Immunity Part II

Type III, Immune-Complex Disorders:

They are mediated by the formation of insoluble antigen-antibody complexes that activate complement which will generates chemotactic and vasoactive mediators that cause tissue damage by a variety of mechanisms, including alterations in blood flow, increased vascular permeability, and the destructive action of inflammatory cells.

The reaction occurs when the antigen combines with antibody, whether in the circulation (circulating immune complexes) or at extravascular sites where antigen may have been deposited.

Immune complexes formed in the circulation produce damage when they come in contact with the vessel lining or are deposited in tissues, including the renal glomerulus, skin venules, lung, and joint synovium.

There are two general types of antigens that cause immune complex mediated injury:

1 -Exogenous antigens such as viral and bacterial proteins.

2 -Endogenous antigens such as self-antigens associated with autoimmune disorders.

Type III reactions are responsible for the **acute glomerulonephritis** that follows a streptococcal infection and the manifestations of **autoimmune disorders** such as systemic lupus erythematosus (SLE).

Unlike type II reactions, in which the damage is caused by binding of antibody to body cells, the harmful effects of type III reactions are indirect (i.e., secondary to the inflammatory response induced by activated complement).

Acute serum sickness is the type of a systemic immune complex disease. Serum sickness is syndrome consisting of rash, lymphadenopathy, arthralgias, and occasionally

neurologic disorders that appeared 7 or more days after injections of horse antisera for prevention of tetanus. Although this therapy is not used today, the name remains.

The most common causes of this allergic disorder include: antibiotics (especially penicillin), various foods, drugs, and insect venoms. Serum sickness is triggered by the deposition of insoluble antigen-antibody (IgM and IgG) complexes in blood vessels, joints, heart, and kidney tissue.

The deposited complexes activate complement, increase vascular permeability, and recruit phagocytic cells, all of which can promote focal tissue damage and edema.

The signs and symptoms include:

1-Urticaria.

2- Patchy or generalized rash.

3- Extensive edema (face, neck, and joints).

4- fever.

