which is a nuclear transcription factor.
All of these mechanisms finally lead to the expression of cytokine genes and now lymphocytes are fully activated with the synthesis and production of many different cytokines.

Done By: AbdelHalim Awidi