PAVENDAR BHARATHIDASAN COLLEGE OF ARTS AND SCIENCE

IMMUNOLOGY

II B.Sc., BIOTECHNOLOGY

16SCCBT4

Unit 1

Antigens

They are named so because they have an ability to induce antibody generation.

There are two terms interchangeably used. They are antigens and immunogens.

Antigens are foreign substances which an ability only to bind with products of immune response i.e. antibodies and T cells.

Immunogens are foreign substances which have an ability to induce production of immune response products like antibodies and activated T cells and to bind with them. Because of this, "all immunogens are antigens but not all antigens are immunogens".

TYPES OF ANTIGENS

1. Sequestered antigens:

These antigens are secluded or sequestered in capsule i.e. it is not exposed to immune system during

development or produced. So, when they exposed, they elicit immune response. Ex: Lens proteins and sperm proteins.

2. Neoantigens:

Neoantigens are newly produced antigens i.e. normal agents become antigens. They are formed due to the change in the chemical, physical and biological status of the agents. Ex: Penicillin can be converted to neoantigen when it bound with protein. It is otherwise known as altered antigen.

3. Hereophile or Heterogenic or Cross reactive antigen:

These antigens interact with antibodies produced against another antigen. For ex: Forssman antigen. These antigens are present on mucosal cells of GI tract and RBCs of horse. When an

antibody produced against any one of the antigens, antibodies will interact with the other antigens also. Thus these antigens are known as cross reactive antigens.

The phenomenon is known as cross reaction. The function of binding of antibody to an antigen to which it is not produced known as cross reactivity.

4. Mitogens:

Since some mitogens activate immune cells, they can be considered as antigens. Mitogen causes cancer due to inducing cell division. EX: Lipopolysaccharides induce B cell proliferation, Concanavalin – A (CON A) and Phytohemagglutinin (PHA) induces T cell proliferation and Pokeweed mitogen (PWM) induces both T and B cell proliferation.

5. Superantigens:

These antigens activate T cells non-specifically. They are of two types namely exogenous and endogenous superantigens.

Haptens:

Haptens are otherwise known as incomplete antigens or partial antigens because they are unable to elicit immune response by itself, but they can gain this ability when bind with carrier molecule. Karl Landsteiner determined Haptens through his studies.

Allergens:

Antigens are responsible for allergic response is called allergens.

Antigenicity and Immunogenicity:

Ability of an antigen to induce immune response is known as antigenicity. Ability of immunogens to induce immune response is known as immunogenicity. These two terms used interchangeably.

Lymphatic System

Lymphatic System is a system of thin tubes that runs throughout the body. These tubes are called 'lymph vessels or lymphatic vessels'. The lymphatic system is like the blood circulation – the tubes branch through all parts of the body like the arteries and veins that carry blood. Except that the lymphatic system carries a colourless liquid called Lymph.

Primary lymphatic organs are where lymphocytes are formed and mature. They provide an environment for stem cells to divide and mature into B- and T- cells: There are two primary lymphatic organs: the red bone marrow and the thymus gland.

Secondary lymphoid organs (SLOs) include lymph nodes, spleen, Peyer's patches, and mucosal tissues such as the nasal-associated lymphoid tissue, adenoids, and tonsils.

Unit 2

- Natural barriers and the immune system defend the body against organisms that can cause infection.
- Natural barriers include the skin, mucous membranes, tears, earwax, mucus, and stomach acid. Also, the normal flow of urine washes out microorganisms that enter the urinary tract.
- Chemical barriers destroy pathogens on the outer body surface, at body openings, and on inner body linings. Sweat, mucus, tears, and saliva all contain enzymes that kill pathogens.
- Tears, mucus and saliva contain an enzyme that breaks down the cell wall of many bacteria. The inner lining of your gut and lungs also produces mucus to trap invading pathogens. Cilia. Very fine hairs (cilia) lining your windpipe move mucus and trapped particles away from your lungs.

Cytokines

- Cytokines are a large group of proteins, peptides or glycoproteins that are secreted by specific cells of immune system.
- Cytokines are a category of signaling molecules that mediate and regulate immunity, inflammation and hematopoiesis.

