Immunologic Mechanisms of Tissue Damage

(Immunopathology)

Immunopathology

Exaggerated immune response may lead to different forms of tissue damage

1) An overactive immune response:

produce more damage than it prevents

e.g. hypersensitivity reactions and graft rejection

2) Failure of appropriate recognition:

as in autoimmune diseases

Hypersensitivity Reaction

Hypersensitivity or allergy

* An immune response results in exaggerated reactions harmful to the host

* There are four types of hypersensitivity reactions:

  Type I, Type II, Type III, Type IV

* Types I, II and III are antibody mediated

* Type IV is cell mediated

Type I: Immediate hypersensitivity

* An antigen reacts with cell fixed antibody (Ig E) leading to release of soluble molecules
  An antigen (allergen)
  soluble molecules (mediators)

* Soluble molecules cause the manifestation of disease

* Systemic life threatening; anaphylactic shock

* Local atopic allergies; bronchial asthma, hay fever and food allergies

Pathogenic mechanisms

* First exposure to allergen

  Allergen stimulates formation of antibody (Ig E type)

  Ig E fixes, by its Fc portion to mast cells and basophiles

* Second exposure to the same allergen

  It bridges between Ig E molecules fixed to mast cells leading to activation and degranulation of mast cells and release of mediators

Pathogenic mechanisms

* Three classes of mediators derived from mast cells:

!) Preformed mediators stored in granules (histamine)

2) Newly sensitized mediators:
leukotrienes, prostaglandins, platelets activating factor

3) Cytokines produced by activated mast cells, basophils
e.g. TNF, IL3, IL-4, IL-5 IL-13, chemokines

* These mediators cause: ↑ smooth muscle contraction, mucous secretion and bronchial spasm, vasodilatation, ↑ vascular permeability and edema

Anaphylaxis

* Systemic form of Type I hypersensitivity

* Exposure to allergen to which a person is previously sensitized

* Allergens:

  Drugs: penicillin

  Serum injection : anti-diphtheritic or ant-tetanic serum

  anesthesia or insect venom

* Clinical picture:

  Shock due to sudden decrease of blood pressure, respiratory distress due to bronchospasm, cyanosis, edema, urticarial

* Treatment: corticosteroids injection, epinephrine, antihistamines

Atopy

* Local form of type I hypersensitivity

* Exposure to certain allergens that induce production of specific Ig E

* Allergens :
  Inhalants: dust mite feces, tree or pollens, mold spore.
  Ingestants: milk, egg, fish, chocolate
  Contactants: wool, nylon, animal fur
  Drugs: penicillin, salicylates, anesthesia insect venom

* There is a strong familial predisposition to atopic allergy

* The predisposition is genetically determined

Methods of diagnosis

1) History taking for determining the allergen involved

2) Skin tests:

   Intradermal injection of battery of different allergens

   A wheal and flare (erythema) develop at the site of allergen to which the person is allergic

3) Determination of total serum Ig E level

4) Determination of specific Ig E levels to the different allergens

Management

1) Avoidance of specific allergen responsible for condition

2) Hyposensitization:

Injection gradually increasing doses of extract of allergen

- production of Ig G blocking antibody which binds allergen and prevent combination with Ig E
- It may induce T cell tolerance

3) Drug Therapy:

corticosteroids injection, epinephrine, antihistamines

species	Shock organ	symptoms	pathology	Major mediators
Ruminants	Respiratory tract	Cough Dyspnea Collapse	Lung edema Emphysema hemorrhage	Serotonin Dopamine Leukotrienes Kinins
Horse	Respiratory tract Intestine	Cough Dyspnea Diarrhea	Emphysema Intestinal hemorrhage	Histamine Serotonin
swine	Respiratory tract Intestine	Cyanosis pruritis	Systemic hypotension	histamine
Dog	Hepatic veins	Collaps Dyspnea Diarrhea Vomiting	Hepatic engorgement Viceral hemorrhage	Histamine Leukotriens prostaglandins
Cat	Respiratory tract Intestine	Dyspnea Vomiting Diarrhea Pruritis	Lung edema Intestinal edema	Histamine Leukotrienes
Human	Respiratory tract	Dyspnea Urticaria	Lung edema Emphysema	Histamine Leukotrienes
Chicken	Respiratory tract	Dyspnea Convulsions	Lung edema	Histamine Serotonin Leukotrienes

