11.3G: Inflammation

Learning Objectives

1. Describe the 4 processes that make up the inflammatory mechanism.
2. Briefly describe the various beneficial effects of inflammation that are associated with plasma leakage and with diapedesis.
3. Briefly describe the process of diapedesis, indicating the role of P-selectins, integrins, and adhesion molecules.
4. Briefly describe the healing stage of inflammation.
5. Briefly describe the problems that arise from chronic inflammation.

The inflammatory response is an attempt by the body to restore and maintain homeostasis after injury and is an integral part of body defense. Most of the body defense elements are located in the blood and inflammation is the means by which body defense cells and defense chemicals leave the blood and enter the tissue around the injured or infected site. Inflammation is essentially beneficial, however, excess or prolonged inflammation can cause harm.

The Mechanism of Inflammation

Essentially, four processes make up the inflammatory mechanism:

a. Smooth muscles around larger blood vessels contract to slow the flow of blood through the capillary beds at the infected or injured site. This gives more opportunity for leukocytes to adhere to the walls of the capillary and squeeze out into the surrounding tissue.

b. The endothelial cells that make up the wall of the smaller blood vessels contract. This increases the space between the endothelial cells resulting in increased capillary permeability. Since these blood vessels get larger in
diameter as a result of this, the process is called vasodilation (see Figure \
\( \PageIndex{1} \)).

Scanning electron micrographs of a cross section of a capillary showing an endothelial cell and a capillary with a red blood cell; courtesy of Dennis Kunkel's Microscopy).

Illustration of arterioles, venules, and a capillary bed.

Animation showing a capillary prior to vasodilation.

Animation showing vasodilation.

html5 version of animation for iPad showing a capillary prior to vasodilation.

html5 version of animation for iPad showing vasodilation.

c. Molecules called selectins are produced on the membrane of the leukocyte and are able to reversibly bind to corresponding selectin glycoprotein receptors on the inner wall of the venule. This reversible binding enables the leukocyte to roll along the inner wall of the venule. This reversible binding enables the leukocyte to roll along the inner wall of the venule. Adhesion molecules are activated on the surface of the endothelial cells on the inner wall of the capillaries. Corresponding molecules on the surface of leukocytes called integrins attach to these adhesion molecules allowing the leukocytes to flatten and squeeze through the space between the endothelial cells. This process is called diapedesis or extravasation.

d. Activation of the coagulation pathway causes fibrin clots to physically trap the infectious microbes and prevent their entry into the bloodstream. This also triggers blood clotting within the surrounding small blood vessels to both stop bleeding and further prevent the microorganisms from entering the bloodstream.

You Tube animation illustrating leukocyte rolling along the inner wall of a blood vessel.

You Tube animation of leukocyte accumulation and extravasation following inflammation
Christopher Dubois

You Tube movie and animation of leukocyte extravasation (diapedesis)
from ImmuneDocumentary

3D animation illustrating white blood cells leaving capillaries and entering
These four events are triggered and enhanced by a variety of chemical inflammatory mediators. We will now divide the inflammatory response into two stages: early inflammation and late inflammation.

Early Inflammation and Diapedesis

Most leukocyte diapedesis (extravasation) occurs in post-capillary venules because hemodynamic shear forces are lower in these venules. This makes it easier for leukocytes to attach to the inner wall of the vessel and squeeze out between the endothelial cells. We will look at this process in more detail below.

1. During the very early stages of inflammation, stimuli such as injury or infection trigger the release of a variety of mediators of inflammation such as leukotrienes, prostaglandins, and histamine. The binding of these mediators to their receptors on endothelial cells leads to vasodilation, contraction of endothelial cells, and increased blood vessel permeability. In addition, the basement membrane surrounding the capillaries becomes rearranged so as to promote the migration of leukocytes and the movement of plasma macromolecules from the capillaries into the surrounding tissue. Mast cells in the connective tissue as well as basophils, neutrophils and platelets leaving the blood from injured capillaries, release or stimulate the synthesis of vasodilators such as histamine, leukotrienes, kinins, and prostaglandins. Certain products of the complement pathways (C5a and C3a) can bind to mast cells and trigger their release their vasoactive agents. In addition, tissue damage activates the coagulation cascade and production of inflammatory mediators like bradykinins.

2. The binding of histamine to histamine receptors on endothelial cells triggers an upregulation of P-selectin molecules and platelet-activating factor or PAF on the endothelial cells that line the venules.

3. The P-selectins then are able to reversibly bind to corresponding P-selectin glycoprotein ligands (PSGL-1) on leukocytes. This reversible binding enables the leukocyte to now roll along the inner wall of the venule.

4. The binding of PAF to its corresponding receptor PAF-R on the leukocyte upregulates the surface expression of an integrin called leukocyte function-associated molecule-1 (LFA-1) on the surface of the leukocyte.

