PATHOPHYSIOLOGY OF II.–IV. TYPE OF HYPERSENSITIVITY

Theoretical Bases of Clinical Medicine

Immunopathologic reactions

the basic concept is that the immune system is required for defending the host against infections, however immune responses are themselves capable of causing tissue injury and disease

injurious, or pathologic, immune reactions are called

„HYPERSENSITIVITY REACTIONS "

most of the hypersensitivity reactions are not confined to a single type; they usually involve a mixture of mechanism

Robin Coombs a Philip Gell

- **Robin Coombs (1921–2006) was British immunologist** who was responsible for the renaissance of British Immunology after the Second World War
  - *he is best remembered for describing the antiglobulin test that bears his name*
  - *the antiglobulin test revolutionized the diagnosis of hemolytic diseases and the compatibility testing of blood for transfusion*
  - *haemagglutination reactions became widely used in the diagnosis of a range of infectious agents.*

together with Philip Gell, he devised the classification of allergic reactions; these were published in the textbook 'Clinical Aspects of Immunology', which he and Gell first edited in 1963 and which became the leading textbook on medical immunology

4 types of immunopathologic reactions according to Coombs and Gell

I **IMMEDIATE HYPERSENSITIVITY** (IgE)

disorders (allergy diseases)

II **ANTIGEN-ANTIBODY INTERACTIONS** (IgG, IgM)

disorders (autoimmune diseases)

III **FORMATION OF IMMUNOCOMPLEXES** (antigen-antibody-complement)

disorders (immunopathologic reactions in infection and cancer)

IV **DELAYED HYPERSENSITIVITY** (T lymphocytes; Th1, Th2, Tc)

disorders (reactions after transplantations, transfusions and vaccinations)

II. type of hypersensitivity

antigen-antibody interactions

type II hypersensitivity reactions are characterized by **antigen–antibody interactions**, resulting in the local production of **C5a complement cleavage component** and recruitment of **polymorphonuclear neutrophils** and subsequent tissue injury

initiated by **antibody** which react with antigenic determinant of **cell membrane**

the consequences on this reaction depend on whether or not complement and accessory molecules become involved, and whether the metabolism of the cell is affected

II. type of hypersensitivity

antigen-antibody interactions

main mechanism of pathologic reaction

complement and Fc-receptor mediated recruitment and activation of leukocytes (neutrophils, macrophages)

opsonization and phagocytosis of cell

abnormalities in cellular functions
(e.g. hormone or neurotransmitter receptor signalling)

II. type of hypersensitivity

antigen-antibody interactions

antibodies against cells or tissues

usually react in places where are these cells and tissues found
(without systemic character of the reaction)

antigen

the antibodies that cause disease most often are autoantibodies against self antigens and less commonly are specific for foreign (e.g., microbial) antigens

II. type of hypersensitivity

antigen-antibody interactions

IgG1 … IgG3 … IgM

complement activation

phagocytosis

ADCC (**A**ntibody **D**ependent **C**ells **C**ytotoxicity)

II. type of hypersensitivity

antibody-dependent cellular cytotoxicity (ADCC)

natural killer (NK) cells and other leukocytes may bind to antibody-coated cells and destroy these cells

NK cells → **Fcγ receptor called FcγRIII (CD16**, which is one of several kinds of NK cell–activating receptors**)** → **binding to arrays of IgG antibodies** attached to the surface of a cell → **generating signals that cause the NK cell to discharge its granule proteins**, which kill the opsonized cell

cells infected with enveloped viruses typically express viral glycoproteins on their surface that can be recognized by specific antibodies, and this may facilitate ADCC-mediated destruction of the infected cells

II. type of hypersensitivity

antigen-antibody interactions

Complement activation

→ lysis of the cell

(e.g. AIHA with cold autoantibodies, myasthenia gravis)

→ binding of C3b (opsonisation) → phagocytosis

(e.g. AIHA with warm autoantibodies, ITP)

→ activation of neutrophils and tissue damage

(e.g. Goodpasture syndrome)

II. type of hypersensitivity

antigen-antibody interactions

Stimulation or blockade of receptor

→ metabolism stimulation (active cell secretion)

(e.g. Graves–Basedow disease)

→ growth stimulation

(e.g. functional struma nodosa)

→ blockade of receptor, mobility or growth

(e.g. pernicious anaemia, Addison disease, some cases of infertility or myxoedema)

III. type of hypersensitivity

formation of immunocomplexes

result from the presence of **immune complexes** in the circulation or in the tissues

it involves soluble antigens that are not bound to cell surfaces (as opposed to those in type II hypersensitivity)

initiated by **immunocomplexes**, if they accumulate in the tissues in large quantities, they may activate complement (C3a and C5a) and accessory cells (polymorphonuclear cells) and produce extensive tissue damage

this type of reaction served to removal of viral particles from blood stream

III. type of hypersensitivity

formation of immunocomplexes

transitional immunocomplex reaction is a physiological mechanism of removal infected cells and presence of transitional immunocomplex damage is typical form various acute infections (arthralgia, myalgia, etc.)

