IMMUNOLOGY AND MEDICAL MICROBIOLOGY

Humoral and Cell - Mediated Immune Response

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Keywords

Antigen presenting cell (APC); T helper cell (T_H); T cytotoxic cell(T_C); major histocompatibility complex (MHC); cluster of differentiation (CD); rough endoplasmic reticulum (RER); T cell receptor (TCR)

Introduction

Immunity is defined as protection from disease. Many of the mechanisms of resistance to infections are also involved in an individual's response to non-infectious substances. Hence, a more accurate definition of immunity is a reaction to harmful agents such as microbes and macromolecules like proteins. The elements of the immune system are the molecules and cells responsible for resistance to foreign agents, living or non-living. An immune response encompasses two main events : immune recognition, which is recognition of the antigen and immune activation as well as response, which involves generation of effector cells and molecules that eventually counterattack, destroy or contain the antigen. There are two main arms of the immune response: humoral (antibody mediated and involving B lymphocytes, plasma cells and secreted antibodies) and cellular (involves specialized cells called antigen presenting cells, T lymphocytes and macrophages and cytokines).

The cell membranes of both T and B lymphocytes have receptors for binding to an antigen. The receptors on B cells are unique in the sense that they are antibody molecules which can recognize and interact directly with free antigen. Hence B cells recognize soluble antigen when it binds to their membrane bound antibody. The epitopes or antigenic determinants recognized by B cells tend to be highly accessible sites on the surface of the immunogen. The receptors on T cells are slightly different, in the sense that they do not recognize free antigen. They recognize only the antigen that is combined with either class I or class II major histocompatibility complex (MHC) molecules on the surface of an antigen presenting cell or an altered self cell. The antigenic peptides recognized by T cells form complexes with an MHC molecule and a T cell receptor(TCR). Therefore, antigens recognized by T cells must have two distinct interaction sites: an epitope, that interacts with a T cell receptor/TCR and an agretope, which interacts with MHC. The following parameters compare the interaction of B and T lymphocytes with antigens.

Table 1: Specificities of antigen interaction with T and B lymphocytes

Parameter	B lymphocyte	T lymphocyte
Chemical nature of antigen	Protein, polysaccharide or lipid	Mostly proteins
Interaction with antigen	Involves binary complex of membrane Ig and Ag	Involves ternary complex of TCR, Ag and MHC molecules
Binding with soluble antigen	Yes	No
MHC molecule requirement	None required	Required to display processed antigen
Properties of Epitope	Hydrophilic mobile peptides containing sequential or non sequential amino acids	Internal linear peptides processed and bound to MHC molecules

The T-helper (T_H) and T-cytotoxic (T_C) cells are the two major subpopulations of T lymphocytes. The T-helper cells express CD4, a membrane glycoprotein, and recognize antigen in complex with class II MHC molecules. The T-cytotoxic cells express CD8 and recognize antigen in association with class I MHC molecules.

The process of an antigen being degraded into small antigenic peptides and in turn complexing with class I or class II MHC molecules is called antigen processing and presentation. In this complexed state, the processed antigen is recognized by T cells.

The pathways for processing and presentation of antigens is different depending on whether the antigen is exogenous or endogenous in nature.

An exogenous antigen is produced outside the host cell and enters the cell by phagocytosis or endocytosis. Antigen presenting cells like macrophages, dendritic cells and B cells degrade ingested exogenous antigens into peptide fragments which bind to class II MHC molecules and are subsequently expressed on the cell surface. Since T-helper cells displaying CD4 recognize antigen combined with class II MHC molecules, they are said to be class II MHC restricted.

An endogenous antigen is produced within the cell as exemplified by viral proteins synthesized within virus infected cells and new proteins such as those synthesized by cancerous cells. Endogenous antigens are degraded into peptide fragments that bind to class I MHC molecules within the endoplasmic reticulum . The peptide-class I MHC complex is then transported to the cell membrane. Class I MHC are expressed on all nucleated cells. Since $CD8^+$ T-cytotoxic cells recognize antigen associated with class I MHC molecules, they are said to be class I restricted.

By convention, cells that display peptides associated with class I MHC molecules to $CD8^+$ T-cytotoxic cells are referred to as **target cells**. And cells that display peptides associated with class II MHC molecules to $CD4^+$ T-helper cells are called **antigen-presenting cells.**

Antigen presenting cells (APCs)

The APCs present the processed antigenic peptides, in association with the class II MHC antigen, on its cell membrane to T cells. The antigen presenting cells are classified into professional APCs and non-professional APCs. The professional APCs include dendritic cells, macrophages and B lymphocytes. The non professional APCs include fibroblasts in skin, glial cells in brain, pancreatic beta cells, vascular endothelial cells, thymic epithelial cells and thyroid epithelial cells. These cells function in antigen presentation only for short periods of time during a sustained inflammatory response.

Dendritic cells

They are so named because they possess long membranous extensions resembling dendrites of nerve cells. There are four types of dendritic cells : Langerhans cell, interstitial dendritic cell, myeloid and lymphoid dendritic cells. All arise from haematopoietic stem cells by different pathways and in different locations. Fig.1 shows

that they descend through both the myeloid and lymphoid lineages. Dendritic cells are said to be the most effective APCs because they constitutively express high levels of class II MHC molecules and co-stimulatory activity, and can activate naïve T-helper cells.