- Cytokines are produced by a broad range of cells, including immune cells like macrophages, B lymphocytes, T lymphocytes and mast cells, as well as endothelial cells, fibroblasts, and various stromal cells; a given cytokine may be produced by more than one type of cell.

Tumor necrosis factor

- Tumor necrosis factor (TNF) is a multifunctional cytokine that plays important roles in diverse cellular events such as cell survival, proliferation, differentiation, and death.
- As a pro-inflammatory cytokine, TNF is secreted by inflammatory cells, which may be involved in inflammation-associated carcinogenesis.

Natural Killer (NK) Cells

- Natural Killer (NK) Cells are lymphocytes in the same family as T and B cells, coming from a common progenitor.
- NK cells are activated in response to interferons or macrophage-derived cytokines. They serve to contain viral infections while the adaptive immune response generates antigen-specific cytotoxic T cells that can clear the infection. NK cells work to control viral infections by secreting IFNγ and TNFα.

Macrophage

- A macrophage is a large white blood cell that is an important part of our immune system. A macrophage has the ability to locate and 'eat' particles, such as bacteria, viruses, fungi, and parasites.

- Macrophages are born from white blood cells called monocytes, which are produced by stem cells in our bone marrow.

- The mucosa-associated lymphoid tissue (MALT), also called mucosa-associated lymphatic tissue, is a diffuse system of small concentrations of lymphoid tissue found in various submucosal membrane sites of the body, such as the gastrointestinal tract, nasopharynx, thyroid, breast, lung, salivary glands, eye, and skin.

- Gut-associated lymphoid tissue (GALT) is a component of the mucosa-associated lymphoid tissue (MALT) which works in the immune system to protect the body from invasion in the gut.

- The gut-associated lymphoid tissue (GALT) is primarily located in the lamina propria. It may be present diffusely or as solitary or aggregated nodules, known as Peyer's patches, in the small intestine.

Unit 3

The continuing health of an animal depends upon its ability to recognise and repel disease; this ability is called immunity.

Two types of immunity exist, innate and adaptive.

Innate immunity, a first line of defence, is furnished by barriers such as skin, tears, saliva, and mucus, and the tissue inflammation that occurs after injury or infection.

Adaptive immunity develops specific defences against an invader that can be invoked whenever this particular intruder attacks again.

Forms of adaptive immunity.

The immune system responds to surface structures of the invading organism called antigens. There are two types of adaptive immune responses: humoral and cell mediated.

In humoral immune responses antibodies appear in the body fluids and stick to and destroy antigens. The response is to toxic substances outside of the cell.

In the cell-mediated immune response cells that can destroy other cells become active (T-cells). They destroy disease infected cells or cells making mutant forms of normal molecules.

Cell-mediated response molecules

When disease associated proteins occur in a cell they are broken into pieces by the cells proteolytic machinery. Cell proteins become attached to antigen fragments and transport them to the surface of the cell, where they are "presented" to the bodies defence mechanisms.

These transport molecules are called the Major Histocompatibility Complex (MHC) proteins. Without these, there would be no presentation of internal or external antigens to the T cells. The importance of MHC proteins is that they allow T cells to distinguish self from non-self. In every cell in your body, antigens are constantly broken up and presented to passing T cells. Without this presentation, other aspects of the immune response cannot occur.

Class I MHC proteins (found on all nucleated cell surfaces) present antigens to cytotoxic T lymphocytes (CTLs) . Most CTLs possess both T-cell receptors (TCR) and CD8 molecules On their surfaces. These TCRs are able to recognize peptides when they are expressed in complexes with MHC Class I molecules. For the TCR to bind a peptide-MHC complex two conditions must be met. Firstly, the TCR must have a structure which allows it to bind the peptide-MHC complex. Secondly, the accessory molecule CD8, must bind to the alpha-3

domain of the MHC Class I molecule. Due to genetic recombination events each CTL expresses a unique TCR which only binds a specific MHC-peptide complex. CTLs which recognize self-peptides (i.e. peptides produced by the normal host body as opposed to a foreign or cancerous cells) are removed in the thymus or tolerized after their release from the thymus. So, if a CTL can bind to a MHC-peptide complex on the cell surface, that cell is producing a peptide which is not native to the host.