5. The LFA-1 molecules on the rolling leukocytes can now bind firmly to an an adhesion molecule called intercellular adhesion molecule-1 (ICAM-1) found on the surface of the endothelial cells forming the inner wall of the blood vessel [see Figure \( \PageIndex{4} \)] .

6. The leukocytes flatten out, squeeze between the constricted endothelial cells, and use enzymes to breakdown the matrix that forms the basement membrane surrounding the blood vessel. The leukocytes then migrate towards chemotactic agents such as the complement protein C5a and leukotriene B4 generated by cells at the site of infection or injury [see Figure \( \PageIndex{5} \)] .

Late Inflammation and Diapedesis

1) Usually within two to four hours of the early stages of inflammation, activated macrophages and vascular endothelial cells release inflammatory cytokines such as TNF and IL-1 when their toll-like receptors bind pathogen-associated molecular patterns - molecular components associated with microorganisms but not found as a part of eukaryotic cells. This enables vascular endothelial cells of nearby venules to increase their expression of adhesion molecules such as P-selectins, E-selectins, intercellular adhesion molecules (ICAMs), and chemokines.
2) The binding of TNF and IL-1 to receptors on endothelial cells triggers an maintains the inflammatory response by upregulation the production of the adhesion molecule E-selectin and maintaining P-selectin expression on the endothelial cells that line the venules.

3). The E-selectins on the inner surface of the endothelial cells can now bind firmly to its corresponding integrin E-selectin ligand-1 (ESL-1) on leukocytes (see Figure \(\PageIndex{4}\)).

4) The leukocytes flatten out, squeeze between the constricted endothelial cells, and move across the basement membrane as they are are attracted towards chemokines such as interleukin-8 (IL-8) and monocyte chemotactic protein-1 (MCP-1) generated by cells at the site of infection or injury (see Figure \(\PageIndex{5}\)). Leakage of fibrinogen and plasma fibronectin then forms a molecular scaffold that enhances the migration and retention of leukocytes at the infected site.

Benefits of Inflammation

As a result of this increased permeability:

a. Plasma flows out of the blood into the tissue.

Beneficial molecules in the plasma (see Figure \(\PageIndex{2}\)) include:

1. Clotting factors. Tissue damage activates the coagulation cascade causing fibrin clots to form to localize the infection, stop the bleeding, and chemotactically attract phagocytes.

2. Antibodies. These help remove or block the action of microbes through a variety of methods that will be explained in Unit 6.

3. Proteins of the complement pathways. These, in turn: 1) stimulate more inflammation (C5a, C3a, and C4a), 2) stick microorganisms to phagocytes (C3b and C4b), 3) chemotactically attract phagocytes (C5a), and 4) lyse...
membrane-bound cells displaying foreign antigens (membrane attack complex or MAC).

For More Information: The Benefits of the Complement Pathways from Unit 5

4. Nutrients. These feed the cells of the inflamed tissue.

5. Lysozyme, cathelicidins, phospholipase A\(_2\), and human defensins. Lysozyme degrades peptidoglycan. Cathelicidins are cleaved into two peptides that are directly toxic to microbes and can neutralize LPS from the gram-negative bacterial cell wall. Phospholipase A\(_2\) hydrolyzes the phospholipids in the bacterial cytoplasmic membrane. Human defensins put pores in the cytoplasmic membranes of many bacteria. Defensins also activate cells involved in the inflammatory response.

6. Transferrin. Transferrin deprives microbes of needed iron.

b. Leukocytes enter the tissue through a process called diapedesis or extravasation, discussed above under early inflammation and late inflammation.

Benefits of diapedesis include (see Figure \(\PageIndex{2}\)):

1. Increased phagocytosis. Neutrophils, monocytes that differentiate into macrophages when they enter the tissue, and eosinophils are phagocytic leukocytes.

2. More vasodilation. Basophils, eosinophils, neutrophils, and platelets enter the tissue and release or stimulate the production of vasoactive agents that promote inflammation.

3. Cytotoxic T-lymphocytes (CTLs), effector T4-cells, and NK cells enter the tissue to kill cells such as infected cells and cancer cells that are displaying foreign antigens on their surface (discussed in Unit 6).

For More Information: Leukocytes from Unit 5

Concept Map for Inflammation

Cytokines called chemokines are especially important in this part of the inflammatory response. They play key roles in diapedesis - enabling white blood cells to adhere to the inner surface of blood vessels, migrate out of the blood vessels into the tissue, and be chemotactically attracted to the injured or infected site. They also trigger extracellular killing by neutrophils.

Finally, within 1 to 3 days, macrophages release the cytokines interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-a). These cytokines stimulate NK cells and T-lymphocytes to produce the cytokine interferon-gamma. (IF-\(?\)). The IF-\(?\) then binds to receptors on macrophages causing them to produce fibroblast growth factor and angiogenic factors for tissue remodeling. With the proliferation of endothelial cells and fibroblasts, endothelial cells form a fine network of new capillaries into the injured area to supply blood, oxygen, and nutrients to the inflamed tissue. The fibroblasts deposit the protein collagen in the injured area and form a bridge of connective scar tissue to close the open, exposed area. This is called fibrosis or scarring, and represents the final healing stage.
Inflammation is normally carefully regulated by cytokines. Inflammatory cytokines such as interferon-gamma and interleukin-12 enhance the inflammatory response whereas the cytokine interleukin-10 inhibits inflammation by decreasing the expression of inflammatory cytokines.