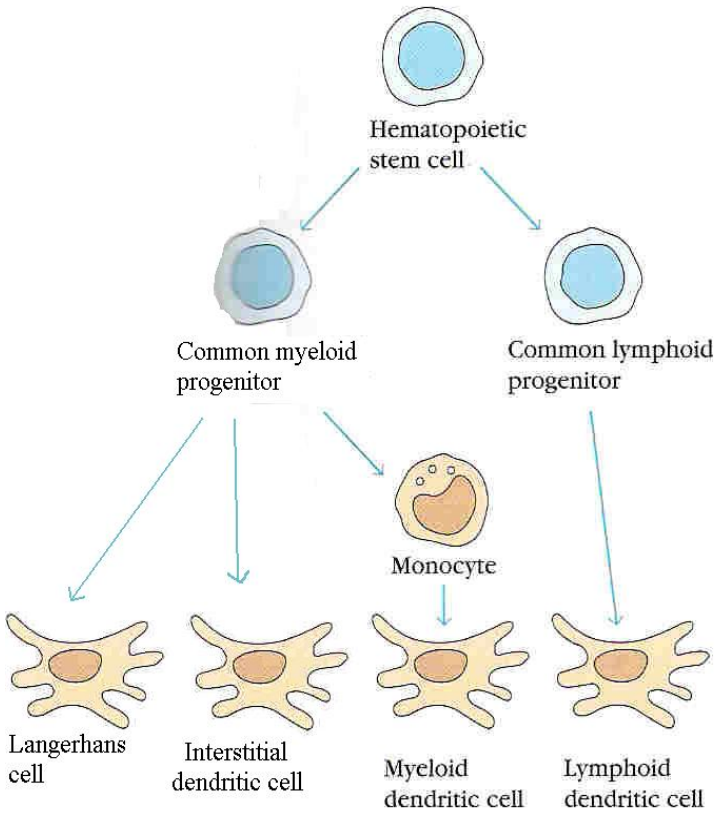

Fig. 1: Dendritic cells arise from both myeloid and Lymphoid lineages.
(Source: Richard A Goldsby, Thomas A Kindt, Barbara Osborne and Janis Kuby. Immunology, 5th ed., 2003, W H Freeman and Co.)

Each immature or precursor dendritic cell acquires the antigen by phagocytosis, processes it and the mature dendritic cell presents it to a T-helper cell. At this stage , it is imperative to mention the follicular dendritic cells, which do not express class II MHC molecules and hence do not function as APCs. The follicular dendritic cell does not arise in the bone marrow and is so named because it is exclusively located in the B-cell rich lymph follicles in the lymph node. It expresses high levels of membrane receptor for antibody and hence can bind to antigen-antibody complexes.

Macrophages

The macrophages are transformed monocytes that leave the blood to move to the tissues. Macrophages can be activated by various stimulants or activators including microbes and their products, antigen – antibody complexes, inflammation, sensitized T lymphocytes, lymphokines and injury. Activated macrophages have an increased number of lysosomes and produce and release interleukin – 1. Interleukin – 1 participates in fever production and in activation of lymphoid cells, resulting in the release of other cytokines. Once activated these cells start expressing the class II MHC molecules as well as the co – stimulatory B7 membrane molecule. B7 is a molecule which is found on professional APCs such as B cells and macrophages. For T cell activation, an interaction is essential between B7 lead to their functional inactivation (anergy) or death.

B lymphocytes

These cells constitutively express class II MHC molecules but must be activated before they express the co-stimulatory B7 molecule.

Cytosolic Pathway for Processing of Endogenous Antigens

Endogenous antigens, both particulate and soluble, have been found to get digested within the cytoplasm into peptides that can associate with class I MHC molecules.
The pathway involves the following steps:

1. Degradation of proteins into peptides by proteasome

All proteins targeted for proteolysis undergo attachment to a small protein called ubiquitin to form a ubiquitin protein conjugate. This conjugate can be degraded by an enzyme complex, called proteasome.

Each proteasome is a large cylindrical particle of size 26s. It consists of four rings of protein subunits with a central channel of 10-50Å. The degradation of the ubiquitin protein complexes occurs within the central channel of proteasome generating a variety of peptides in a reaction that is ATP - dependent.

2 .Transport of the peptides from the cytosol to the rough endoplasmic reticulum

The peptides formed in the cytosol by the proteasome complex are then translocated into the Rough Endoplasmic Reticulum (RER) by a special transporter protein called TAP (transporters for antigen processing).

The transporter protein TAP is a heterodimer made of TAP1 and TAP2 traversing the membrane. Each of the TAP1 and TAP2 proteins have two parts:

1. a hydrophobic domain which projects through the membrane into the lumen of RER.
2. an ATP binding domain which projects into the cytosol.

It has been noted that TAP has high affinity for peptides made up of 8-13 amino acids and this also seems to be the optimal length of peptides for binding to class I MHC. It

has also been observed that TAP appears to bind prefentially to peptides with hydrophobic or basic carboxy-terminal amino acids , which are the preferred anchor residues for class I MHC molecules. Hence, it may be concluded that TAP is uniquely designed to transport peptides that will later interact with class I MHC molecules.

3. Assembly of peptides with class I MHC molecules

The class I MHC molecule consists of an alpha chain and beta2-microglobulin which are synthesized on polysomes along the RER. The entire assembly process leading to the formation of a stable and functional class I MHC molecule involves the participation of a class of proteins called molecular chaperones. These molecular chaperones facilitate the optimal folding of the class I MHC polypeptides.

The first molecular chaperone that participates in class I MHC assembly is calnexin which is a resident membrane protein of the RER. Calnexin associates with the free class I alpha chain and promotes its folding. As the beta-2 micro globulin binds to the alpha chain, calnexin is released. The class I molecule then associates with calreticulin and tapasin (TAP associated protein).

Tapasin brings the TAP transporter protein near the class I molecule and helps it to capture an antigenic peptide. The close physical stoichiometric interaction of the class I MHC molecule with the TAP protein facilitates the capture of peptides, before they are exposed to the luminal environment of the RER. This is particularly important in the light of the fact that the peptides which are not bound by class I molecules are rapidly degraded.

Subsequently the class I molecule breaks away from calreticulin and tapasin, exits from the RER, and proceeds to the cell surface via the Golgi apparatus.