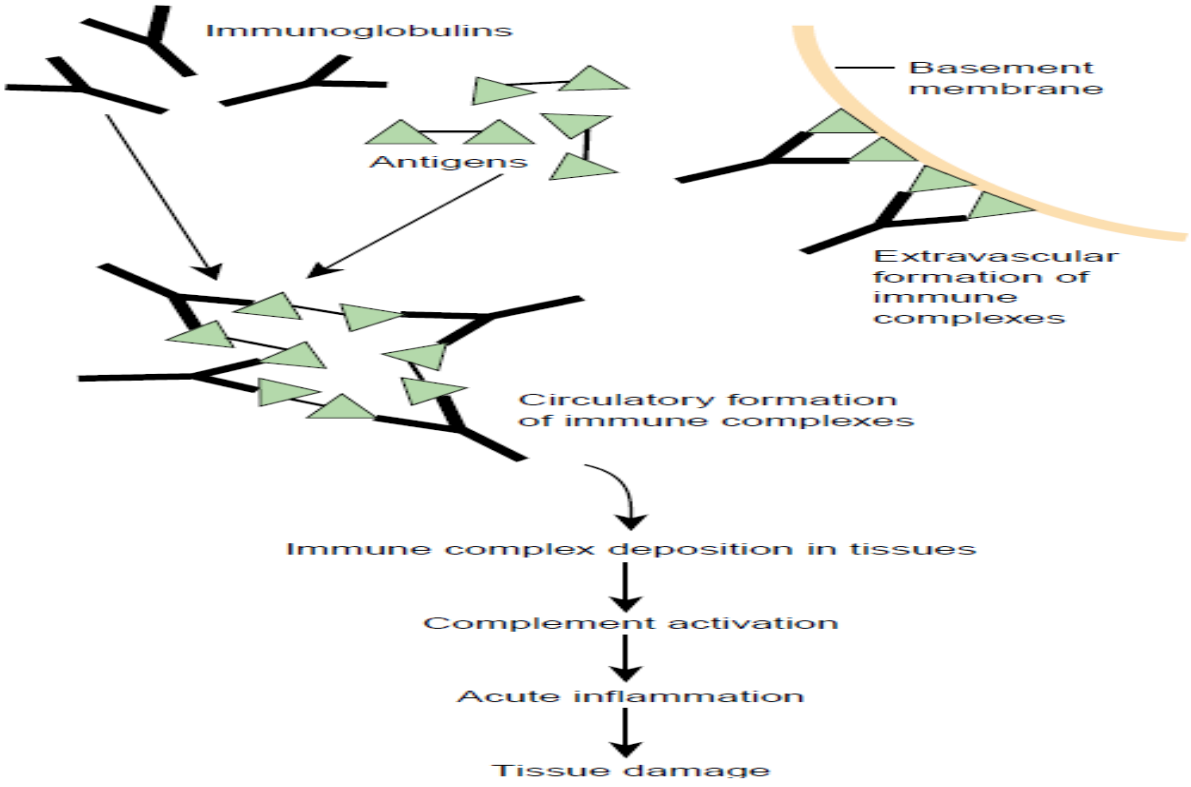


FIGURE 10-3 Type III, immune complex reactions involve complement-activating IgG and IgM immunoglobulins with formation of blood-borne immune complexes that are eventually deposited in tissues. Complement activation at the site of immune complex deposition leads to recruitment of leukocytes, which are eventually responsible for tissue injury.

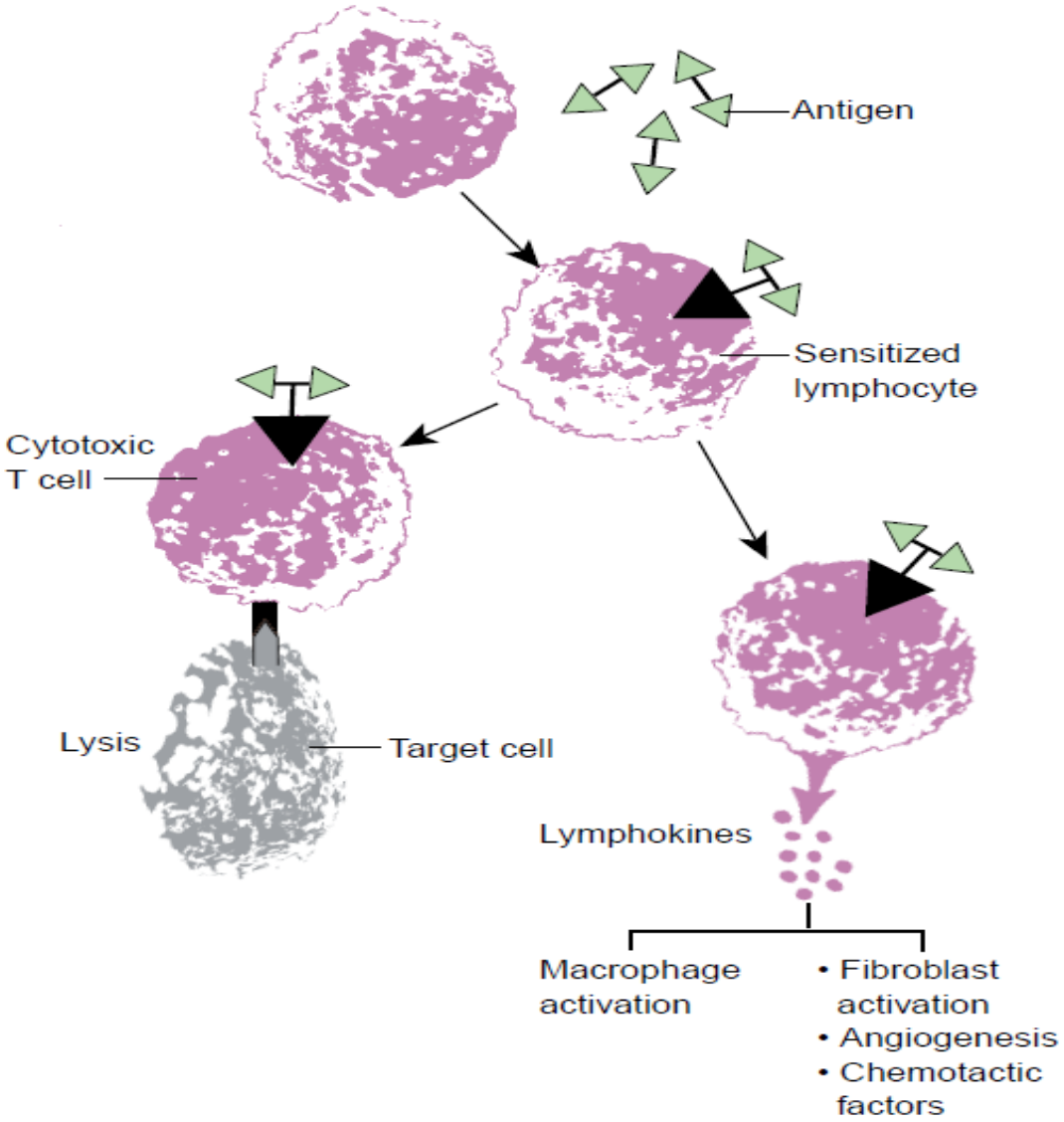
Type IV, Cell-Mediated Hypersensitivity Disorders:

It is mediated by cells, **not antibodies**; occur 24 to 72 hours after exposure of a sensitized individual to the offending antigen. They are mediated by helper T lymphocytes that are directly cytotoxic or that secrete inflammatory mediators like cytokines that cause tissue changes. Cytokines will attract T or B lymphocytes as well as monocytes, neutrophils, eosinophils, and basophils. Some of the cytokines promote differentiation and activation of macrophages that function as phagocytic and antigen-presenting cells (APCs).

