Lecturer : ***Karama T.Al-Taee*** ***Seven lecture for third year***

MSc. Medical microbiology

The immune system general consideration

Innate immunity:

Complement system

Complement is very much involved in the inflammatory response and is one of group of plasma proteins the key effector mechanisms of the immune system. It consists of at least 30 components– enzymes, regulators and membrane receptors – which interact in an ordered and tightly regulated manner to bring about phagocytosis or lysis of target cells Complement components are normally present in body fluids as inactive precursor complement proteins are synthesized mainly by the liver. Complement activation enhances both innate & adaptive defenses.

Complement activation pathways

1- **Classic pathway**

- Activated by antibody(IgM,IgG)

- **Activation**

*The proteins in this pathway are named C1-C9 .

*C1 is complex of 3 proteins (C1q,C1r,C1s)

*C1q binds to Fc region of antibody which activates C1r which activates C1s,

*Most efficient at activating complement IgM, IgG1 and IgG3.

*Once activated C1s is eventually cleaved which activates C4 and C2

*C4b & C2b come together to form the **C4b2b** which is the **C3 convertase**

*C3 convertase activates **C3** to C3a and C3b

***C3a** binds to receptors on **basophils** and **mast cells** triggering them to release there vasoactive compounds (enhances vasodilation and vasopermeability) .**C3a** is called an **anaphylatoxin** that caused mast cell degranulation and smooth muscle contraction .

***C3b** serves as an opsonin which facilitates immune complex clearance**(phagocytosis)** .

- **AMPLIFICATION**

-Each C1s creates many C4b and C2b fragments

-Each C4bC2b creates many C3b (activated C3)

-Each C3b goes on to create many Membrane Attack Complexes (MAC).

- **ATTACK**

Most C3b serves an opsonin function

Some C3b binds to C4bC2b to form the **C5 convertase (C4bC2bC3b**).

C5 convertase cleaves **C5** to C5a and C5b leading to the formation of the Membrane attack Complex (C5-C6-C7-C8-C9) .The MAC "punches holes" in cell walls resulting in lysis.

2- Alternative pathway

Requires no specific recognition of antigen in order to cause activation

Activated by some bacterial cell surfaces ,Antibody not involved

Major proteins: C3 , Factor B ,Factor D, and Properdin .

First step: binding of C3b to foreign cell or surface

ACTIVATION

_Spontaneous conversion from C3 to C3b occurs in body .Normally, C3b is very short lived and quickly inactivated by proteins on the surface of the body's own cell walls.

_However, bacteria or other foreign material may lack these surface proteins allowing C3b to bind and stay active.

AMPLIFICATION

:Factor **B** binds to C3b **.**Factor **B** is then cleaved by factor D into Ba and Bb

C3bBb remains which acts as a **C3 convertase** (C3 ➔ C3a and C3b).

ATTACK :

The complex C3bBb is believed to be unstable until it binds properdin, a serum protein. The addition of properdin forms the complex C3bBbP, a stable compound which can bind an additional C3b to form alternative pathway C5-convertase. (PC3bBbC3b) this enzyme substrate is C3 and C5 its amplifies C3b production and activates the membrane attack pathway .

The **membrane attack complex** (**MAC**) is a structure typically formed on the surface of pathogen cell membranes as a result of the activation of the host's complement system, It's effector proteins of the immune system. The membrane-attack complex (MAC) forms transmembrane channels. These channels disrupt the cell membrane of target cells, leading to cell lysis and death. Active MAC is composed of the subunits C5b, C6, C7, C8 and several C9 molecules

Since C3b is free and abundant in the plasma, it can bind to either a host cell or a pathogen surface. To prevent complement activation from proceeding on the host cell, there are several different kinds of regulatory proteins like DAF (Decay Accelerating Factor) ,CR1, Factor 1, Factor H that disrupt the complement activation process.

-Complement Factor H can inhibit the formation of the C3 convertase by competing with factor B for binding to C3b accelerate the decay of the C3 convertase .Bacterial endotoxin and LPS inhibit factor H.

3- Lectin pathway : Activated by mannose binding lectin **.**Antibody not involved **.**

Biological effects of complement activation!

1. Cell lysis: The most important purpose of complement activation is to lyse the microbes that have entered into the host.

2-Inflammation: the smaller fragments play important roles in inflammation.