Endocytic Pathway for Processing of Exogenous Antigens

Exogenous antigens can be internalized by endocytosis, phagocytosis or both. Macrophages internalize antigens by both processes. Other APCs are not phagocytic and internalize exogenous antigens only by endocytosis.
Once the antigen is internalized it is processed by the endocytic pathway in the following steps:

1. Peptide generation in endocytic vesicles
After internalization, an antigen takes 1-3 hrs. to be degraded to peptides. During this time the antigen is cycled through compartments of increasing acidity, starting with early endosomes (pH 6.0-6.5), followed by late endosomes (pH 5.0-6.0) and finally lysosomes (pH 4.5-5.0). The lysosomes are found to contain more than forty types of hydrolytic enzymes like proteases, nucleases, glycosidases, lipases, phospholipases and phosphatases.

The antigen is degraded into oligopeptides of 13-18 residues which can bind to class II MHC molecules.

Because the hydrolytic enzymes are operational only at low pH, agents which increase the pH of the endocytic compartment like chloroquin and leupeptin, can inhibit the process of antigen processing.

2. Transport of class II MHC molecules to endocytic vesicles

As a class II MHC molecule is synthesised inside RER, it associates with another protein Ii or invariant chain. This binds with the peptide binding cleft of class II MHC, so that endogenously derived peptides cannot bind to the class II MHC molecule. The Ii protein then helps the class II MHC molecule to traverse to the endocytic processing pathway by the Golgi network.

3. Binding of peptides to class II MHC molecule by displacement of CLIP

The class II MHC invariant chain complex moves through the entire sequence of the endocytic pathway, during which time the invariant chain is slowly degraded but only partially. A small fragment of the invariant chain called CLIP (class II associated invariant chain peptide) remains bound to the class II MHC molecule in its peptide binding groove. Presumably this prevents any premature binding of antigenic peptide to the peptide binding groove.

CLIP is eventually removed by a non- classical class II MHC molecule called HLA-DM, which catalyses the displacement of CLIP with antigenic peptide. The peptide class II MHC complex is then transported to the plasma membrane surface, where the complex assumes a more stable form because of neutral pH. Fig. 2 shows the comparative steps in the cytosolic and endocytic pathway of antigen processing.

Humoral Immunity

In the antibody – mediated arm, $CD4^+$ T lymphocytes recognize the antigens complexed with class II MHC proteins on the surface of an APC. As a result, they produce cytokines that activate B cells expressing antibodies that specifically match the antigen.
B cells are responsible for antigen interaction, antibody production and immune memory. A mature B cell leaves the bone marrow expressing membrane bound immunoglobulin (mIgM and mIgD) with a single antigenic specificity. These surface immunoglobulins are copies of the single type of antibody that a given B cell will produce later in its development. Surface immunoglobulins on B cells recognize antigens in native conformation usually on the pathogen surface, and this property uniquely distinguishes the B cells from the T cells.

The B cells that have not encountered the antigen as yet are known as naïve or virgin B cells and they circulate in the blood and lymph. They are then carried to the secondary lymphoid organs , and get concentrated in the spleen and cortex of the lymph node, which provide the micro - environment for efficient interaction with the antigen.

The process of antibody formation is complex, which involves T cells, B cells and APCs, and intimate interactions between these cell types. It can be considered to consist of the following steps:

