Eidgenössische Technische Hochschule Zürich
Swiss Federal Institute of Technology Zurich

Übung 11

Vorlesung Bio-Engineering

Frühlingssemester 2021

Tissues of all types are vulnerable to injury and, inevitably, aging. Understanding how tissues respond to damage, and how these changes with age can guide strategies to aid repair.

Many diseases involve biological processes and mechanisms that are involved in wound healing and can even be caused by "wound healing gone wrong". Some of these diseases involve mechanical feedback loops that are central to the problem.

Tissue injury and repair

Inflammation is the standard, initial response of the body to injury. Whether biological, chemical, or physical, all injuries lead to the same sequence of physiological events. Inflammation limits the extent of injury, partially or fully eliminates the cause of injury, and initiates repair and regeneration of damaged tissue. **Necrosis**, or accidental cell death, causes inflammation. **Apoptosis** is programmed cell death, a normal step-by-step process that destroys cells no longer needed by the body. By mechanisms still under investigation, apoptosis does not initiate the inflammatory response. Acute inflammation resolves over time by the healing of tissue. If inflammation persists, it becomes chronic and leads to diseased conditions. Arthritis and tuberculosis are examples of chronic inflammation. The suffix "-itis" denotes inflammation of a specific organ or type, for example, peritonitis is the inflammation of the peritoneum, and meningitis refers to the inflammation of the meninges, the tough membranes that surround the central nervous system

The four cardinal signs of inflammation—redness, swelling, pain, and local heat—were first recorded in antiquity. Cornelius Celsus is credited with documenting these signs during the days of the Roman Empire, as early as the first century AD. A fifth sign, loss of function, may also accompany inflammation.

Upon tissue injury, damaged cells release inflammatory chemical signals that evoke local **vasodilation**, the widening of the blood vessels. Increased blood flow results in apparent redness and heat. In response to injury, cells present in tissue release the potent vasodilator **histamine**. Increased blood flow and inflammatory mediators recruit white blood cells to the site of inflammation. The endothelium lining the local blood vessel becomes "leaky" under the influence of histamine and other inflammatory mediators allowing **neutrophils**, **macrophages**, and fluid to move from the blood into the interstitial tissue spaces. The excess liquid in tissue causes swelling, more properly called edema. The swollen tissues squeezing pain receptors cause the sensation of pain. Prostaglandins released from injured cells also activate pain neurons. Non-steroidal anti-inflammatory drugs (NSAIDs) reduce pain because they inhibit the synthesis of prostaglandins. High levels of NSAIDs reduce inflammation. Antihistamines decrease allergies by blocking histamine receptors and as a result the histamine response.

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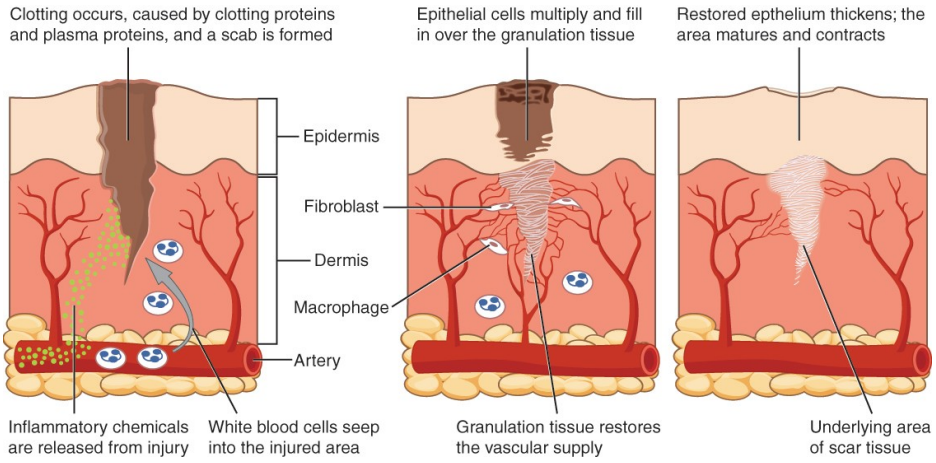
After containment of an injury, the tissue repair phase starts with removal of toxins and waste products. **Clotting** (coagulation) reduces blood loss from damaged blood vessels and forms a network of **fibrin** proteins that trap blood cells and bind the edges of the wound together. A scab forms when the clot dries, reducing the risk of infection. Sometimes a mixture of dead leukocytes and fluid called pus accumulates in the wound. As healing progresses, **fibroblasts** from the surrounding connective tissues begin to replace the collagens and other extracellular matrix lost by the injury. Angiogenesis, the growth of new blood vessels, results in vascularization of the new tissue known as granulation tissue. The clot retracts, with highly contractile cells called myo- fibroblasts pulling the edges of the wound together, and it slowly dissolves as the tissue is repaired. When a large amount of granulation tissue forms and capillaries disappear, a pale scar is often visible in the healed area.



