**Assignment Title:** WOUND HEALING  
**Course Title:** Introduction to Histopathology  
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**Human Anatomy**

**Questions**  
1. Write on cytokine signaling and its role in wound healing.

2. When is wound healing referred to as 'impaired'? And why?

3. Examine the role of oxidative stress in the development and progression of impaired wound healing.

(1)

**Cytokine signaling and its role in wound healing**

Cytokine signaling is an important part of the human body regulation. Most cytokines are cell-secreted proteins from glial cells in the nervous system and are necessary for intracellular signaling. Most cytokines are local regulators that alert and activate lymphocytes. Some cytokine-signaling pathways involve hormones such as growth hormones and leptin, the hormone that controls fat storage.

The immune system depends on cytokine signaling to keep the human body healthy. Macrophages and dendritic cells engulf foreign particles and send a cytokine signal to nearby dormant lymphocytes. The receptors on the lymphocytes recognize the signal and activate. Those cells are specialized to recognize certain antigens. The combination of the macrophages and activation of lymphocytes through cytokine signaling help keep the body in homeostasis — or the proper internal equilibrium.

Cytokines play important role in health and disease, specifically in host responses to infection, immune responses, inflammation, trauma, sepsis, cancer, and reproduction.  
1, Role of Cytokines in depression  
2, Role of Pyrogenic cytokines  
3, Role of Cytokines in cancer  
4, Role of Angiogenic cytokines  
5, Role of Cytokines in asthma  
6, Role of Cytokines in rheumatoid arthritis  
7, Role of Cytokines in sepsis  
8, Role of Neutrophil cytokines

**Role of Cytokines in Depression**

Depressed patients have been found to have higher levels of proinflammatory cytokines, acute phase proteins, chemokines and cellular adhesion molecules. In addition, therapeutic administration of the cytokine interferon-α leads to depression in up to 50% of patients. Moreover, proinflammatory cytokines have been found to interact with many of the pathophysio-logical domains that characterize depression, including neurotransmitter metabolism, neuroendocrine function, synaptic plasticity and behavior. Stress, which can precipitate depression, can also promote inflammatory responses through effects on sympathetic and para-sympathetic nervous system pathways. Finally, depression might be a behavioral byproduct of early adaptive advantages conferred by genes that promote inflammation. These findings suggest that targeting proinflammatory cytokines and their signaling path-ways might represent a novel strategy to treat depression

It is now known that cytokines have effects on cells outside the immune system, and that non-immune cells can synthesize and secrete cytokines. Thus, cytokines can be regarded as classical hormones that can function locally or systemically to orchestrate immune responses, and can also coordinate immune responses with those of other physiological systems in the body, including the nervous system. The cytokine hypothesis of depression derives from both clinical and experimental observations. The clinical observations were made on patients treated with interferons (IFN's) and interleukin-2 (IL-2). Such patients often displayed influenza-like symptoms and nonspecific neuropsychiatric symptoms, some of which are characteristics of depression. Whereas the flu - like side effects tend to attenuae as cytokine treatment continues, the neuropsychiatric adverse effects may only disappear after termination of cytokine administration, or treatment with anti-depressants, e.g. the selective serotonin re-uptake inhibitor (SSRI) paroxetine.

Cytokines have been shown to be effective in the treatment of medical conditions, such as hepatitis C, multiple sclerosis, some infections, leukemia, Kaposi's sarcoma, melanoma, myeloma, renal carcinoma and other forms of cancer. The cytokines most commonly used are IFNα, IFNβ, IFNγ and IL-2. Each of these cytokines has been reported to produce side effects such as asthenia, myalgia, confusion and influenza-like symptoms. Depression is most commonly associated with treatment with IFNα and IL-2, and occasionally with IFNβ but not with IFNγ.

**Role of Pyrogenic cytokines**

The febrile response is thought to be mediated by endogenous mediators, generically called "endogenous pyrogens." In the classical model of pathogenesis, induction of fever is mediated by the release of pyrogenic cytokines such as tumor necrosis factor (TNF), interleukin (IL)-1, IL-6, and interferons into the bloodstream in response to exogenous pyrogens.