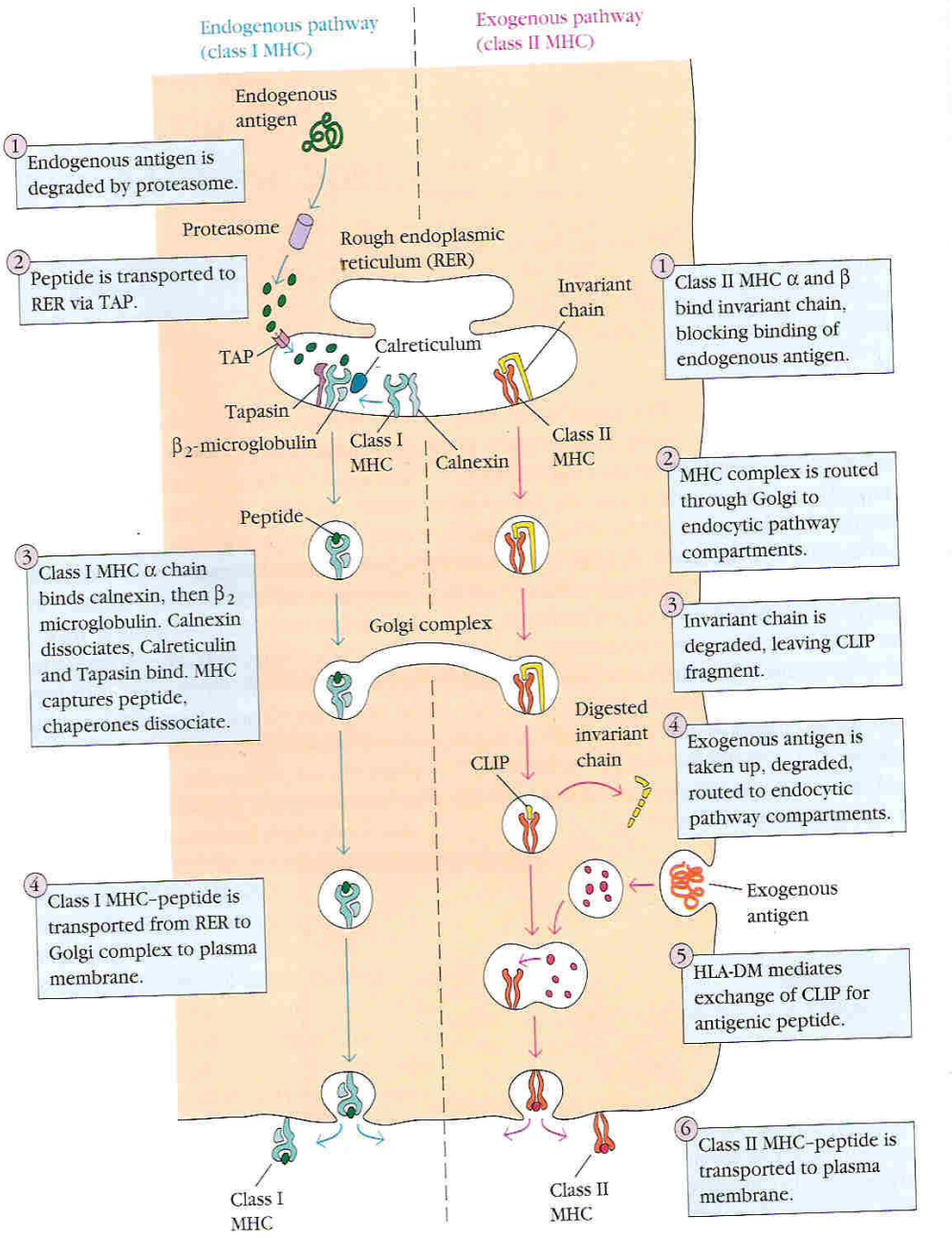

Fig. 2: Processing of endogenous antigen by cytosolic pathway (left) and of exogenous antigen by the endocytic pathway (right).
(Source: Richard Goldsby, Thomas J Kindt, Barbara A Osborne, Janis Kuby. Immunology, 5th ed., 2003 by W H Freeman and Co.)

Exposure to antigen

An antigen may be introduced in any part of the body. After introduction, the antigen is carried by the lymphatic and blood circulatory system, to nearby secondary lymphoid organs such as lymph nodes, spleen or MALT (mucosa – associated lymphoid tissue). For example, if an antigen is injected intra-venously, it travels via the blood to the spleen. If

an antigen is introduced subcutaneously, intradermally, topically or intra-peritoneally, the lymphatic system drains the site and deposits the antigen in adjacent lymph nodes. Similarly, antigen introduction or deposition on the mucosal surface, as by ingestion of antigen into the gut by feeding, delivers the antigen to the proximal MALT.

Interaction of B cell with antigen

When a B lymphocyte with its membrane bound immunoglobulins, encounters a foreign antigen for which that immunoglobulin is specific, there is an interaction between the immunoglobulin and the antigen, that initiates B cell activation. The activation of the B cell leads to clonal expansion and differentiation. **Clonal expansion** involves the division of the specific activated B lymphocyte resulting in a population of genetically identical B lymphocytes. This stage is followed by **differentiation** , in which the B cells differentiate to form antibody secreting plasma cells and memory cells. **Plasma cells** are relatively short - lived (less than one week) but produce and secrete large amounts of IgM antibody in the primary response to the antigen. They are found in the medulla of the lymph nodes , where the immunoglobulins can drain directly into an efferent lymph vessel. The **memory cells**, in contrast, live for several years and remain in the cortical areas. If re-exposure to the immunizing antigen occurs, memory cells need no T cell help. They quickly transform to produce more memory cells and plasma cells which start producing IgG antibody. This secondary response, of which immunological memory is a distinct component, results in a more rapid and abundant antibody production, and it also shows the antibody **class switch** phenomenon from IgM to IgG. In fact, **affinity maturation** and antibody **class switching** are phenomena that accompany the activation and differentiation of B cells after antigen exposure. Affinity maturation refers to the progressive increase in the average affinity of the antibodies produced and class switching is the change in the isotype of the antibody by the B cells from mu (μ) to gamma (γ) , alpha (α) or epsilon (ε).

Depending on the nature of the antigen, B cell activation follows two different routes, one dependent on T- helper cells and the other not requiring the participation of T-helper cells. The B cell response to thymus-dependent (TD) antigens requires direct contact with T-helper cells, and not simple exposure to T_H - derived cytokines.

Antigens that can activate B cells without requiring any help from T – helper cells are called thymus independent (TI) antigens. The TI antigens are of two types: TI – 1 and TI – 2.

Type 1 thymus independent antigens or TI – 1 are known mitogens or polyclonal B cell activators, as they are able to activate B cells regardless of their antigenic specificity. A typical example of a TI – 1 antigen is the bacterial lipopolysaccharide (LPS), a major component of the cell walls of gram – negative bacteria.

Type 2 thymus independent antigens or TI – 2 activate the B cells by cross – linking extensively the immunoglobulin receptor on the surface of B cells. These antigens are highly repetitive molecules as exemplified by bacterial flagellin and capsular polysaccharides such as dextran.

Process of B cell activation

The immunoglobulin receptor on the surface of a B cell is associated with additional polypeptides that are believed to play a major role in the transduction of a signal to the interior of the B cell, that eventually leads to B cell activation.

Studies have shown that membrane immunoglobulin is associated with a disulfide - linked heterodimer Ig – α / Ig – β , forming the B cell receptor (BCR). Careful biochemical analysis has shown that only one Ig – α /Ig – β heterodimer associates with a single membrane immunoglobulin molecule to form the receptor complex. Thus , the BCR is functionally divided into the ligand binding immunoglobulin molecule and the signal transducing Ig – α /Ig - β heterodimer.