pathological reaction

overdose of antigen

persistence of antigen in the body

III. type of hypersensitivity

formation of immunocomplexes

localization of **immune complexes** depends on their size, their charge, and the nature of the antigen and the local concentration of complement

if they accumulate in the tissues in large quantities, they may activate complement and accessory cells and produce extensive tissue damage

*A classic example is the **Arthus reaction** or **serum sickness** … further clinical examples include **systemic lupus erythematodes (SLE), glomerulonephritis or extrinsic allergic alveolitis***

III. type of hypersensitivity

formation of immunocomplexes

impaired physiological transport and clearance of immunocomplexes
→ activation of local inflammation

type of reaction → ***Arthus reaction*** *in case of* ***antibody overdose***

e.g. extrinsic alveolitis

type of reaction → ***serum sickness*** *in case of* ***antigen overdose***

e.g. autoimmune diseases or SLE

III. type of hypersensitivity

formation of immunocomplexes

Arthus reaction

it is induced by subcutaneous administration of a protein antigen to a previously immunized animal

it results in the formation of immune complexes at the site of antigen injection and a local vasculitis after 6–24 hours after injection of antigen

in a small percentage of vaccine recipients who have previously been vaccinated or already have antibodies against the vaccine antigen, a painful swelling that develops at the injection site represents a clinically relevant Arthus reaction

III. type of hypersensitivity

formation of immunocomplexes

Serum sickness

the first immune complex disease studied was serum sickness

it is seen in subjects who repeatedly received animal serum for the treatment of infections, this illness could be re-created in experimental animals

serum sickness is induced by systemic administration of a protein antigen, which elicits an antibody response and leads to the formation of circulating immune complexes

III. type of hypersensitivity

formation of immunocomplexes

small soluble immunocomplexes

overdose of antigen

circulating immunocomplexes in the blood which are deposited into the wall of vessels (vasculitis) or glomeruli (glomerulonephritis)

large insoluble immunocomplexes

overdose of antibodies

immunocomplexes are deposited in their place of origin

IV. type of hypersensitivity

delayed-type hypersensitivity

initiated by **T cells** that react with antigen and release **Th1 cytokines**

these cytokines attract other cells (particularly **macrophages**, which in turn liberate lysosomal enzymes) and **Th17 cells**

the resultant acute lesions consist of **infiltrating lymphocytes**, **macrophages**

and occasionally **eosinophil polymorfonuclear leukocytes**

chronic lesions show ***necrosis***, ***fibrosis*** and sometimes ***granulomatous reactions***

IV. type of hypersensitivity

delayed-type hypersensitivity

in different T cell–mediated diseases, tissue injury is caused by inflammation induced by cytokines that are produced mainly by **CD4+ T cells** or by killing of host cells by **CD8+ T cells**

these mechanisms of tissue injury are the same as the mechanisms used by T cells to eliminate cell-associated microbes

IV. type of hypersensitivity

delayed-type hypersensitivity

CD4+ T cells may react against cell or tissue antigens and secrete cytokines that induce local inflammation and activate macrophages

different diseases may be associated with activation of ***Th1 and Th17 cells***

Th1 cells → IFN-γ (the principal ***macrophage***-activating cytokine)

Th17 cells → responsible for the recruitment of ***leukocytes*** (including ***neutrophils***)

the actual tissue injury in these diseases is caused mainly by the macrophages and neutrophils

IV. type of hypersensitivity

delayed-type hypersensitivity

Tc cells specific for antigens on host cells may directly kill these cells

Tc cells also produce cytokines that induce inflammation, but they are usually not the major sources of cytokines in immune reactions

*in many T cell–mediated autoimmune diseases, both **Th1 cells** and **Tc cells** specific for self antigens are present, and both contribute to tissue injury*

IV. type of hypersensitivity

delayed-type hypersensitivity

many organ-specific autoimmune diseases in humans are believed to be caused by **T cells**

identification of these cells in lesions

similarities with animal models in which the diseases are known to be T cell mediated

these disorders typically are **chronic and progressive**

in part because T cell reactions tend to be prolonged and often self-perpetuating

the inciting antigens (tissue antigens or proteins expressed by resident microbes) are often never cleared

IV. type of hypersensitivity

delayed-type hypersensitivity

tissue injury causes release and alteration of self proteins, which may result in reactions against these newly encountered proteins

this phenomenon has been called **epitope spreading** to indicate that the initial immune response against one or a few self antigen epitopes may expand to include responses against many more self antigens

chronic inflammatory diseases that are initiated by immune reactions are sometimes called ***immune-mediated inflammatory diseases***

„V. type of hypersensitivity“

formation of granulomas that encapsulate and isolate the pathogen

it is possible that there is another strategy that is used by the body to deal with a class of infectious agents, for which there is perhaps a deleterious outcome as well

this paradigm is phylogenetically ancient, and perhaps to be used by many metazoan genera (even phyla) to deal with large, metazoan extracellular parasites

driven by

innate immunity (foreign body)

type 1 cytokines (M. tuberculosis infections)

type 2 cytokines (Schistosome eggs)

possible untoward consequences (sarcoidosis)

Rajan TV. The Gell-Coombs classification of hypersensitivity reactions: a re-interpretation. Trends Immunol 2003; 24:376-379