Cytokines are highly inducible, secreted proteins mediating intercellular communication in the nervous and immune system. Fever is the multiphasic response of elevation and decline of the body core temperature regulated by central thermoregulatory mechanisms localized in the preoptic area of the hypothalamus. The discovery that several proinflammatory cytokines act as endogenous pyrogens and that other cytokines can act as antipyretic agents provided a link between the immune and the central nervous systems and stimulated the study of the central actions of cytokines. The proinflammatory cytokines interleukin 1 (IL-1), interleukin 6 (IL-6) and the tumor necrosis factor alpha (TNF) as well as the anti-inflammatory cytokines interleukin 1 receptor antagonist (IL-1ra) and interleukin 10 (IL-10) have been most investigated for their pyrogenic or antipyretic action.

Studies performed at the end of the 1970s demonstrated that leukocytes, when stimulated with bacterial products, synthesize protein mediators called cytokines, some of which have potent EP-like properties. It thus became apparent that the EP activity in the plasma is represented by several of these cytokines with proinflammatory properties: IL-1, TNF and lymphotoxin, IL-6, and IFNs. These proinflammatory cytokines reach the CNS where, through induction of central mediators such as prostaglandins (PGs), they are able to increase the temperature set point and cause fever. The increase in body temperature has several advantages during infections: it results in inhibition of bacterial growth, increased bactericidal activities of neutrophils and macrophages, stimulation of acute-phase protein synthesis, iron sequestration, anorexia, and somnolence.

**Role of Cytokines in cancer**

The mixture of cytokines that is produced in the cancer microenvironment has an important role in cancer pathogenesis. Cytokines that are released in response to infection, inflammation and immunity can function to inhibit cancer development and progression. Alternatively, cancer cells can respond to host-derived cytokines that promote growth, attenuate apoptosis and facilitate invasion and metastasis.  
**Role of Angiogenic cytokines**

Angiogenesis, the formation of new blood vessels from existing vasculature, is fundamental for a variety of physiological and pathological processes including tumor growth andmetastasis. Among these factors, vascular endothelial growth factor (VEGF) and transforming growth factor- β1 (TGF-β1) are preeminent glioblastoma-associated multifunctional cytokines that stimulate migration, tissue invasion and angiogenesis.

VEGF is a secreted heparin-binding glycoprotein and one of the most potent endothelial cell-specific mitogens. It is known to play a key role in tumor angiogenesis. TGF-β1 overexpression has been associated with several cancers and correlates with tumor progression, angiogenesis and poor prognosis.

**Role of Cytokines in asthma**

Asthma is a chronic inflammatory disorder of the airways superimposed upon structural changes that include an increase in smooth muscle and airway wall remodeling. In addition to a background of chronic mediator release, asthma is characterized by consider-able variations in airway function brought about by important interactions with the environment, including allergen, pollutant and virus exposure. At least in mild–moderate disease, cytokines released from Th2 cells appear important in orchestrating the inflammation.

**Role of Cytokines in rheumatoid arthritis** Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease that is characterized by persistent intense immunological activity, local destruction of bone and cartilage, and a variety of systemic manifestations. CD4 T cells play a central role in initiating and perpetuating the chronic autoimmune response characteristic of rheumatoid inflammation. Here, you can see the briefly summary about the functions of the key cytokines of Th subsets and their roles in rheumatoid arthritis.

**Role of Cytokines in sepsis**

Sepsis – the most common cause of death in hospitalized patients – affects over 18 million people worldwide and has an expected 1% increase of incidence per year. Recent clinical trials indicate that therapeutic approaches effective in diseases with similar pathogenesis have a modest effect against sepsis. Future clinical trials might define patient populations and therapeutic strategies according to the profile of expression of cytokines.

Infection, trauma, ischemia and severe injury contribute to the pathogenesis of severe sepsis, which is characterized by an overwhelming production of proinflammatory cytokines, such as tumor necrosis factor (TNF), interleukin (IL)-1b and high-mobility group box (HMGB)-1. These cytokines trigger a beneficial inflammatory response that promotes local coagulation to confine tissue damage. However, the excessive production of these proinflammatory cytokines can be even more dangerous than the original stimulus, overcoming the normal regulation of the immune response and producing pathological inflammatory disorders.