The membrane bound immunoglobulin molecule (mIg) have very short cytoplasmic tails : 3 aminoacids for mIgM and mIgD, 14 aminoacids for mIgA, and 28 aminoacids for mIgG and mIgE. The Ig – α / Ig – β heterodimers have longer cytoplasmic tails (61 aminoacids for Ig – α and 48 aminoacids for Ig – β). These long cytoplasmic tails have tyrosine residues that can be phosphorylated by intracellular protein kinases. When a B cell with surface immunoglobulin, encounters a specific antigen, the antigen can complex with more than one antigen combining site and effectively cross – link membrane – bound immunoglobulins. The cross – linking of surface Ig by antigen activates tyrosine kinases that phosphorylate and dephosphorylate the cytoplasmic tails of the Ig – α /Ig – β heterodimers. As a result of this phosphorylation and dephosphorylation, several enzymes in the cell are activated, which include the following :

- **(i)** **Phospholipase C** (PLC) gets activated. PLC splits phospholipid (PL) into **diacetylglycerol (DAG**) and **inositol triphosphate IP3.**
- **(ii)** **Diacetylglycerol** activates **protein kinase C (PKC**) leading to formation of nuclear factor NF – κB.
- **(iii)** **Inositol triphosphate (IP 3)** causes release of calcium from stores in the endoplasmic reticulum and influx of calcium. Increase in the calcium concentration leads to activation of calmodulin, which subsequently causes phosphorylation of **DNA binding protein ets – 1**.
- **(iv)** Activation of *RAS*, an oncogene, leads to activation of serine or threonine kinases and phosphorylation of *cJUN*, an oncogene.

The DNA binding proteins are nuclear factors that enter the nucleus of the B cell and effect transcription of specific genes, thus activating the B cell. These events are summarized in Fig. 3.

After cross – linking of membrane immunoglobulin molecules by binding with bivalent or multivalent antigen, the antigen is internalized by receptor mediated endocytosis and processed within the endocytic pathway into peptides. It generally takes 30 to 60 min. after internalization of antigen for processed antigenic peptides to be displayed on the B cell membrane in association with class II MHC molecules. As a result of this interaction, the B lymphocyte becomes an antigen presenting cell (APC).

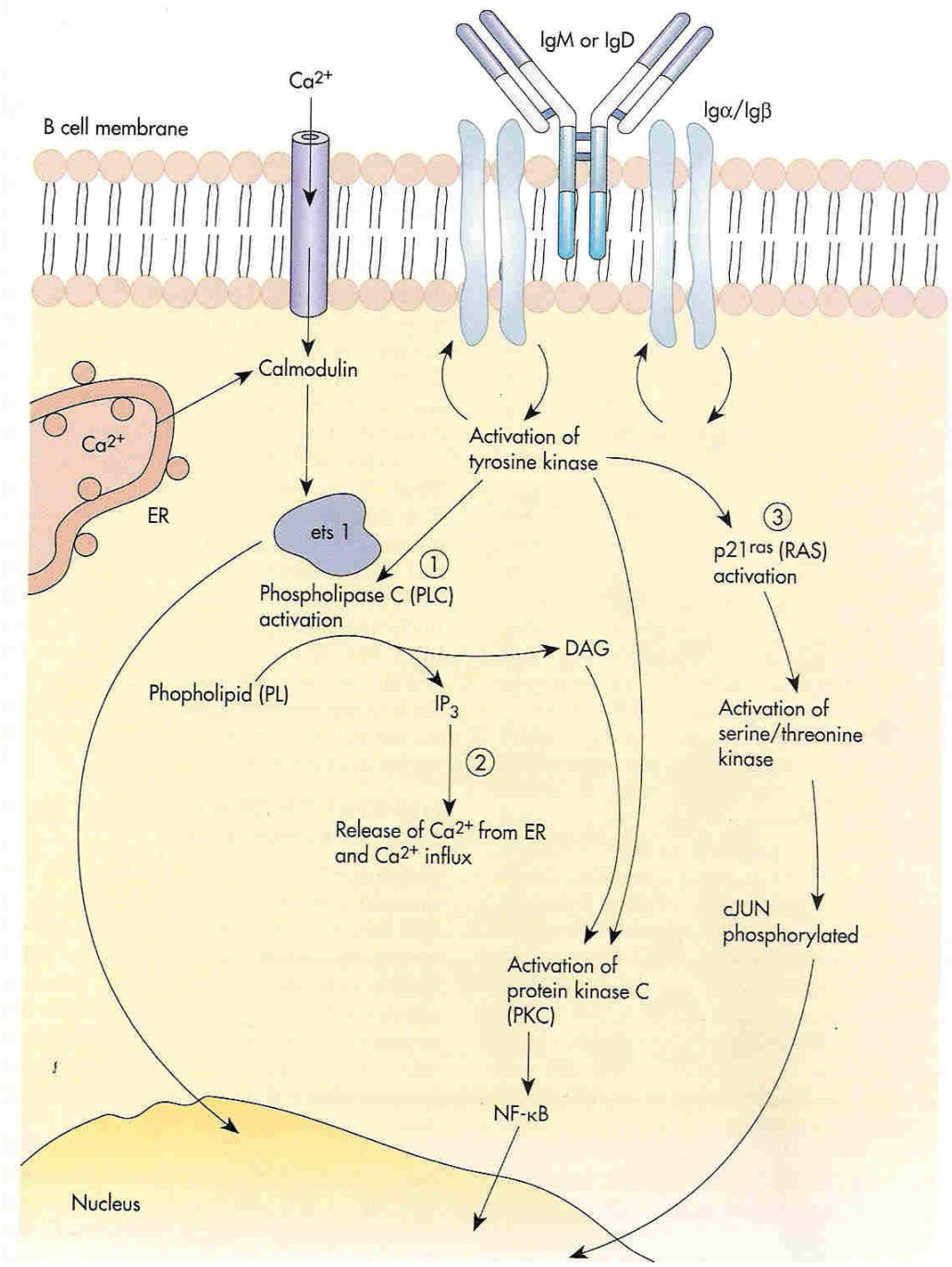

Fig. 3: B Cell Receptor Complex and the Process of B Cell Activation
(Source: Ronald M Atlas, Principles of Microbiology, 2nd ed. , Wm. C Brown Publishers

The T – helper cell (T_H) recognises a processed antigenic peptide displayed by a class II MHC molecule on the membrane of a B cell and the two cells interact via the T cell receptor and class II MHC molecule to form a T – B conjugate. Formation of a T – B conjugate is followed by the expression of CD40L (CD154) on the T_H cell membrane, which interacts with CD40 on B cells, to provide a signal for T – cell – dependent B cell activation. CD40 is a member of the TNF (Tumour necrosis factor) family of cell surface proteins and soluble cytokines that regulate cell proliferation and programmed cell death by apoptosis. CD40L belongs to the TNF receptor (TNFR) family. Several lines of evidence have identified the CD40 – CD40L interaction as the primary mediator of contact dependent help, that activates the B cell . This is followed by the release of cytokines towards the interacting B cell by T_H cell which specifically stimulate the B lymphocytes into cell growth and proliferation.

