Reading Chapters 15 and 16

A local NON-adaptive response

keeps infection from moving to other sites
deliver the bug to local lymph nodes
A non-adaptive response [generic and always present]

direct damage to the invader
no memory, no long lasting or improved protection.

no change in the hosts ability to resist a subsequent challenge
recognition by relatively invariant receptors the same response is made to all pathogens

An Adaptive immune response

memory cells which provide long lasting and improved protection

2 major non-adaptive host pathways: Complement and Phagocytosis

1. Phagocytosis by tissue macrophages and circulating monocytes

Who are phagocytes?
PMN
monocytes
tissue macrophages

Phagocytosis

--ingestion of particulate material. Can include tissue debris, living or dead bacteria, other foreign cells. Neutrophils, monocytes and macrophages are the most important phagocytic cells.
How do phagocytes bind particles?

success:

Phagocytosis by neutrophils begins the human body's non-specific response to a foreign invader. In the first video, a neutrophil engulfs an Escherichia coli bacterium, enclosing it in a phagosome. Neutrophil granules fuse with the phagosome and destroy the bacterium.

one that gets away: Some bacteria develop defenses of their own to avoid phagocytosis. In the second video, a polysaccharide capsule encloses this Streptococcus pneumoniae. The phagocyte cannot engulf the encapsulated cells, allowing the bacterium to become established and cause disease in the host.

another way to get away

An attached particle is internalized via pseudopodial extensions from the cell surface. A vesicle with a membrane enclosed foreign particle is called a phagosome. Phagosomes fuse with cytoplasmic lysosomes. This is then called a phagolysosome. PMNs are the first phagocytes to arrive followed by macrophages. Lysosomes [containing lysozyme and other substances] fuse with the phagosomes. PMNs degranulate [fuse granules] into the phagolysosome.

THE CHEMISTRY of Killing of Microbes within PMNs and Macrophages

a. Oxygen dependent [most important]
Phagocytosis initiates the hexose monophosphate shunt--which causes an oxidative burst. This supplies electrons to an enzyme called NADPH oxidase which is located in the phagosomal membrane.
Superoxide anion \([\cdot O_2^-]\) is produced. And singlet \(O\)
This is further converted to \(H_2O_2\) [hydrogen peroxide by SOD [super oxide dismutase].
\(H_2O_2\) may be further converted to the activated hydroxyl radical \([OH.]\) So we now have hydroxyl radical, singlet oxygen, superoxide and hydrogen peroxide--- ALL of which are toxic.
In the presence of myeloperoxidase and a halide [such as chloride], hypochlorous acid [\(HClO\)] attacks amino acids in proteins and degrades them to chloramines----Meaning \(NH_2\) goes to \(NCl\)
It also disrupts cell walls. This is known as the myeloperoxidase-halide system. The iron in myeloxperoxidase makes pus green. Nitric oxide \([NO]\) is produced by an enzyme called NO synthetase. Peroxynitrite \([N\dot{2}O_2^-]\), has anti-microbial activity and acts as a messenger to increase inflammatory responses of the phagocyte.
b. Oxygen-independent killing
less effective
mediated by lysozyme, this catalyses hydrolysis of cell wall mucopolysaccharides and cationic proteins--these make pores in lipid bilayers, also in this pathway arginase, lactoferrin, cathespins.
Result is digestion of all ester bonds in proteins, polysacharrides, lipids and nucleic acids. Fortunately, the granules in PMN and the lysosomes in the phagocytes do not come into contact with the cytoplasm.

Catalase
Catalase positive organisms can destroy H2O2 [their own and at least some of the phagocytes'].
So what about individuals with an X-linked disorder which results in NADPH oxidase deficiency?
This is called chronic granulomatous disease [occurs in childhood]
Their phagocytes ingest but do not kill CERTAIN micro-organisms.
Catalase positive organisms are ingested but not easily killed.
Catalase negative organisms are ingested and killed.

The white cell components of the blood include:

granulocytes:
basophils
mast cells .5% [contain histamine]
eosinophils 2-4% large red staining granules,

PMN 55-65%, lobed nucleus polymorphonuclear leukocyte=polys
short lived--only one day--arrive 1st, die 1st

mononuclear phagocytes 3-8%
monocytes (circulating forms, less mature than those resident in tissues)
mature to become macrophages [found resident in tissues and populating lymphoid tissues]
lymphocytes 25-35%

More non adaptive host responses to infection:
cytokines

more on interferons:

alpha and beta interferons are induced by double stranded RNA. They prevent replication in infected cells, activates innate and adaptive host responses and increases expression of MHC class I

inflammation - Figure

Bacterial infection triggers an inflammatory response. Macrophages encountering bacteria in the tissues are triggered to release cytokines that increase the permeability of blood vessels, allowing fluid and proteins to pass into the tissues. The stickiness of the endothelial cells of the blood vessels is also changed, so that cells adhere to the blood vessel wall and are able to crawl through it; first neutrophils and then macrophages are shown entering the tissue from a blood vessel. The accumulation of fluid and cells at the site of infection causes the redness, swelling, heat, and pain, known collectively as inflammation. Neutrophils and macrophages are the principal inflammatory cells. Later in an immune response, activated lymphocytes may also contribute to inflammation.