So as can be seen, acute inflammation is essential to body defense. Chronic inflammation, however, can result in considerable tissue damage and scarring. With prolonged increased capillary permeability, neutrophils continually leave the blood and accumulate in the tissue at the infected or injured site. As they discharge their lysosomal contents and reactive oxygen species or ROS, surrounding tissue is destroyed and eventually replaced with scar tissue. Anti-inflammatory agents such as antihistamines or corticosteroids may have to be given to relieve symptoms or reduce tissue damage.

For example, as learned in Unit 3, during severe systemic infections with large numbers of microorganisms present, high levels of pathogen-associated molecular patterns (PAMPs) are released resulting in excessive cytokine production by macrophages and this can harm the body. In addition, neutrophils start releasing their proteases and reactive oxygen species that kill not only the bacteria, but the surrounding tissue as well. Harmful effects include high fever, hypotension, tissue destruction, wasting, acute respiratory distress syndrome or ARDS, disseminated intravascular coagulation or DIC, damage to the vascular endothelium, hypovolemia, and reduced perfusion of blood through tissues and organs resulting to shock, multiple system organ failure (MOSF), and often death. This excessive inflammatory response is referred to as Systemic Inflammatory Response Syndrome or SIRS or the Shock Cascade.

Exercise: Think-Pair-Share Questions

1. Briefly describe the mechanisms that enable to slow the flow of blood at an infection site and get phagocytes, complement proteins and antibodies to the infection site.
2. Why is it important to deliver plasma to an infection site?
3. Why is it important for diapedesis to occur during inflammation?

Chronic inflammation also contributes to heart disease, Alzheimer's disease, diabetes, and cancer.

- In the case of cancer, it is proposed that when macrophages produce inflammatory cytokines, such as TNF-alpha, these cytokines activate a gene switch in the cancer cell that turns on the synthesis of proteins that promote cell replication and inflammation while blocking apoptosis of the cancer cell.
- In heart disease, it is thought that macrophages digest low density lipoprotein or LDL, the bad cholesterol, and are then encased in a fibrous cap that forms arterial plaque.
- With diabetes, it is thought that the metabolic stress of obesity triggers innate immune cells and fat cells to produce cytokines such as TNF-alpha that can interfere with the normal function of insulin.
- In the case of Alzheimer's disease, microglial cells, macrophage-like cells in the brain, interact with the beta-amyloid proteins that build up in neurons of those with Alzheimer's and subsequently produce inflammatory cytokines and free radicals that destroy the neurons.
Summary

1. Most of the body defense elements are located in the blood and inflammation is the means by which body defense cells and defense chemicals leave the blood and enter the tissue around the injured or infected site.

2. As part of the mechanism for inflammation, smooth muscles around larger blood vessels contract to slow the flow of blood through the capillary beds at the infected or injured site. This gives more opportunity for leukocytes to adhere to the walls of the capillary and squeeze out into the surrounding tissue.

3. As part of the mechanism for inflammation, the endothelial cells that make up the wall of the smaller blood vessels contract. This increases the space between the endothelial cells resulting in increased capillary permeability.

4. As part of the mechanism for inflammation, adhesion molecules are activated on the surface of the endothelial cells on the inner wall of the capillaries and corresponding molecules on the surface of leukocytes called integrins attach to these adhesion molecules allowing the leukocytes to flatten and squeeze through the space between the endothelial cells. This process is called diapedesis or extravasation.

5. As part of the mechanism for inflammation, activation of the coagulation pathway causes fibrin clots to physically trap the infectious microbes and prevent their entry into the bloodstream.

6. Acute inflammation is essential to body defense.

7. As a result of this increased permeability, plasma flows out of the blood into the tissue delivering clotting factors, antibody molecules, complement pathway proteins, nutrients, antibacterial enzymes and peptides, and transferrin for innate body defense.

8. As a result of this increased permeability, leukocytes enter the tissue delivering phagocytic cells, inflammation-inducing cells, cytotoxic T-lymphocytes, effector T4-lymphocytes, and NK cells.

9. Inflammatory cytokines also, enable endothelial cells form a fine network of new capillaries into the injured area to supply blood, oxygen, and nutrients to the inflamed tissue, and enable fibroblasts to deposit the protein collagen in the injured area and form a bridge of connective scar tissue to close the open, exposed area.

10. Chronic inflammation can result in considerable tissue damage and scarring, primarily to extracellular killing by phagocytes and hypoperfusion.

11. Chronic inflammation is thought to also contribute to heart disease, Alzheimer’s disease, diabetes, and cancer.