Once activated, the B cell begins to express receptors for various cytokines such as interleukin – 2 (IL – 2), interleukin – 4 (IL - 4), interleukin – 5 (IL – 5) and others. The receptors bind the cytokines produced by the interacting T_H cell. The signals produced by these cytokine – receptor interactions support B cell proliferation and induce their differentiation into plasma and memory cells, class switching and affinity maturation.

Cell Mediated Immunity

Cell-mediated immunity (CMI) refers to an immune response generated by the activities of non-antibody producing cells such as T cells. CMI is particularly important in combating infections that involve reproduction of pathogens within host cells . This includes infections by viruses, rickettsiae, chlamydiae and some parasitic protozoa such as trypanosomes. Also, CMI is important in the surveillance and destruction of tumour cells, which arise in the body.

Cell mediated immune responses include:
i) **Antigen – specific $CD8^+$ cell toxicity** : Cytotoxic (killer) T cells express CD8 and recognize foreign peptides generated from cytotoxic pathogens, such as viruses, as well as tissue transplants and tumours, and associated with class I MHC molecules.

ii) Delayed Type hypersensitivity : Cell – mediated or delayed hypersensitivity is a function of specifically sensitized T lymphocytes, macrophages, fibroblasts and giant cells, not of antibody. The response is delayed i.e. it starts hours or days after contact with the antigen and often lasts for days. The delayed type response is introduced by intracellular bacteria such as *Mycobacterium tuberculosis, M. leprae and Listeria monocytogenes,* most helminthic parasite larvae and ova, and systemic fungi such as *Coccidioides immitis, Histoplasma capsulatum* and *Cryptococcus neoformans.* CMI may also develop in many viral infections such as herpes simplex and mumps.

iii) Natural killer(NK) cell mediated cell toxicity : The NK cells are a subpopulation of lymphocytes which are neither T or B cells. They attack tumour cells and virally infected cells. They recognize their targets in any of two ways. They possess Fc receptors that bind to IgG antibody. These receptors link the NK cells to IgG – coated target cells, which they kill by a process called antibody – dependent cell mediated

cytotoxicity(ADCC). The NK cells can also induce killing of virally infected cells and cancer cells by recognizing changes in the distribution or expression of class I MHC molecules on these cells. Any cell showing such a change is perceived as abnormal by the NK cells, and hereby killed.

Table 2: Classes of T Cells and their major functions

Class	Function
T_C (cytotoxic cells) called $CD8^+$ cells	Cause cytolysis and death of virus-infected cells and tumour cells
T_H (helper) cells called $CD4^+$ cells T_H1, T_H2, T_H0 subsets	1. Help B cells make antibodies 2. Stimulate CMI.
T_S (suppressor) cells	Suppress activity of naïve or effector T cells

Effector T Cells

Cytotoxic T cells (TC) are $CD8^+$ effector cells which are also known as cytotoxic lymphocytes (CTLs). These cells have the lytic potential and are critical in the recognition and elimination of altered self cells (for e.g. Virus infected cells and tumours) and in graft rejection reaction. In general, CTLs are class I MHC restricted, and hence can recognize and eliminate almost any altered body Cell. The cytotoxic T cell (T_C) attaches by T cell receptor protein to viral antigen- class I MHC complexes on the surface of virally infected cell. A co-stimulatory signal is required in the form of a CD28-B7 interaction. Finally, the T_C cell requires exposure to IL-2 from T_{H1} cells to proliferate and differentiate to form active CTLs which can destroy virus infected cells.

The target cells can be destroyed by CTLs by any of the following two ways:

(i) The CD95 pathway
(ii) The perforin pathway

CD95 Pathway

In this pathway, cytotoxicity is mediated by Fas or CD95 protein receptor found on many eucaryotic cells. It is a transmembrane orotein which is encoded by the *fas* gene , a member of the TNF-family of genes. *Fas* ligand or CD95 L is found in high concentrations on the surface of CTLs. When the Fas ligand binds to the target cell Fas protein , the CD95- CD95 L interaction activates several cytoplasmic proteins that initiate a cellular suicide cascade , leading to apoptosis. A feature of cell death by apoptosis is the involvement of the caspase family of cysteine proteases which on activation lead to systematic and orderly disassembly of the cell that is hallmark of apoptosis.

Perforin Pathway

This pathway begins when contact between the target cell and CTL is initiated by the TCR-Ag—MHC complex. On contact with the target cell granules in the CTL are drawn to the plasma membrane in contact with the target site and contents of granules are released. The granules contain perforin monomers, which enter the membrane of the target cell, polymerize and form a pore. This can lead to osmotic lysis. Finally the CTL secretes granzymes, which are proteolytic enzymes that enter the target cell and induce apoptosis. The CTLs lyse only the specific target cell displaying the foreign antigen; killing of neighbouring cells seldom occurs. The CTL disengages from the dying target cell and recycles its cytoplasmic components in preparation for another attack (Fig. 4).