The best-known type of delayed hypersensitivity response is the **reaction to the tuberculin test**, in which inactivated tuberculin or purified protein derivative is injected under the skin. In a previously sensitized person, redness and indurations of the area develop within 8 to 12 hours, reaching a peak in 24 to 72 hours. A positive tuberculin test indicates that a person has had sufficient exposure to the M. tuberculosis organism to incite a hypersensitivity reaction.

Certain types of antigens induce cell mediated immunity with an especially pronounced macrophage response. This type of delayed hypersensitivity commonly develops in response to particulate antigens that are **large, insoluble,** and difficult to eliminate. The accumulated macrophages are often transformed into so-called **epithelioid cells** because they resemble epithelium. A microscopic aggregation of epithelioid cells, which usually are surrounded by a layer of lymphocytes, is called **a granuloma**. Inflammation that is characterized by type IV hypersensitivity is called **granulomatous inflammation.**

Direct T-cell–mediated cytotoxicity, will cause necrosis of antigen-bearing cells. It is important in the eradication of virus infected cells, autoimmune diseases such as Hashimoto's thyroiditis, and host-versus-graft or graft-versus host transplant rejection. Allergic **contact dermatitis** and hypersensitivity **pneumonitis** are presented as examples of cell mediated hypersensitivity reactions.



■ **FIGURE 10-4** ■ Type IV, cell-mediated or delayed-type hypersensitivity reactions involve sensitization of T lymphocytes with the subsequent formation of cytotoxic T cells that lyse target cells or T cells that release cell-damaging lymphokines.

I. Hypersensitivity reaction (Allergy)

II. Transplantation immunopathology:

Transplantation of solid organs (e.g., liver, kidney, heart) and bone marrow become nearly routine with the greater understanding of humoral and cellular immune response, the development of immunosuppressive drugs such as cyclosporine, and understanding of the role of the major histocompatibility complex (MHC) antigens (human leukocyte

antigen =HLA) which is cell surface antigens that determine whether transplanted tissue is recognized as foreign or not.

Transplanted tissue can be categorized as:

1 -Allogeneic if the donor and recipient are related or unrelated but share similar HLA types.

2 -Syngeneic if the donor and recipient are identical twins.

3 -Autologous if donor and recipient are the same person.