The MHC Class II proteins (found only on B lymphocytes, macrophages, and other cells that present antigens to T cells), which primarily present peptides which have been digested from external sources, are needed for T-cell communication with B-cells and macrophages. Class II MHC proteins presenting antigens are detected by a different group of T cells (called T-helper or TH cells) to Class I MHC proteins (which are detected by CTLs cells).

T Cells

- Lymphoid progenitors which have developed from hematopoietic stem cells in the bone marrow migrate to the thymus to complete their antigen-independent maturation into functional T cells.
- In the thymus, T cells develop their specific T cell markers, including TCR, CD3, CD4 or CD8, and CD2.
- T-cell development in thymus. T cells are derived from haematopoietic stem cells that are found in the bone marrow.
- The developing progenitors within the thymus, also known as thymocytes, undergo a series of maturation steps that can be identified based on the expression of different cell surface markers.
- The T cell receptor (TCR) complex is made up of the TCR a and b chains, which are responsible for antigen recognition, and the CD3 complex and z homodimers, which are required for signal transduction.

B Cells

- B-cells are activated by the binding of antigen to receptors on its cell surface which causes the cell to divide and proliferate.
- Some stimulated B-cells become plasma cells, which secrete antibodies. Others become long-lived memory B-cells which can be stimulated at a later time to differentiate into plasma cells.
- After B cells mature in the bone marrow, they migrate through the blood to SLOs, which receive a constant supply of antigen through circulating lymph. At the SLO, B cell activation begins when the B cell binds to an antigen via its BCR.

- B cell development is a highly regulated process whereby functional peripheral subsets are produced from hematopoietic stem cells, in the fetal liver before birth and in the bone marrow afterward.

Immunoglobulins

Immunoglobulins are glycoproteins formed in response to as antigen and react specifically with that antigen.

Immunoglobulins, also known as antibodies, are glycoprotein molecules produced by plasma cells (white blood cells). They act as a critical part of the immune response by specifically recognizing and binding to particular antigens, such as bacteria or viruses, and aiding in their destruction.

- It is abbreviated as Ig
- They are commonly called antibodies (Ab).
- They are synthesize by B lymphocytes and secreted by plasma cells
- It is Y-shaped
- Immunoglobulins exist in two forms namely
- Soluble immunoglobulins and membrane bound immunoglobulins

There are five immunoglobulin classes (isotypes) of antibody molecules found in serum: **IgG, IgM, IgA, IgE and IgD**.

They are distinguished by the type of heavy chain they contain. IgG molecules possess heavy chains known as γ-chains; IgMs have μ-chains; IgAs have α-chains; IgEs have ε-chains; and IgDs have δ-chains.

Unit 4

Passive Immunization

Passive immunization is performed without injecting any antigen. In this method, vaccines contain antibodies obtained from the blood of an actively immunized human being or animal. The antibodies last for two to three weeks, and during that time the person is protected against the disease. Although short-lived, passive immunization provides immediate protection, unlike active immunization, which can take weeks to develop. Consequently, passive immunization can be lifesaving when a person has been infected with a deadly organism. Occasionally there are complications associated with passive immunization. Diseases such as botulism and rabies once posed a particular problem. Immunoglobulin

(antibody-containing plasma) for these diseases was once derived from the blood serum of horses. Although this animal material was specially treated before administration to humans, serious allergic reactions were common. Today, human-derived immune globulin is more widely available and the risk of side effects is reduced.

Active Immunization

Vaccines that provide active immunization are made in a variety of ways, depending on the type of disease and the organism that causes it. The active components of the vaccinations are antigens, substances found in the disease-causing organism that the immune system recognizes as foreign. In response to the antigen, the immune system develops either antibodies or white blood cells called T lymphocytes, which are special attacker cells. Immunization mimics real infection but presents little or no risk to the recipient. Some immunizing agents provide complete protection against a disease for life. Other agents provide partial protection, meaning that the immunized person can contract the disease, but in a less severe form. These vaccines are usually considered risky for people who have a damaged immune system, such as those infected with the virus that causes acquired immunodeficiency syndrome (AIDS) or those receiving chemotherapy for cancer or organ transplantation. Without a healthy defense system to fight infection, these people may develop the disease that the vaccine is trying to prevent. Some immunizing agents require repeated inoculations—or booster shots—at specific intervals.