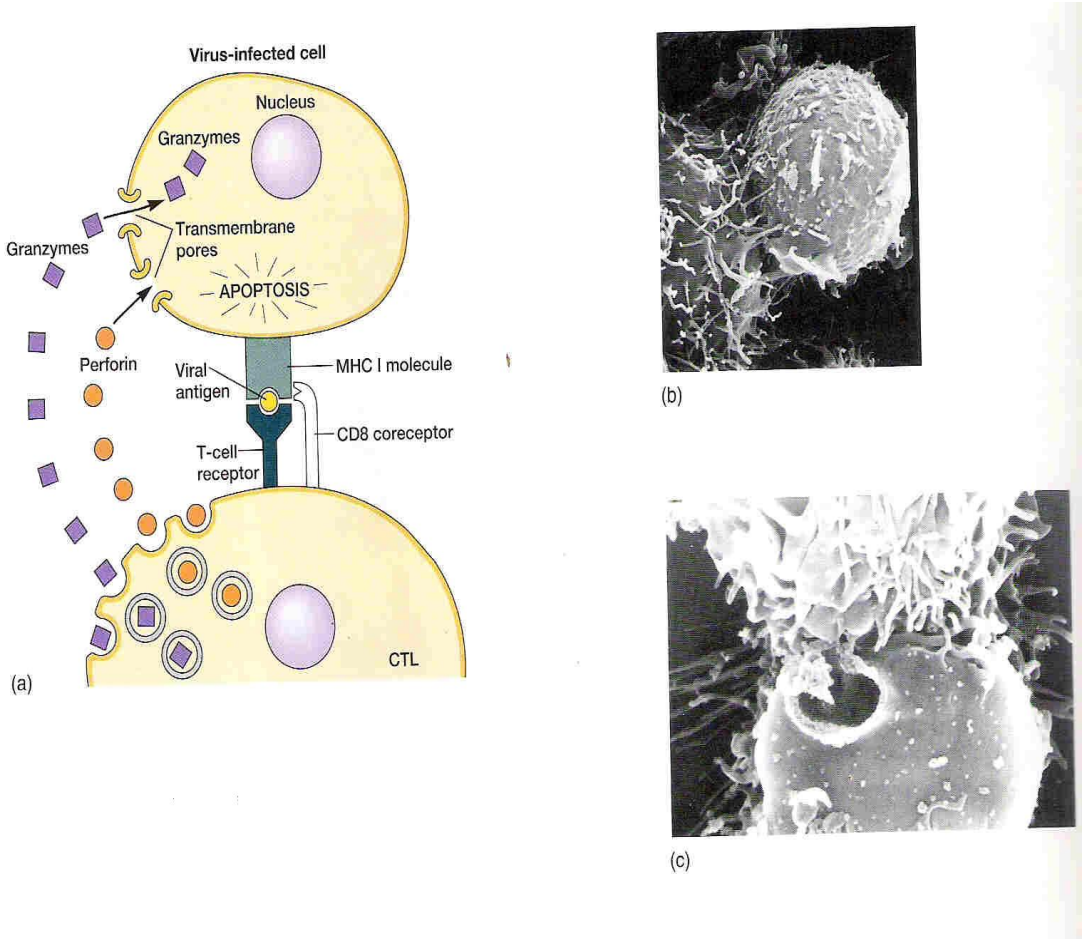

Fig. 4 Destruction of a virus infected target cell by an effector cytotoxic T Cell
(a) Perforin pathway leading to apoptosis and cytolysis
(b) A cytotoxic T cell (left) makes contact with a target cell (right)
(c) The T cell secretes perforin that forms transmembrane pores in the targetcell's membrane

(Source: L M Prescott, J P Harley, D A Klein, Microbiology , 5th ed.,2002, Mc Graw Hill)

Regulator T Cells

Regulator T cells control the development of effector T cells, and exist in two subpopulations: T – helper cells (T_H) and T – suppressor cells (T_S). There are three subsets of T –helper cells : T_H1, T_H2 and T_H0. The T_H1 cells produce IL – 2, IFN – γ and TNF – β that are involved in cellular immunity. These cytokines are involved in delayed type hypersensitivity reactions and activation of macrophages. The T_H2 cells produce cytokines such as IL – 4, IL – 5 and IL – 6 which stimulate B – cell proliferation and differentiation into antibody forming plasma cells. T_H2 cells are hence helpers for B – cell antibody responses and defense against helminths. To be stimulated by an antigen T_H1 cells need two signals:

(i) The first signal is the presentation of the antigen fragments to a T cell by a macrophage, dendritic cell or an activated B cell. The combination of antigen fragment and class II MHC is needed for recognition by the T cell receptor protein (TCR) on the surface of T_H1 and it represents activation signal 1.

(ii) The second signal involves the CD28 protein receptor on T_H1 cells. When CD28 binds to a protein called B7 on the surface of a macrophage, it delivers a second signal to the T_H1 cell.

Signal 1 activates a tyrosine kinase present in the cytoplasm. The activated tyrosine kinase adds phosphate groups to the amino acid tyrosine in proteins. As a result of this phosphorylation, the enzyme phospholipase Cγ1 cleaves phosphatidyl – inositol bisphosphate, located in the T – helper cell plasma membrane. Two cleavage products are formed. One of the cleavage products, diacylglycerol activates protein kinase C. The latter moves into the nucleus and causes formation of a protein complex AP – 1. The second cleavage product inositol triphosphate, causes Ca^{+2} ions to rush into the cytoplasm leading to activation of calmodulin, calcineurin and nuclear factor of activated T_H1 cells (NF – AT). NF – AT moves to the nucleoplasm where it binds to AP – 1 forming a NF – AT /AP – 1 complex. This complex is a transcription factor which causes interleukin - 2 mRNA to be transcribed. Interleukin – 2 mRNA moves out of the nucleus to the ribosomes where IL – 2 is produced.

Signal 2 is mediated by the CD28 receptor and B7 molecule. This activates another tyrosine kinase causing formation of the transcription factor CD28RC, and stabilizes the mRNA transcribed from IL – 2 gene, increasing the concentration of IL – 2. T_H1 cells activated by these two signals secrete large amounts of IL – 2 which activates cytotoxic T cells. T_{H1} cells also secrete gamma – interferon which can activate macrophages.
The above interaction is depicted in Fig. 5.