Specific allergic condition

- **1-milk allergy**
- Jersey cattle and the alpha casein
- **2-Food allergy**
- 30% of skin diseases in dogs due to allergic dermatitis and 1% of them due to ingested allergens
- **3-Allergic inhalant dermatitis**
- In dogs and cats with atopic dermatitis
- Allergic rhinitis in cattle

- **4-Allergies to vaccines and drugs**
- The use of FMD killed vaccine, rabies vaccine
- The use of penicillin
- **5-Allergies to parasites**
- Allergies are commonly associated with the response to helminthes and arthropod parasites. Insect stings account of a significant number of human deaths. Anaphylaxis can also occur in cattle infested with Hypoderma bovis

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- **6-Eosinophilic Granuloma Complex**
- This is a confusing group of clinical conditions associated with various types of skin lesions (ulcer, plaque, granuloma) in cats. Although their causes unknown, they have been associated with flea or food allergies or inhalant dermatitis
- **7-lymphocytic-Plasmocytic Enteritis**
- This is a diarrheal disease in which weight loss or vomiting is infrequent. The disease results from hypersensitivity to food.

Type II: Cytotoxic or Cytolysis Reactions

* An antibody (Ig G or Ig M) reacts with antigen on the cell surface

* This antigen may be part of cell membrane or circulating antigen (or hapten) that attaches to cell membrane

Mechanism of Cytolysis

* Cell lysis results due to :

1) Complement fixation to antigen antibody complex on cell surface

The activated complement will lead to cell lysis

2) Phagocytosis is enhanced by the antibody (opsinin) bound to cell antigen leading to opsonization of the target cell

Mechanism of cytolysis

3) Antibody depended cellular cytotoxicity (ADCC):

- Antibody coated cells

e.g. tumour cells, graft cells or infected cells can be killed by cells possess Fc receptors

- The process different from phagocytosis and independent of complement

- Cells most active in ADCC are:
NK, macrophages, neutrophils and eosinophils

Clinical Conditions

1) Transfusion reaction due to ABO incompatibility

2) Rh-incompatibility (Hemolytic disease of the newborn)

3) Autoimmune diseases

The mechanism of tissue damage is cytotoxic reactions

autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, myasthenia gravis, nephrotoxic nephritis, Hashimoto's thyroiditis

4) A non-cytotoxic Type II hypersensitivity is Graves's disease

It is a form of thyroiditis in which antibodies are produced against TSH surface receptor

This lead to mimic the effect of TSH and stimulate cells to over-produce thyroid hormones

Clinical Conditions

5- Graft rejection cytotoxic reactions:

In hyperacute rejection the recipient already has performed antibody against the graft

6- Drug reaction:

Penicillin may attach as haptens to RBCs and induce antibodies which are cytotoxic for the cell-drug complex leading to hemolysis

Quinine may attach to platelets and the antibodies cause platelets destruction and thrombocytopenic purpura

In Animals

- **Blood Transfusion**
  - **Blood is easily transfused from one animal to another. If the donor red cells are identical to those of the recipient, no immune response will result. If, however, the recipient possesses natural antibodies to donor red cell antigens, they will be attacked immediately. Natural antibodies are usually (but not always) of the IgM class.**

- When these abs combine with foreign red cell antigens, they may cause agglutination, or hemolysis or stimulate opsonozation and phagocytosis of the transfused cells. In the absence of natural antibodies, foreign antigens on transfused red cells will stimulate an immune response in the recipient.

- The transfused cells then circulate for a period before abs are produced and immune elimination occurs.
- A second transfusion with identical foreign cells results in their immediate destruction. The rapid destruction of large numbers of foreign red cells can lead to serious pathological reaction known as type II hypersensitivity reaction.