3-Complement fragments act as anaphylatoxins:

C3a, C4a, and C5a fragments formed during complement activation are generally called anaphylatoxins. (Anaphylatoxins are complement fragments, which cause mast cell degranulation and smooth muscle contraction.) These fragments bind to their respective receptors (C3a, C4a, or C5a receptors) on mast cells in the inflammatory site and basophils in blood.

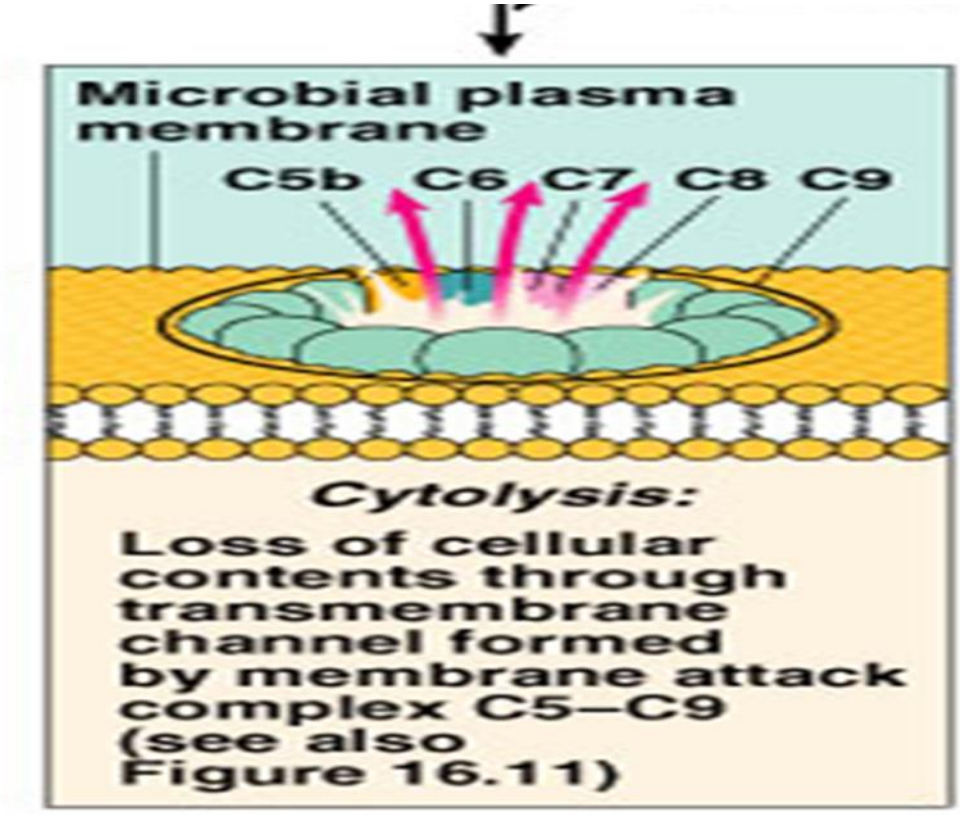
4-Complement fragments act as opsonins: Phagocytic cells such as neutrophils and macrophages have receptors for C3b, C4b, and iC3b. Binding of phagocytic cells through these receptors result in the bridging of microbes to the phagocytic cells.

The complement system role in diseases

_The complement system might play a role in many diseases with an immune component, such as Barraquer-Simons Syndrome, asthma, lupus erythematosus, glomerulonephritis, various forms of arthritis, autoimmune heart disease, and rejection of transplanted organs.

_The complement system is also becoming increasingly implicated in diseases of the central nervous system such as Alzheimer's disease and other neurodegenerative conditions such as spinal cord injuries.

_ Deficiencies of the terminal pathway predispose to both autoimmune disease and infections (particularly Neisseria meningitidis, due to the role that the membrane attack complex ("MAC") plays in attacking Gram-negative bacteria.