acute phase reactions

Figure

The acute-phase response produces molecules that bind bacteria but not host cells. Acute-phase proteins are produced by liver cells in response to cytokines released by phagocytes in the presence of bacteria. They include serum amyloid protein (SAP) (in mice but not humans), C-reactive protein (CRP), fibrinogen, and mannan-binding lectin (MBL). SAP and CRP are homologous in structure; both are pentraxins, forming five-membered disks, as shown for SAP (upper photograph). CRP binds phosphorylcholine on bacterial surfaces but does not recognize it in the form in which it is found in host-cell membranes, and can both act as an opsonin in its own right and activate the classical complement pathway by binding C1q to augment opsonization. MBL is a member of the collectin family, which includes C1q, which it resembles in its structure). MBL binds mannose residues on bacterial cell surfaces and, like CRP, can both act as an opsonin in its own right and activate complement. MBL activates the lectin complement pathway by binding and activating two serine esterases, resembling C1rs, that in turn activates C4 and C2. Thus, CRP and MBL can lead to bacterial clearance in the same way as an IgM antibody.
Tissue macrophages recruit more phagocytic cells to the site of the infection. Cytokines -- IL1, IL6, and TNF-a -- help to coordinate the body's responses to infection. IL-1, IL-6, and TNF-a activate hepatocytes to synthesize acute-phase proteins, and bone-marrow endothelium to release neutrophils. The acute-phase proteins act as opsonins, whereas the disposal of opsonized pathogens is augmented by enhanced recruitment of neutrophils from the bone marrow. IL-1, IL-6, and TNF-a are also endogenous pyrogens, raising body temperature, which is believed to help eliminate infections. A major effect of these cytokines is to act on the hypothalamus, altering the body's temperature regulation, and on muscle and fat cells, altering energy mobilization to increase the body temperature. At elevated temperatures, bacterial and viral replication are decreased, whereas processing of antigen is enhanced. Finally, they help activate B and T cells by inducing migration to lymph nodes and maturation of dendritic cells to induce an adaptive immune response. The major local effect of TNF-a is to initiate an inflammatory response.

To get out of the blood they need to do the following!

Example: a local infection with Gram neg [G-] bac
TNF-a causes the arteriole to dilate
so increased blood flow --- pain and heat increased vascular permeability [swelling and pain due to local accumulation of fluid]

near the site of tissue damage and inflammation leukocytes undergo MARGINATION.

TNF-a [within minutes] causes endothelium- to express adhesion molecules weak adhesion of the leukocytes to the vessel walls.
The next step is expression of other molecules -- stronger interactions through these molecules: ICAM on endo and LFA and Mac-1 on leukocytes. Tight binding arrests the rolling and now diapedesis can occur.

Phagocytic leukocytes are directed to sites of infection through interactions between adhesion molecules induced by cytokines. The first step (top panel) involves the reversible binding of leukocytes to vascular endothelium through interactions between selectins induced on the endothelium and their carbohydrate ligands on the leukocyte, shown here for E-selectin and its ligand the sialyl-Lewisx moiety (s-Lex). This interaction cannot anchor the cells against the shearing force of the flow of blood and instead they roll along the endothelium, continually making and breaking contact. The binding does, however, allow stronger interactions, which occur as a result of the induction of ICAM-1 on the endothelium and the activation of its receptors LFA-1 and Mac-1 (not shown) on the leukocyte. Tight binding between these molecules arrests the rolling and allows the leukocyte to squeeze between the endothelial cells forming the wall of the blood vessel (ie to extravasate). The leukocyte integrins LFA-1 and Mac-1 are required for extravasation, and for migration toward chemoattractants. Adhesion between molecules of CD31, expressed on both the leukocyte and the junction of the endothelial cells, is also thought to contribute to diapedesis. The leukocyte also needs to traverse the basement membrane. Finally, the leukocyte migrates along a concentration gradient of chemokines (here shown as IL-8) secreted by cells at the site of infection. The electron micrograph shows a neutrophil extravasating between endothelial cells. Photograph (x 5500) courtesy of I Bird and J Spragg.

PUS
lots of dead white cells and dead bacteria too

NK [natural killer] cells
checks for certain molecules on host cells--if they are absent or in reduced numbers--the NK cells kill it. [Brutality can mean survival!].

When the whole body is involved: septic shock

Complement

2. Alternative [+ classical in special cases] pathway of complement

and PMN exit cause inflammation --[heat, redness, increase blood flow, vascular leak, swelling]
this is more detailed than required for this class:
C3
spontaneous cleavage in plasma to generate C3a and C3b or
initiated by bacterial cell wall polysaccharides.
C3a goes off to initiate inflammation and to recruit new phagocytes.
C3b binding also INDUCES a response from the host.
Factor B binds non-covalently to C3b and is cleaved to Bb by a protease called factor D

How to stop the destruction?:
C3b is rapidly inactivated unless it binds covalently to a CELL surface.
complement regulatory proteins including factor H--normally provide host cell
protection]

C3bBb is a complex that can convert both C3 and C5.
Binding of factor P stabilizes the 3bBb complex deposits MANY molecules of C3b on
the pathogen surface
opsonization by phagocytes [increases with number and affinity of membrane binding
sites]
activation of the terminal components of complement = lysis of the invader

So there are the 3 biological activities of C’
inflammation
opsonization
lysis

C’ control proteins H, MCP and DAF bind to C3b
H and DAF displace Bb = no amplification of cascade. The bound C3b is cleaved by
factor I to yeild inactive C3bi.

Classical pathway
C4b,2b3b [new uniform nomenclature]

Go to lower respiratory tract--first the organizer and anatomy and then the notes.