This results in:-

1-Massive hemolysis and complement activation.
2-Hemolysis leads to the release of large amounts of free hemoglobin, hemoglobinemia, and hemoglobinuria.
3-The presence of large numbers of lysed red cells may trigger blood clotting and disseminated intravascular coagulation.
4-Complement activation results in anaphylatoxin release, mast cell degranulation, and the release of vasoactive agents.
5-These agents provoke circulatory shock with hypotension, bradycardia and apnea.
6-The animal may show signs of sympathetic activity, such as sweating, salivation, lacrimation, diarrhea, and vomiting.
7-This may be followed by hypertension, cardiac arrhythmias, and increased heart and respiratory rates.

Transfusion reaction can be prevented by prior testing of the recipient for antibodies against the donor's red cells.

The test is known as cross matching. Ideally, serum and washed red cells are first obtained from both donor and recipient.

Donor red cells are mixed with recipient serum and then incubated at 37 C for 30 minutes.

If the red cells are lysed or agglutinated by the recipient's serum, then no transfusion should be attempted with those cells.

It is occasionally found that the donor's serum may react with the recipient's red cells.

Species	Blood Group Systems	Serology
Bovine	A, B, C, F, J, L, R′, S, Z, T′	Hemolytic
Sheep	A, B, C, D, M, R	Hemolytic and agoutination of D only
Pig	A, B, C, D, E, F, G, H, I, J, K, L, M, N, O, P.	Agglutination Hemolytic Antiglobulin
Horse	A, C, D, K, P, Q, U	Hemolytic Agglutination
Dog	DEA 1.1, 1.2, 3, 4, 5, 6, 7, 8 DEA (Dog Erythrocyte Antigen)	Agglutination Hemolytic Antiglobulin
Cat	AB	Agglutination Hemolytic

Domestic Animal Blood Groups

Hemolytic Disease of Newborn (HDN)

-HDN in calves is rare but may result from vaccination against anaplasmosis or babesiosis.

-Some of these vaccines contain large quantities of red cells obtained from infected calves.

-In case of Anaplasma vaccines, for example, the blood from age number of donor animals is pooled, freeze dried, and then mixed with adjuvant before being administered to cattle.

-The vaccine against babesiosis consist of fresh, and infected calf blood.

-Both vaccines result in infection and, consequently, the development of immunity in the recipient animals.

-They may also stimulate the production of antibodies directed primarily against blood group antigens of A and F systems.

- Cows sensitized by these vaccines and then mated with bulls carrying the same blood groups can transmit colostral antibodies to their calves, which may then develop hemolytic disease.

The clinical signs of HDN in calves are related to the amount of colostrum ingested. Calves are usually healthy at birth but begin to show symptoms from 12 hours to 5 days afterward.

In acute cases, death may occur within 24 hrs after suckling, with the animals developing respiratory distress and hemoglobinuria. On necropsy these calves have severe pulmonary edema, splenomegaly, and dark kidneys.

Less severely affected animals develop anemia and jaundice and may die during the first week of life.

1-HDN may occur in foals from mares that have been sensitized by previous blood transfusion or administration of vaccines containing equine tissues.

2-Most commonly, however, mares are sensitized by exposure to fetal red cells through repeated pregnancies.

3-The mechanism of this sensitization is unclear, but fetal red cells are assumed to gain access to maternal circulation as a result of transplacental hemorrhage.

4-Mares have been shown to respond to fetal red cells as early as day 56 after conception.

5-The greatest leakage probably occurs during the last month of pregnancy and during parturition as a result of the breakdown of placental blood vessels.

The pathogenesis of hemolytic disease of newborn in foals. In the first stage, fetal lymphocytes leak into the maternal circulation and sensitize her. In the second stage, these antibodies enter the foal's circulation and cause red cell destruction

In cats,

1-hemolytic disease of the newborn has been recorded in Persian and related (Himalayan) breeds but is very rare.

2-It occurs in kittens from queens of blood group B bred to sires of blood group A.

3-The queens subsequently develop high-tittered anti-A antibodies. Although healthy at birth these kittens develop severe anemia as a result of intravascular hemolysis.

4-Affected kittens show depression and possibly hemoglobinuria. Necropsy may reveal splenomegaly and jaundice.

5-Antibodies to the sire's and the kitten's red cells are detectable in the queen's serum.