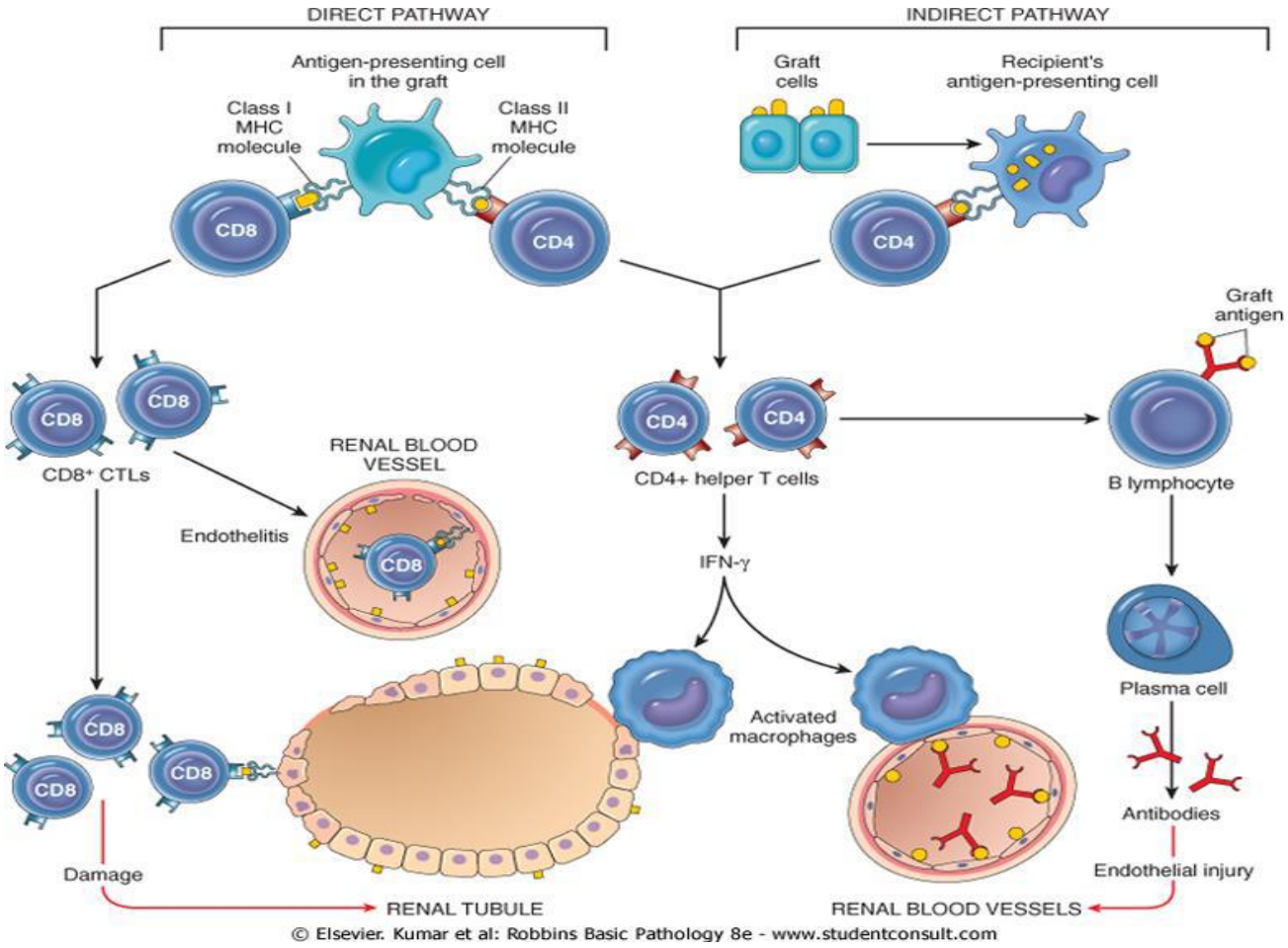
Immune Recognition of Allografts Rejection of allografts is a response to MHC molecules, which are so polymorphic that no two individuals are likely to express exactly the same set of MHC molecules (except twins). There are two main mechanisms by which the host immune system recognizes and responds to the MHC molecules on the graft: Direct recognition. Host T cells directly recognize the allogeneic (foreign) MHC molecules that are expressed on graft cells. Because DCs in the graft express high levels of MHC, they are the most likely APCs in direct recognition.

1-Host CD4+ helper T cells are triggered into proliferation by recognition of foreign MHC molecules and produce cytokine. causing delay type hypersensitivity (DTH).

2-CD8+ T cells recognize foreign MHC and differentiate into cytotoxic T cells (TCLs) which kill the cells in the graft. Indirect recognition.

1-Host CD4+ T cells recognize donor MHC molecules after these molecules are picked up, processed, and presented by the host's own APCs activating DTH reaction.

2-Production of antibodies by host B cells against graft alloantigen. Helper T cells, stimulate antibody responses.



Host-Versus-Graft Disease: (HVGD)

If the transplanted graft bearing foreign MHC antigens, the recipient's immune system, attack the donor cells of the transplanted organ. Rejection involves T cell-mediated and circulating antibodies. The initial target of the recipient antibodies is graft vasculature.

There are three basic patterns of transplant rejection:

1-Hyperacute reaction occurs immediately after transplantation; in kidney transplants, as soon as blood flow from the recipient to the donor organ begins, it takes on a cyanotic, mottled appearance.

2-**Acute rejection** usually occurs within the first few months after transplantation and it is evidenced by signs of organ failure.

3-Chronic HVGD occurs over a prolonged period. It is manifest by dense fibrosis of the intimal layer of blood vessels in the transplanted organ.

Graft-Versus-Host Disease (GVHD):

In GVHD, the cellular immune system of the transplanted graft (donor T-cells) recognizes and attacks the unrelated recipient HLA. Occurs mainly in:

1- Bone marrow transplant.

2- Severely immuno-compromised patients, who have received blood products containing HLA-incompatible lymphocytes.

3- After transplantation of solid organs rich in lymphoid cells (*e.g.*, the liver).

III. Autoimmune disorders

They are caused by a breakdown in the ability of the immune system to differentiate between self and nonself antigens. Normally, there is a high degree of immunologic tolerance to self-antigens, which prevents the immune system from destroying the host. Autoimmune diseases can affect almost any cell or tissue in the body. Some autoimmune disorders are tissue specific; others affect multiple organs and systems.