The T_H0 cells are simply undifferentiated precursors of T_H1 and T_H2 cells. Some immunologists believe in the existence of T – suppressor cells (T_S) that can suppress B and T cell responses. This subpopulation of T cells can be stimulated to proliferate by IL – 2 from activated T helper cells. But actual isolation of T_S cells is a matter of dispute and controversy among immunologists.

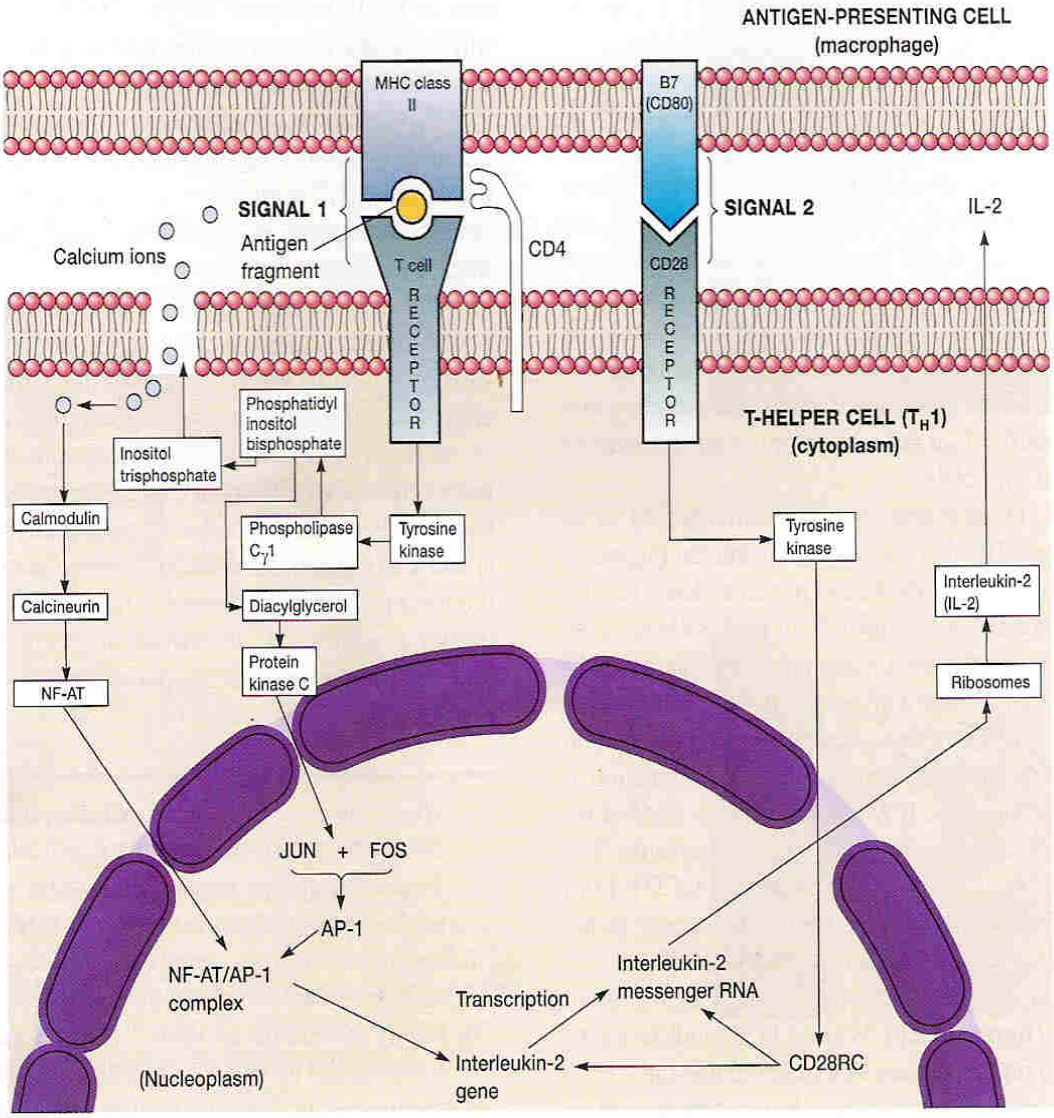

Fig. 5: Activation of T Helper Cell leading to secretion of interleukin – 2. This activation is brought about by the interaction between classII MHC – antigen complex and TCR which constitutes signal 1. The second signal which is costimulatory is the interaction between B7 protein on the macrophage and the CD 28 receptor on the T helper cell.

(Source: L M Prescott , J P Harley , D A Klein , Microbiology , 5th ed. 2002, Mc Graw Hil)

Natural Killer Cells

These are constituted by a population of large granular lymphocytes (LGLs) which were named natural killer cells for their non – specific cytotoxicity. They are involved in

immune defenses against viruses, tumours and intracellular bacteria. They kill tumour cells and virus infected cells by processes similar to those used by CTLs. They have a Fas ligand (CD95L) on their surface and readily induce death in target cells bearing the Fas protein (CD95). They are constitutively cytotoxic and have large granules in their cytoplasm containing perforin and granzymes. After an NK cell adheres to a target cell, **degranulation** occurs with release of perforin and granzymes at the junction of the interacting cells. It is to be pointed out that NK cells do not express antigen specific T cell receptors and the recognition of target cells by NK cells is not MHC restricted.

The NK cells do not have T cell receptors or immunoglobulin in their plasma membrane but can recognize target cells in two ways:

(i) an NK cell may employ NK cell receptor to distinguish abnormalities, in the form of reduction in the display of class I MHC molecules and the unusual surface antigen profile displayed by tumourous cells and virally infected cells.

(ii) NK cells express CD16, a membrane receptor for the carboxy – terminal end of the IgG molecule called the Fc region. The tumour cell and virus infected cells which have bound antibodies, can be attacked by NK cells via CD16 receptors and destroyed consequently. This process is called Antibody – dependent cell cytotoxicity (ADCC).

Suggested Readings

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