**Role of Neutrophil cytokines**

A great body of evidence has accumulated that the human neutrophil is both a target and a source of various proinflammatory cytokines, chemokines, and growth factors, and therefore often exerts its proinflammatory functions through an autoregulatory pathway. Neutrophils are exquisite targets of proinflammatory cytokines, eg, IL-1 and TNF- a, of chemokines such as IL-8, and growth factors such as granulocyte/ monocyte colony stimulating factor (G-CSF and GM-CSF). Indeed, these cytokines have been shown to amplify several functions of neutrophils, including their capacity of adhering to endothelial cells and to pro-duce ROS, as described above; likewise, chemokines act as potent attractants and favor their orientated migration toward the inflammatory site. An important issue is that both cytokines and chemokines may also act as priming agents of neutrophils.

Indeed, neutrophils were long considered to be devoid of transcriptional activity and capable of performing no or little protein synthesis. However, convincing molecular evidence has now been afforded that neutrophils either constitutively or in an inducible manner can synthesize and release a wide range of proinflammatory cytokines, antiinflammatory cytokines, and other cytokines and growth factors (Table 1). The production of cytokines by activated neutrophils is striking in its diversity. However, it remains much lower in its degree than that produced by the mononuclear phagocytes, namely the monocytes. This important dis-crepancy between the two cell types leads to the use of extremely purified neutrophil preparations when studying their cytokine production.

(2)

**When is wound healing referred to as 'impaired'? And why?**

Wound healing is referred to as impaired when factors interfere with one or more phases of wound healing (hemostasis, inflammation, proliferation, and remodeling). For a wound to heal successfully, all four phases must occur in the proper sequence and time frame. Many factors can interfere with one or more phases of this process, thus causing improper or impaired wound healing. This article reviews the recent literature on the most significant factors that affect cutaneous wound healing and the potential cellular and/or molecular mechanisms involved. The factors discussed include oxygenation, infection, age and sex hormones, stress, diabetes, obesity, medications, alcoholism, smoking, and nutrition. A better understanding of the influence of these factors on repair may lead to therapeutics that improve wound healing and resolve impaired wounds.

(3)

**Examine the role of oxidative stress in the development and progression of impaired wound healing**

Oxidation is a basic part of the aerobic life and our metabolism. The body uses oxygen (O2) to produce energy by oxidizing glucose. In the biochemical process involving oxygen, i.e., during oxidation, many highly unstable reactive molecules called free radicals are produced. The free radicals are atoms or molecules having odd number of electrons. Atoms of oxygen or nitrogen having central unpaired electron are called reactive oxygen or nitrogen species.  These species are natural by-products produced by the normal metabolism of oxygen in living organisms. These reactive oxygen species (ROS) are various forms of activated oxygen which causes oxidative damage. They include free radicals such as superoxide anion radicals (O2)−, hydroxyl radicals (OH˙), and non-free radical species such as peroxyl radicals (O2)−2 and singlet oxygen (1O2) which are various forms of activated oxygen generated in the body

In small amounts, these ROS can be beneficial as signal transducers and growth regulators. However, during oxidative stress, large or excessive amounts of these ROS can be produced and may be dangerous and harmful to the body. The free radicals have the potential to damage biological tissues by disrupting cell membranes. This then affects the ability of the cell to transport substances across the membranes. The immune system is vulnerable to oxidative stress. Oxidative stress refers to an imbalance between the production of free radicals and the antioxidant defense system. It is the accumulated damage due to free radical activity in the human body. Excessive amounts of ROS may be a primary cause of biomolecular oxidation. The ROS have the ability to attack numerous molecules in the membrane that contain carbon–carbon double bonds (C〓C). For instance, polyunsaturated fatty acids are particularly sensitive to free radicals. The free radicals are destructive to these molecules including proteins and lipids through oxidation