Tetanus shots, for example, are recommended every ten years throughout life. In order to make a vaccine that confers active immunization, scientists use an organism or part of one that has been modified so that it has a low risk of causing illness but still triggers the body's immune defenses against disease. One type of vaccine contains live organisms that have been attenuated—that is, their virulence has been weakened. This procedure is used to protect against yellow fever, measles, smallpox, and many other viral diseases. Immunization can also occur when a person receives an injection of killed or inactivated organisms that are relatively harmless but that still contain antigens. This type of vaccination is used to protect against bacterial diseases such as poliomyelitis, typhoid fever, and diphtheria.

Some vaccines use only parts of an infectious organism that contain antigens, such as a protein cell wall or a flagellum. Known as acellular vaccines, they produce the desired immunity with a lower risk of producing potentially harmful immune reactions that may result from exposure to other parts of the organism. Acellular vaccines include the Haemophilus influenzae type B vaccine for meningitis and newer versions of the whooping cough vaccine. Scientists use genetic engineering techniques to refine this approach further by isolating a gene or genes within an infectious organism that code for a particular antigen. The subunit vaccines produced by this method cannot cause disease and are safe to use in people who have an impaired immune system. Subunit vaccines for hepatitis B and pneumococcus infection, which causes pneumonia, became available in the late 1990s.

Active immunization can also be carried out using bacterial toxins that have been treated with chemicals so that they are no longer toxic, even though their antigens remain intact. This procedure uses the toxins produced by genetically engineered bacteria rather than the organism itself and is used in vaccinating against tetanus, botulism, and similar toxic diseases.

Live attenuated vaccines

Live attenuated vaccines usually are created from the naturally occurring germ itself. The germs used in these vaccines still can infect people, but they rarely cause serious disease. Viruses are weakened (or attenuated) by growing them over and over again in a laboratory under nourishing conditions called cell culture. The process of growing a virus repeatedly-also known as passing--serves to lessen the disease-causing ability of the virus.

Vaccines are made from viruses whose disease-causing ability has deteriorated from multiple passages. For example vaccine for TB produced by Calmette-Guerin by growing Mycobacterium bovis in a culture medium rich in bile salts. It is an adverse condition for the bacteria. After 13 yrs, it was used as live attenuated vaccine.

Examples of live attenuated vaccines include:

- Measles vaccine (as found in the MMR vaccine)
- Mumps vaccine (MMR vaccine)
- Rubella (German measles) vaccine (MMR vaccine)
- Oral polio vaccine (OPV) (sabin vaccine)
- Varicella (chickenpox) vaccine
- BCG (Bacillus Calmette-Guerin) vaccine for TB

Inactivated (killed) vaccines

Inactivated (killed) vaccines cannot cause an infection, but they still can stimulate a protective immune response. Viruses are inactivated with chemicals such as formaldehyde. In this vaccine, the replicating ability of the infecting agents is inhibited.

Examples of inactivated (killed) vaccines:

- Inactivated polio vaccine (IPV), which is the shot form of the polio vaccine
- Inactivated influenza vaccine
- Salk polio vaccine

conjugated vaccine

- Some vaccines are made by using only parts of the viruses or bacteria. These vaccines cannot cause disease, but they can stimulate the body to produce an immune response that protects against infection with the whole germ. Four of the newest vaccines are made this way.

Examples of component vaccines:

- *Haemophilus influenzae* type b (Hib) vaccine

- Hepatitis B (Hep B) vaccine
- Hepatitis A (Hep A) vaccine
- Pneumococcal conjugate vaccine

The virulence of some pathogenic bacteria depends primarily on the antiphagocytic properties of their hydrophilic polysaccharide capsule. Coating of the capsule with antibodiesd and /or complement greatly increases the ability of macrophages and neutrophils to phagocytose such pathogens. These finding provide the rationale for vaccines consisting of purified capsular polysaccharides.