Tissue and Aging

According to poet Ralph Waldo Emerson, "The surest poison is time." In fact, biology confirms that many functions of the body decline with age. All the cells, tissues, and organs are affected by **senescence** (loss of cellular activity with age), with noticeable variability between individuals owing to different genetic makeup and lifestyles. The outward signs of aging are easily recognizable. The skin and other tissues become thinner and drier, reducing their elasticity, contributing to wrinkles and high blood pressure. Hair turns gray because follicles produce less melanin, the brown pigment of hair and the iris of the eye. The face looks flabby because elastic and collagen fibers decrease in connective tissue and muscle tone is lost. Glasses and hearing aids may become parts of life as the senses slowly deteriorate, all due to reduced elasticity. Overall height decreases as the bones lose calcium and other minerals. With age, fluid decreases in the fibrous cartilage disks intercalated between the vertebrae in the spine. Joints lose cartilage and stiffen. Many tissues, including those in muscles, lose mass through a process called **atrophy**. Lumps and rigidity become more widespread. Consequently, the passageways, blood vessels, and airways become more rigid. The brain and spinal cord lose mass.

Nerves do not transmit impulses with the same speed and frequency as in the past. Some loss of thought clarity and memory can accompany aging. More severe problems are not necessarily associated with the aging process and may be symptoms of underlying illness.

As exterior signs of aging increase, so do the interior signs, which are not as noticeable. The incidence of heart diseases, respiratory syndromes, and type 2 diabetes increases with age, though these are not necessarily age-dependent effects. Wound healing is slower in the elderly, accompanied by a higher frequency of infection as the capacity of the immune system to fend off pathogen declines.

Aging is also apparent at the cellular level because all cells experience changes with aging. Telomeres, regions of the chromosomes necessary for cell division, shorten each time cells divide. As they do, cells are less able to divide and regenerate. Because of alterations in cell membranes, transport of oxygen and nutrients into the cell and removal of carbon dioxide and waste products from the cell are not as efficient in the elderly. Cells may begin to function abnormally, which may lead to diseases associated with aging, including arthritis, memory issues, and some cancers.

The progressive impact of aging on the body varies considerably among individuals, but studies indicate, however, that exercise and healthy lifestyle choices can slow down the deterioration of the body that comes with old age.

Atherosclerosis – Wound healing processes in vascular disease

Atherosclerosis (also known as arteriosclerotic vascular disease or ASVD) is a specific form of arteriosclerosis in which an **artery wall** thickens as a result of invasion and accumulation of white blood cells (WBCs).

The accumulation of the WBCs is termed "fatty streaks" early on because of appearance being similar to that of marbled steak. These accumulations contain both living, active WBCs (producing inflammation) and remnants of dead cells, including cholesterol and triglycerides. The remnants eventually include calcium and other crystallized materials, within the outermost and oldest plaque. The "fatty streaks" reduce the elasticity of the artery walls. However, they do not affect blood flow for decades, because the artery muscular wall enlarges at the locations of plaque. The wall stiffening may eventually increase pulse pressure; widened pulse pressure is one possible result of advanced disease within the major arteries.

Atherosclerosis is therefore a syndrome affecting arterial blood vessels due to a chronic inflammatory response of WBCs in the walls of arteries. This is promoted by low-density lipoproteins (LDL, plasma proteins that carry cholesterol and triglycerides) without adequate removal of fats and cholesterol from the macrophages by functional high-density lipoproteins (HDL). It is commonly referred to as a "hardening" of the arteries.

Atherosclerosis is a chronic disease that remains asymptomatic for decades. Atherosclerotic lesions, or atherosclerotic plaques, are separated into two broad categories: Stable and unstable (also called vulnerable). The pathobiology of atherosclerotic lesions is very complicated but generally, stable atherosclerotic plaques, which tend to be asymptomatic, are rich in extracellular matrix and smooth muscle cells, while, unstable plaques are rich in macrophages and foam cells and the extracellular matrix separating the lesion from the arterial lumen (also known as the fibrous cap) is usually weak and prone to rupture.