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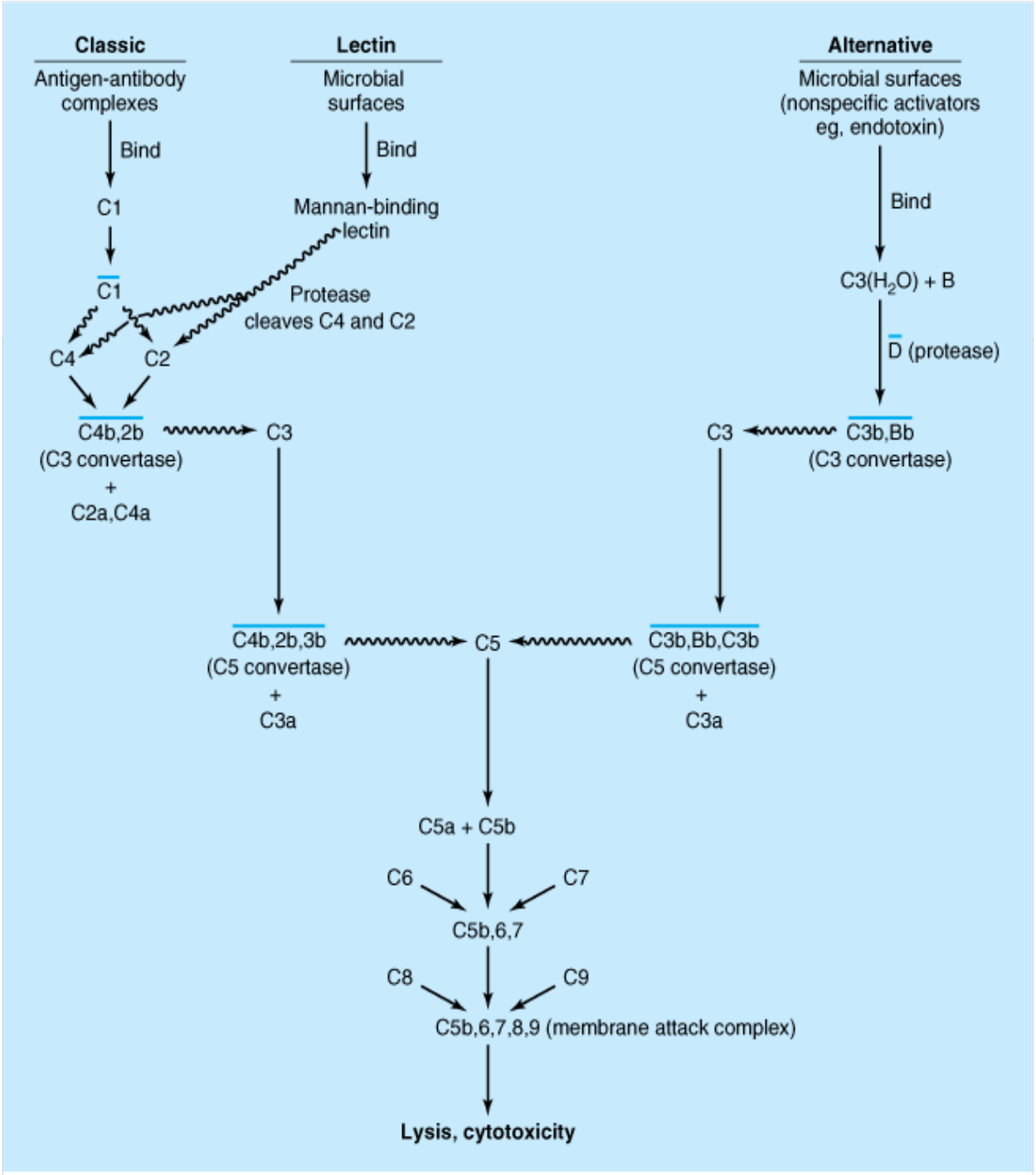


Source: Levinson W: *Review of Medical Microbiology and Immunology*, 10th Edition: http://www.accessmedicine.com

Comparison between the three pathways of complement activation

	Classical pathway	Alternative pathway	Lectin pathway
Type of immunity	Acquired (specific)	Innate (non-specific)	Innate (non-specific)
Initiation	Antigen-antibody complex	Microbial components (e.g. endotoxin)	Mannose bindin lectin binds mannose on pathogen surface
Role of antibodies	Needed for initiation (activation of C1)	No role	No role
Role of properdin	No role	Needed for activation of C3	No role
C3 convertase	C4b2b	C3bBb	C4b2b
C5 convertase	C4b2b3b	C3bBb3b	C4b2b3b
Involved components	C1-C9	Factor B, factor D, properdin, C3, 5-9	MBL, MASP1 & 2, C2-C9
MAC (C5b6789)	Formed	Formed	Formed

Inflammation

Inflammation is the response of living tissue to injury. It involves a well-organized cascade of fluidic and cellular changes. It is recognizable grossly and histologically and has both beneficial and detrimental effects locally and systemically.