Immunostimulating complexes (ISCOMS)

It is an alternative vaccine vehicle. The antigen is presented in an accessible, multimeric, physically well defined complex. Composed of adjuvant (Quil A) and antigen held in a cage like structure. Adjuvant is held to the antigen by lipids. It can stimulate CMI. Its mean diameter is 35nm. In the most successful procedure, a mixture of the plant glycoside saponin, cholesterol and phosphatidylcholine provides a vehicle for presentation of several copies of the protein on a cage-like structure.

Such a multimeric presentation mimics the natural situation of antigens on microorganisms. These Immunostimulating complexes have activities equivalent to those of the virus particles from which the proteins are derived, thus holding out great promise for the presentation of genetically engineered proteins.

Similar considerations apply to the presentation of peptides. It has been shown that by building the peptide into a framework of lysine residues so that 8 copies instead of 1 copy are present, the immune response induced was of a much greater magnitude. A novel approach involves the presentation of the peptide in a polymeric form combined with T cell epitopes. The sequence coding for the foot and mouth disease virus peptide was expressed as part of a fusion protein with the gene coding for the Hepatitis B core protein. The hybrid protein, which forms spherical particles 22nm in diameter, elicited levels of neutralizing antibodies against foot and mouth disease virus that were at least a hundred times greater than those produced by the monomeric peptide.

Vaccine production in plants

As a new direction in the development of affordable new vaccines, transgenic plants have been developed that express surface proteins of viruses that are pathogenic to animals or humans. For example, Agricultural Genetics in England has genetically engineered the cowpea mosaic virus to include a surface antigen from the foot-and-mouth disease virus; this virus affects life stock. This genetically engineered virus was used to infect its natural host, black-eyed pea, and the introduced gene from the foot-and-mouth disease virus was expressed handsomely in the plant. The cowpea mosaic virus eventually kills the plant, and therefore the plant needs to be sacrificed a few weeks after infection. One leaf from the infected pea plant produces enough surface antigen to serve as vaccine for 200 doses.

Unit 5

AUTOIMMUNITY

The state of adaptive immune system responsiveness to self antigens that occurs when mechanisms of self-tolerance fail was defined as autoimmunity. A disease caused by a breakdown of self-tolerance such that the adaptive immune system responds to self antigens and mediates cell and tissue damage known as autoimmune disease. Autoimmune diseases can be organ specific e.g., thyroididits or systemic e.g., systemic lupus erythromatosus. An antibody produced in an individual that is specific for a self antigen called as autoantibodies. Autoantibodies can cause damage to cells and tissues and are produced in excess in systemic autoimmune diseases. The self-antigens, which are responsible for autoimmune disorders, were known as autogens.

Autoimmunity is a condition in which structural or functional damage is produced by the action of immunologically competent cells or antibodies against the normal components of the body. Autoimmunity literally means protection against self but it actually implies injury to self and therefore it has been criticized as a contradiction in terms. Autoallergy has been suggested as an acceptable alternative but the term autoimmunity has the sanction of wide usage.

The earliest example of autoimmunity was the observation by Metalnikoff (1900) that guinea pigs injected with their own spermatozoa produced sperm immobilizing antibodies. Donath and

Landsteriner (1904) identified circulating autoantibodies in paroxysmal cold hemoglobinuria – a hemolysin which binds with the patient's erythrocytes at low temperatures and produces complement dependent hemolysis on warming. This was the first description of an autoimmune disease in human beings. Dameshek and Schwarts (1938) established the autoimmune basis of acute hemolytic anemia.

The following criteria have to be satisfied before establishing the autoimmune etiology of disease:

1. An autoimmune response, humoral, cellular or both, must be regularly associated with the disease.
2. The antigen responsible for the immune response must be identified, isolated and characterized.
3. The same antigen must induce in experimental animals immunopathological changes as in the disease.
4. Passive transfer of the disease must be possible by transfer of antibodies or sensitized lymphocytes.

Diseases of autoimmune origin usually exhibit the following features:
i) An elevated level of immunoglobulins
ii) Demonstrable autoantibodies
iii) Deposition of immunoglobulins or their derivatives at sites of election, such renal glomeruli.
iv) Accumulation of lymphocytes and plasma cells at the sites of lesions.
v) Temporary or lasting benefit from corticosteroid or other immunosuppressive therapy.
vi) The occurrence of more than one type of autoimmune lesion in an individual.
vii) A genetic predisposition towards autoimmunity.