Ruptures of the fibrous cap expose thrombogenic material, such as collagen to the circulation and eventually induce thrombus formation in the lumen. Upon formation, intraluminal thrombi can occlude arteries outright (e.g. coronary occlusion), but more often they detach, move into the circulation and eventually occluding smaller downstream branches causing thromboembolism (release of the thrombus into the blood flow). Apart from thromboembolism, chronically expanding atherosclerotic lesions can cause complete closure of the lumen.

Atherosclerosis affects the entire artery tree, but mostly larger, high-pressure vessels such as the coronary (heart feeding), renal (kidney), cerebral (brain) arteries. These are termed "clinically silent" because the person having the vessel blockage does not notice the problem and does not seek medical help, or when they do, physicians do not recognize what has happened.

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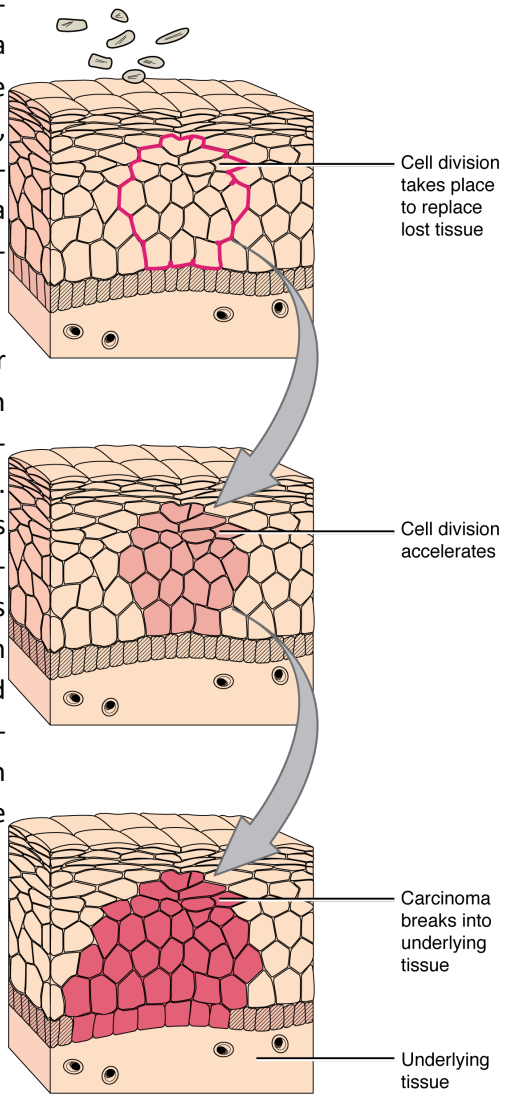
Wound healing mechanisms in cancer

Cancer is a generic term for many diseases in which cells escape regulatory signals. Uncontrolled growth, invasion into adjacent tissues, and colonization of other organs, if not treated early enough, are its hallmarks. Health suffers when tumors “rob” blood supply from the “normal” organs. Many of these processes involve mechanisms of tissue repair, however toward often very dangerous outcome.

A **mutation** is defined as a permanent change in the DNA of a cell. **Epigenetic modifications**, changes that do not affect the code of the DNA but alter how the DNA is decoded, are also known to generate abnormal cells.

Alterations in the genetic material may be caused by environmental agents, infectious agents, or errors in the replication of DNA that accumulate with age. Many mutations do not cause any noticeable change in the functions of a cell. However, if the modification affects key proteins that have an impact on the cell’s ability to proliferate in an orderly fashion, the cell starts to divide abnormally. As changes in cells accumulate, they lose their ability to form regular tissues. A tumor, a mass of cells displaying abnormal architecture, forms in the tissue.



Many tumors are benign, meaning they do not metastasize nor cause disease. A tumor becomes malignant, or cancerous, when it breaches the confines of its tissue, promotes angiogenesis, attracts the growth of capillaries, and metastasizes to other organs. The specific names of cancers reflect the tissue of origin. Cancers derived from epithelial cells are referred to as carcinomas. Cancer in myeloid tissue or blood cells form myelomas. Leukemias are cancers of white blood cells, whereas sarcomas derive from connective tissue. Cells in tumors differ both in structure and function. Some cells, called cancer stem cells, appear to be a subtype of cell responsible for uncontrolled growth. Recent research shows that contrary to what was previously assumed, tumors are not disorganized masses of cells, but have their own structures.