RUBOR, TUMOR, CALOR et DOLOR

The four principal effects of inflammation (rubor, tumor, calor et dolor) were described nearly 2,000 years ago.

1-Redness (rubor) An acutely inflamed tissue appears red, due to dilatation of small blood vessels within the damaged area (hyperemia).

2 -Swelling (tumor) Swelling results from edema, the accumulation of fluid in the extravascular space as part of the inflammatory fluid exudate, and to a much lesser extent, from the physical mass of the inflammatory cells migrating into the area.

3-Heat (calor) Increase in temperature is readily detected in the skin. It is due to increased blood flow (hyperemia) through the region, resulting in vascular dilation and the delivery of warm blood to the area.

4- Pain (dolor) Pain results partly from the stretching and distortion of tissues due to inflammatory edema and, in part from some of the chemical mediators of acute inflammation, especially bradykinin and some of the prostaglandins stimulate nerve endings making the area more sensitive.

Causes of Inflammation

1-Microbial infections: One of the most common causes of inflammation is microbial infection. Microbes include viruses, bacteria, protozoa, fungi and various parasites.

2-Hypersensitivity reactions: A hypersensitivity reaction occurs when an altered state of immunologic responsiveness causes an inappropriate or excessive immune reaction that damages the tissues

3- Physical agents, irritant and corrosive chemicals Tissue damage leading to inflammation may occur through physical trauma, ultraviolet or other ionizing radiation, burns or excessive cooling.

4- Tissue necrosis Death of tissues from lack of oxygen or nutrients resulting from inadequate blood flow (infarction) is a potent inflammatory stimulus.

Effects of Inflammation

The effects of inflammation can be both local and systemic. The systemic effects of acute inflammation include fever, malaise, and leukocytosis. The local effects are usually clearly beneficial, for example the destruction of invading microorganisms, but at other times they appear to serve no obvious function, or may even be harmful.

Beneficial effects of inflammation	Harmful effects of inflammation
1-Dilution of toxins **2-Entry of antibodies** **3-Fibrin formation** **4-Delivery of nutrients and oxygen** **5-Stimulation of immune response**	**1-Persistent cytokine release** **2-Destruction of normal tissues** **3-Swelling .** **4-Inappropriate inflammatory response**

The adaptive immunity system:

Cells of immune system:

All the cells of the immune system are derived from self-regenerated hematopoiesis stem cell present in bone marrow and fetal liver figure(8.8) .B-cell in the bone marrow expresses a BCR(B-cell receptors) on its membrane for antigen binding ,T-lymphocyte mature in thymus expresses TCR T-cell receptors on its membrane .B-cell secreting Ig antibodies and act as antigen presenting cells (APCs)for T-lymphocyte .T-cells divided in two type T-helper cell bear the cluster of differentiation marker CD4, T-cytotoxic CD8**.** T-helper cells are required for activation the effector function of B-cells. Dendritis cell and monocyte / macrophage antigen presenting cells(APCs).