PATHOGENESIS OF AUTOIMMUNITY

Many diseases are considered to be autoimmune origin, based on their association with cellular or humoral immune responses against selfantigens. Autoantibodies are more easily detected then cellular autosensitisation. However, the mere presence of autoantibodies during the course of a disease does not prove their eitiological role. Autoantibody formation may be a result of tissue injury and the antibody may help in promoting immune elimination of the damaged cell or tissue elements. A typical example is lepromatous leprosy in which large amounts of autoantibodies are regularly found. It has been said that but for the lepra bacillus, lepromatous leprosy may have bee proposed as an autoimmune disease.

The relative importance of humoral and cellular immune processes in the etiology of autoimmune disease is not known. Antibodies may cause damage by the cytolytic or cytotoxic (i.e type 2 hypersensitivity mechanism) and toxic complex (i.e type 3 mechanisms) reactions. They are obviously important in hemocytolytic autoimmune diseases. A third mechanism of autoimmune tissue damage is by sensitized T lymphocytes (i.e type 4 hypersensitivity). It is likely that humoral and cellular immune responses may act synergistically in the production of some autoimmune diseases. For example experimental orchitis can be induced only when both types of immune responses are operative. Once initiated, most autoimmune responses tend to be self perpetuating. Their progress can be arrested by immunosuppressive therapy, though the degree of response to such therapy varies in different diseases.

HYPERSENSITIVITY

Clinical problems that have immune components arise when there is a loss of control of the immune response leading to tissue injury. These deleterious reactions are termed hypersensitivity, and the types are classified based on the mechanism by which the injury is caused . The types I, II and III are all mediated by antibody so effects are seen quickly; i.e., within a few minutes (allergic responses) to a couple of hours. Type IV is mediated by T cells particularly Th1 cells. Type IV injury is caused by accumulation of mononuclear cells at the site of reaction, so the peak response is not reached until between 24and 72 hours.

Type I Hypersensitivity

Asthma

Asthma affects about 5% of the population. Of those, about half have attacks brought on by known allergens. Many of the others are thought to be triggered by allergens that have not yet been identified.

Pathophysiology: Allergens reaching the lungstrigger mast cell degranulation. Histamine induces constriction of bronchioles (H1 receptors) and relaxation of capillaries (H2receptors). C. TreatmentTreatment is usually viainhaled -andrenergic bronchodilators for acute attacks. Epinephrine is the most common prophylactic drug.

Type II Hypersensitivity : (Type II Tissue Injury)

Cytotoxic antiself antibodies are responsible for type II injuries. The antibody may come from a transfusion, from the mother via the placenta erythroblastosis fetalis, or may be made by the host. If they cause tissue injury, it is, by definition, autoimmunity. When the antiself antibody bindsto its target tissue, it opsonizes the tissue for phagocytosis by macrophages and PMNs. When the phagocytes try to engulf the tissues, they release some lysosomal enzymes and reactive O2compounds. The injury to the surrounding tissue induces some inflammation. If the target antigen is on a cell surface, the antibody would be expected to disrupt cell function, and except for Graves' disease, would probably kill the cell. Complement would also be fixed if the antibody is IgM or IgG. This would exacerbate the injury by enhancing the inflammatory response and increasing the number of PMNs in the area. However, it is important to recognize that complement fixation is not required for tissue injury. Macrophages and PMNs will cause significant tissue injury in the complete absence of complement. If the target antigen is soluble, there may be formation of soluble immune complexes, so the tissue injury would result from type III mechanisms. This is the situation in systemic lupus erythematosisin which the target antigen is one or more proteins from the cell nucleus. If the autoantibody is being produced by the body rather than being passively acquired, it must be treated by immune suppression to prevent continued antibody production. Maintenance immunosuppression must usually be continued indefinitely.

Immune Complex Disease (Type –III Hypersensitivity):

The actual tissue injury is due to an intense, localized inflammatory reaction. The reaction is initiated by C3a and C5a produced during complement fixationinduced by immune complexes deposited in the tissue.