Development of cancer

Cancer treatments vary depending on the disease's type and stage. Traditional approaches, including surgery, radiation, chemotherapy, and hormonal therapy, aim to remove or kill rapidly dividing cancer cells, but these strategies have their limitations. Depending on a tumor's location, for example, cancer surgeons may be unable to remove it. Radiation and chemotherapy are difficult, and it is often impossible to target only the cancer cells. The treatments inevitably destroy healthy tissue as well. To address this, researchers are working on pharmaceuticals that can target specific proteins implicated in cancer-associated molecular pathways.

Review Questions

(from texts above, and the introductory lecture)

I. TRUE/FALSE - Decide whether each of these statements is true or false.

- A main of neutrophils is to destroy bacteria.
- A main of macrophages is to destroy bacteria.
- Apoptosis is central to a well-functioning immune system response.

II. Which of the following statements is **INCORRECT** regarding stages of wound healing?

- The first phase is inflammatory, or reactive, phase.
- The most important cell in the proliferative phase is the neutrophil.
- The remodeling phase can take from 6 weeks to 1 year.
- Connective tissue regeneration involves contraction.

III. What are the 3 stages of wound healing, in order?

- Proliferative phase, substrate phase, remodeling phase
- Fibrin phase, remodeling phase, inflammatory phase
- Inflammatory phase, Proliferative phase, remodeling phase
- Substrate phase, dynamic stage, neutrophil phase

IV. When does a wound have maximum tensile strength?

- 0---10 days
- 10---20 days
- 20---30 days
- 30---40 days
- 40---50 days

V. The following are features of the inflammatory phase of wound healing **EXCEPT**:

- This phase lasts a finite length of time of approximately 4 days in primary intention healing.
- The inflammation is mediated by a number of factors that cause dilation of capillaries at the wound site and lymphatic blockade, as well as migration of leukocytes through vessel wall into the wound.
- This phase is marked by loss of function of the wounded area, as well as pain, redness, heat and swelling.
- This phase is marked by an increased rate of collagen synthesis from fibroblasts.
- In this phase, neutrophil phagocytosis aids in the removal of clot, bacteria, and other debris from the wound.

VI. Which is the smallest blood vessel?

- artery
- arteriole
- vein
- capillary

VII. Which of the following is associated with atherosclerosis?

- Including fruit and vegetables in every meal
- High cholesterol diet
- High---fiber diets
- Low---salt diets
- Increased exercise

VIII. **TRUE/FALSE** - Decide whether each of these statements is true or false.

- In the natural history of atherosclerosis, a correct order of disease progression is: clean artery => fatty streaks => fibrous plaques => clinical lesion
- The onset of atherosclerosis involves LDL Cholesterol.
- The onset of atherosclerosis involves macrophages that engulf oxidized LDL Cholesterol.

IX. The cells that aggregate at this cite in the artery lumen are called:

- Leukocytes
- Platelets
- Erythrocytes
- Fibroblasts

X. Platelets release factors that result in

- Inflammation
- Oxidation
- Vasodilation
- Smooth muscle proliferation

XI. Cancer is more common in older people because

- their immune systems have degenerated.
- the supply of certain hormones declines with age.
- a change in the rate of cell replacement takes place.
- They have accumulated more mutations.
- Their bodies are unable to adjust to the changing environment.

XII. **TRUE/FALSE** – Indicate for each statement if it's true or false.
The formation of bone tissue after injury from granulation tissue depends on

- the cells found in the initial blood cloth.
- the right amount of healing time.
- right amount of mechanical stress (tissue shear strain and fluid flow).
- the previous vascularization of the bone tissue.

XIII. assign the following cells to their function: neutrophils, erythrocytes, basophils, lymphocytes, monocytes, and eosinophils

- coordination of body defense by identification of foreign substances.
- transport of gases from lung to the tissues.
- helping the immune system fighting of infections by ingesting foreign cells.

XIV. **TRUE/FALSE** – Indicate for each statement if it's true or false.

- Endothelial cells are needed for angiogenesis.
- Endothelial cells can only migrate from surrounding tissue.
- Endothelial cells are part of the endothelium.