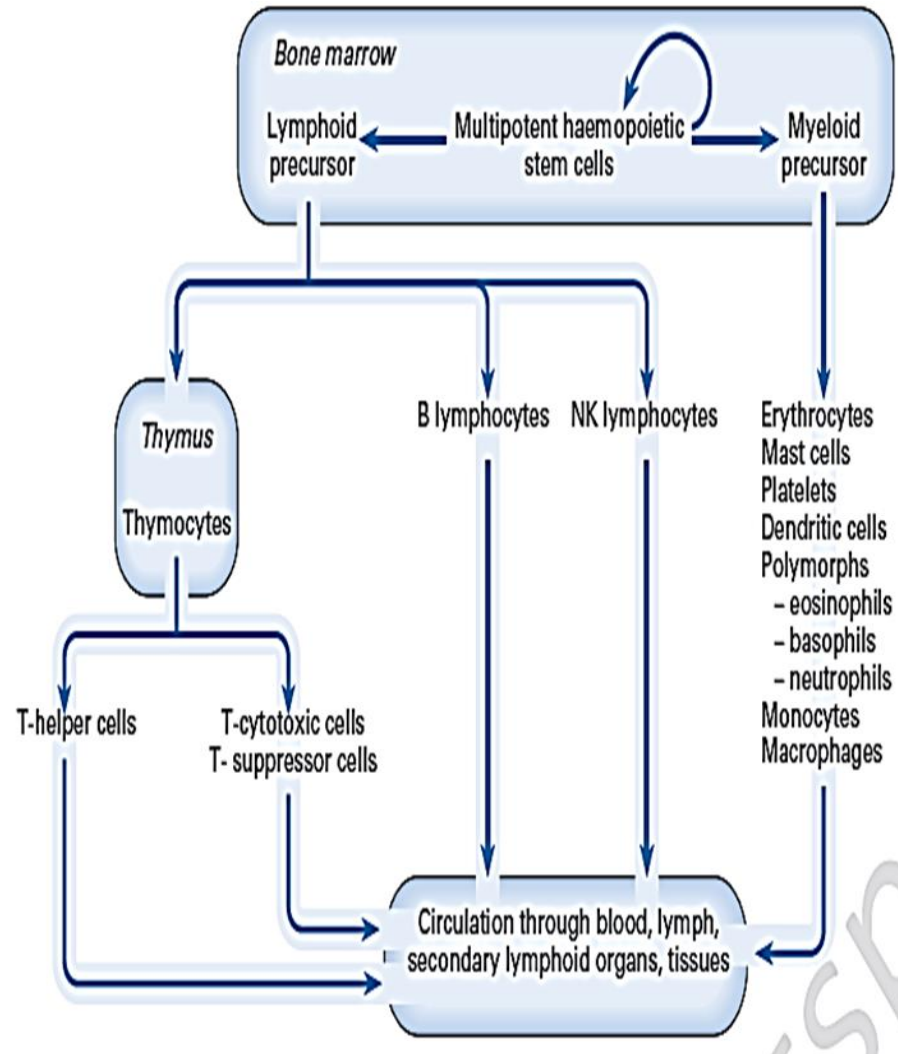


Fig. 8.8 Cells and organs of the immune system. NK, natural killer.

Antigen recognition

T and B lymphocyte are responsible for specify in the immune response .Each T or B cells recognize single antigen .

-The TCR recognizes linear peptide bound to MHC molecules on the surface of APCs .

-The BCR bind directly to often non linear antigenic determinant (epitopes) and dose not require MHC presentation .

Major Histocompatibility Complex(MHC)

In humans ,MHC genetic loci on chromosome 6 known as histocompatibility locus antigens **Human Leukocyte Antigens** (HLAs) .Their function is to bind APCs –processed short antigenic peptide and present them on the APC surface to T-cell .HLA phenotype responsible for tissue transplant rejection .there are two classes of HLA :-

1-Class I – are found on all nucleated cells in the body .MHC I molecule present peptide to CD8 T lymphocyte

2-Class II – are found on monocyte /macrophage B-cells dendrites cells ,some epithelial cell and activated T cells . MHC II molecule present peptide to CD4 T cells .

Disorder of the immune system

Hypersensitivity is an immunological state in which the immune system "over-reacts" to foreign antigen such that the immune response itself is more harmful than the antigen. All types of hypersensitivity involve:

• The adaptive immune response • i.e., highly specific reactions via T or B cells.

• prior exposure to the antigen • the initial exposure sensitizes the individual but does NOT cause a hypersensitive reaction.

• hypersensitivity is only seen on secondary exposure.