Complement fixation is an absolute requirement for type III injury. C5b can sometimes bind to normal cells and provide the anchor for elaboration of the membrane attack complex which then lyses the cells. Tissue injury may activate the kinin system and produce platelet activating factor both of which intensify the inflammatory response. Much of the damage is caused by lysosomal enzymes and toxic oxygen products released into the tissues as PMNs try to engulf immune complexes. PMNs accumulate in the area in response to C5a and receptors expressed on endothelial cells in response to inflammatory signals. Immune complexes in the ratio of 2

antigens to 1IgG or IgA (monomeric) are often barely soluble. These complexes are often filtered out in capillary beds, particularly in the kidney and lungs, or may be driven into the vessel walls at places of especially turbulent flow. Larger, insoluble complexes are usually cleared quickly by phagocytic cells and cause little damage. This accounts for the typical kidney and lung damage produced by Type III injuries. Deposition at sites of turbulent flow with subsequent tissue injury at those sites is characteristic of polyarteritis nodosa.

Delayed Hypersensitivity (Type –IV):

This is the only type of hypersensitivity mediated by T cells. Th1 cells respond preferentially to processed antigen on macrophage-lineage cells. Activated Th1 cells produce Il-2, GM-CSF, and IFN-all of which stimulate resting macrophages to become activated, "angry" macrophages with increased cytotoxic activity. In addition, Th1 cells secrete lymphokines (principally MIP-1and MIP-2) that attract macrophages and additional T cells to the site.

They also secrete migration inhibitory factor (MIF) which prevents macrophages from leaving the area once they arrive. Activated macrophages exacerbate the problem by secreting IL-8 and IP-10 which are also chemotactic for mononuclear cells. So many mononuclear cells may accumulate in response to prolonged secretion of the chemotacticfactors that their pressure can block off arterioles. The tissue then dies from anoxia (lack of oxygen). Damage is exacerbated by release of hydrolytic enzymes, TNF-, prostaglandins, PFP, and toxic oxygen products from macrophages. Cytotoxic T cells may also make minor contributions to the tissue injury by releasing TNF-and additonal PFP. Since the injury is dependent on accumulation of T cells and macrophages, it usually takes 20 - 72 hours for symptoms to appear, but they may persist for a week or more. Individuals who are very sensitive to a particular substance may have symptoms as quickly as six hours.A delayed hypersensitivity reaction may be induced by recognition of "altered self" due to a drug or chemical binding to self protein; e.g., most penicillin reactions are due to this type of type IV reaction. They may also arise from persistent antigen the phagocytic system is unable to remove normally; e.g., schistosome eggs. In a few cases, Th cells become sensitized to self antigens and produce autoimmune tissue injury.

TRANSPLANTATION

Transplantation refers to the act of transferring cells, tissues or organs from one site to another within individuals or between different individuals or between different species of genetically identical or not. The tissue or organ transplanted is known as the transplant or graft.

The individual from whom the graft is obtained is known as the donor and the individual on whom it is applied known as recipient or acceptor. After transplantation, if the graft is survived in the recipient then the graft said to be accepted and it the graft is not survived then the graft is said to be rejected. Rejected graft usually in white color, so it is called as white graft.

There are mainly four different types of grafts namely Autograft, Isograft (Syngraft), Allograft (Homograft) and Xenograft (Heterograft).

Autograft: It is self tissue transferred from one body site to another in the same individual. These grafts are often performed on patients with burns by transferring healthy skin to the burned area. Always graft is accepted. Isograft: It is the tissue transferred between genetically identical individuals. In humans, this type of graft transfer possible usually between identical (Monozygotic) twins. This type of graft was also accepted. This type of graft is formerly known as syngraft or syngenic graft.

Allograft: It is the tissue transferred between genetically non-identical members of the same species. Most of the organs (grafts) transplanted in human populations are found to be allograft. Normally allgorafts are rejected after transplantation, but immunosuppressive drugs and immune tolerance properties utilized for the survival of graft. This graft is also otherwise known as homograft by considering the factor that the graft is transferred within species.

Xenograft: It is the tissue transferred between different species. This graft is also normally rejected. Pigs' hearth volve usually transplanted to humans. Through immunosuppressive and tolerance properties, graft survived in transplanted individuals. This graft is also otherwise called as heterograft due to the transfer of tissues or organs from one species to other species.