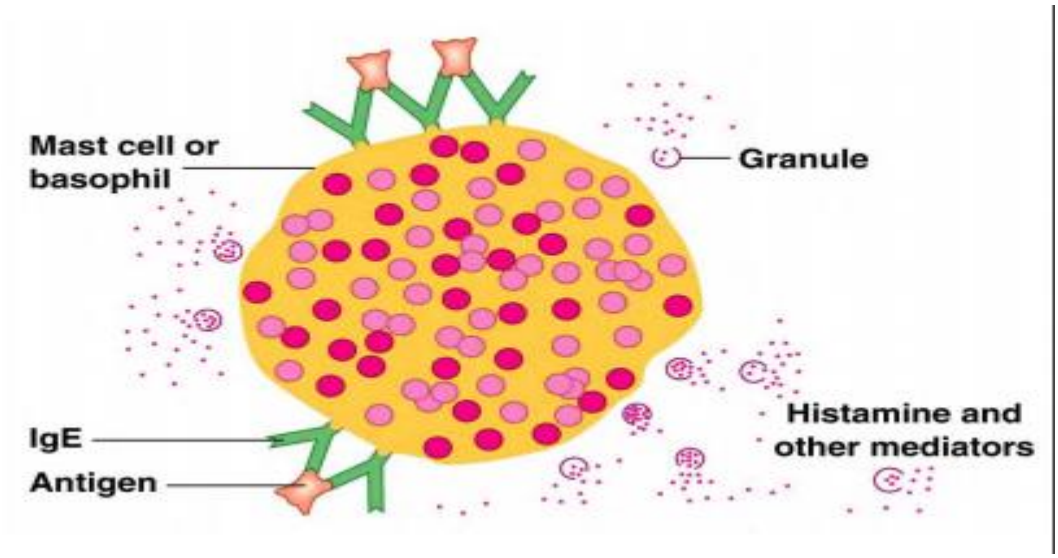
Types of Hypersensitivity

Hypersensitivity following secondary exposure to antigen comes in 4 basic forms:

***Type I: allergic reactions** ("immediate" hypersensitivity) • IgE mediated and very rapid (2-30 minutes).

(Anaphylactic) reactions involve the activation of mast cells or basophils through the binding of antigen to IgE on the cell surface: • mast cells & basophils have IgE receptors that bind the constant region of any IgE antibody • "cross-linking" of IgE molecules on the cell surface by binding to antigen triggers the release of "mediators" • mediators = histamine, prostaglandins & leukotrienes. The release of these mediators causes the redness, swelling, itching, mucus, etc, that characterize allergic reactions: Most allergic reactions are **local**: • itching, redness, hives in the skin, mucus, sneezing.

- **Systemic allergic** reactions can be **lethal**: • severe loss of blood pressure, breathing difficulty (anaphylactic shock) • usually due to inhaled or ingested antigens • usually due to animal venoms or certain foods . Foods • e.g., corn, eggs, nuts, peanuts, onions Grains of pollen Dust mites • the allergen is actually dust mite feces .



***Type II: cytotoxic reactions •**

Involve destruction of cells bound by IgG or IgM antibodies via the activation of complement: • most commonly observed with blood transfusions • reaction to ABO blood antigens • reaction to Rh antigen • can occur via the Rh antigen in newborns. requires Rh- mother and Rh + child • Rh- mother produces anti-Rh + IgG following birth • subsequent Rh + children are vulnerable.

***Type III: immune complex reactions •**

Caused by high levels of antigen-antibody complexes (due to foreign or self Ag) that are not cleared efficiently by phagocytes and tend to deposit in certain tissues: • blood vessel endothelium in kidneys, lungs • joints This can result

in local cell damage via: • complement activation • attraction of phagocytes, other cells involved in inflammation (e.g., neutrophils).

***Type IV: delayed cell-mediated reactions •**

Delayed cell-mediated hypersensitivity takes 1 or 2 days to appear and involves the action of T cells & macrophages, NOT antibodies: • macrophages release toxic factors to destroy ALL cells in the immediate area **general response to intracellular bacteria but can also occur with other antigens (latex, poison ivy)

*** Types I,II,III are all antibody-mediated, Type IV is not.**

Autoimmunity refers to the generation of an immune response to self antigens: • normally the body prevents such reactions • T cells with receptors that bind self antigens are eliminated (or rendered anergic*) in the thymus • B cells with antibodies that bind self antigens are eliminated or rendered anergic in the bone marrow or even in the periphery (i.e., outside the bone marrow) • however in rare cases T and/or B cells that recognize self antigens survive & are activated *anergic = non-reactive or non-responsive.

Common Autoimmune Diseases

Lupus • antibodies to self including DNA and histone proteins.

Rheumatoid Arthritis • immune response to self antigens in synovial membranes of joints.

Type I Diabetes • immune response to self antigens in pancreatic β cells (insulin-producing cells)

Multiple Sclerosis • immune response to myelin basic protein in Schwann cells (form myelin sheath of neurons).

References

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Chapter 63: Complement.

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