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16/MHS01/196

ANA 404

HISTOPATHOLOGY

AN ASSIGNMENT SUBMITTED TO THE

DEPARTMENT OF ANATOMY,

FACULTY OF BASIC MEDICAL SCIENCES,

COLLEGE OF MEDICINE AND HEALTH SCIENCES,

AFE BABALOLA UNIVERSITY,ADO-EKITI,

EKITI STATE,NIGERIA

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR

THE AWARD OF THE DEGREE OF

BACHELOR OF SCIENCE (B.Sc)

IN ANATOMY

Question 1

**Write on cytokine signalling and its role in wound healing.**

Cytokines are a broad and loose category of small proteins (~5–20 kDa) important in cell signaling. Cytokines are peptides and cannot cross the lipid bilayer of cells to enter the cytoplasm. Cytokines have been shown to be involved in autocrine, paracrine and endocrine signaling as immunomodulating agents. Their definite distinction from hormones is still part of ongoing research. (John ,2010)

Cytokines include chemokines, interferons, interleukins, lymphokines, and tumour necrosis factors, but generally not hormones or growth factors (despite some overlap in the terminology). Cytokines are produced by a broad range of cells, including immune cells like macrophages, B lymphocytes, T lymphocytes and mast cells, as well as endothelial cells, fibroblasts, and various stromal cells; a given cytokine may be produced by more than one type of cell.

Cytokine signaling is a significant part of the human body homeostasis. Most cytokines are cell-secreted proteins from glial cells in the nervous system and are necessary for intracellular communication. Most cytokines are local regulators that stimulate 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.

Some cytokine signals are not local but rather travel a long distance throughout the body. These cytokines are sometimes classified as hormones. This classification is changing, however, because cytokines are not secreted from glands. Instead, they are secreted from glial cells of the nervous system. These growth hormones are essential for embryonic development. Cytokines bind to receptors on target cells and activate a cascade of intercellular signals. The most common of these pathways is the protein kinase transduction cascade. After the cytokine binds to the receptor embedded in the membrane of the cell, inactive protein kinases are activated by a process known as phosphorylation.

**Cytokine signaling pathway**

Cytokine receptors contain one to three chains, one or more of which generally have limited similarity in the membrane-proximal region (often referred to as box1/box2 motifs). According to the nomenclature the ligand-binding subunit of a receptor is referred to as the alpha chain. Other signal transducing subunits are named beta chains, or gamma chains. All cytokine receptors are associated with one or more members of JAKs, which couple ligand binding to tyrosine phosphorylation of various signaling proteins (STATs) recruited to the receptor complex.

Molecular cloning of cytokine receptors and subsequent structure–function studies has revealed that unlike growth factor receptors, cytokine receptors are devoid of catalytic activity. Nevertheless, interaction of a cytokine with its receptor rapidly induces tyrosine phosphorylation of the receptor and a variety of cellular proteins, suggesting that these receptors transmit their signals through cellular tyrosine kinases. During the past 10–15 years, a large amount of experimental data have accumulated to

indicate that most cytokines transmit their signals via a distinct family of tyrosine kinases termed *Janus* kinases or JAKs.

Cytokine receptors activate many signaling pathways generally by means of phosphotyrosine residues, which are recognized by SH2 domains on the signaling molecules. The STATs contain a carboxy-terminal SH2 domain, an SH3-like domain and several conserved amino-terminal regions, and a conserved region in the middle of the protein that binds DNA. Tyrosine phosphory lation of a carboxy-terminal site mediates homo- or heterodimerization through the SH2 domains, triggering movement to the nucleus and DNA binding.

A native un-liganded receptor in complex with a JAK is in a catalytically inactive latent state. Receptor dimerization/oligomerization due to ligand binding results in the juxtapositioning of the JAKs, which are in the vicinity through either homo- or heterodimeric interactions. The recruitment of JAKs appears to result in their phosphorylation, either via autophosphorylation and/or cross phosphorylation by other JAKs or via other families of tyrosine kinases. This activation is presumed to result in increased JAK activity. Activated JAKs then phosphorylate receptors on target tyrosine sites. The phosphotyrosine sites on the receptors can then serve as docking sites that allow the binding of other SH2-domain containing signaling molecules such as STATs, Src-kinases, protein phosphatases and other adaptor signaling proteins such as Shc, Grb2 and phosphatidylinositol 3-kinase (PI3K).

ROLE IN WOUND HEALING

IL-33 is a member of the IL-1 family of cytokines. Given the right combination of signals and cellular damage, stored IL-33 is released from the cell where it can interact with its receptor ST2, triggering danger-associated responses and act as a cellular “alarmin”. Whilst IL-33/ST2 signalling has been shown to induce potent pro-inflammatory responses that can be detrimental in certain disease states, a dichotomous, protective role of IL-33 in promoting wound healing has also emerged in multiple tissues types. (Millar, O’Donnell et al. 2017)

**Table 1.**Major growth factors and cytokines that participate in wound healing with cell types and their respective roles in both acute and chronic wounds are listed

| **GrowthFactors** | **Cells** | **Acute Wound** | **Function** | **Chronic Wound** |
| --- | --- | --- | --- | --- |
| EGF | PlateletsMacrophagesFibroblasts[44](https://onlinelibrary.wiley.com/doi/full/10.1111/j.1524-475X.2008.00410.x#b44), [45](https://onlinelibrary.wiley.com/doi/full/10.1111/j.1524-475X.2008.00410.x#b45) | Increased levels[46](https://onlinelibrary.wiley.com/doi/full/10.1111/j.1524-475X.2008.00410.x#b46), [47](https://onlinelibrary.wiley.com/doi/full/10.1111/j.1524-475X.2008.00410.x#b47) | Reepithelialization[48](https://onlinelibrary.wiley.com/doi/full/10.1111/j.1524-475X.2008.00410.x#b48) | Decreased levels[51](https://onlinelibrary.wiley.com/doi/full/10.1111/j.1524-475X.2008.00410.x#b51) |
| FGF‐2 | KeratinocytesMast CellsFibroblastsEndothelial cellsSmooth muscle cellsChondrocytes[58](https://onlinelibrary.wiley.com/doi/full/10.1111/j.1524-475X.2008.00410.x#b58), [75](https://onlinelibrary.wiley.com/doi/full/10.1111/j.1524-475X.2008.00410.x#b75), [76](https://onlinelibrary.wiley.com/doi/full/10.1111/j.1524-475X.2008.00410.x#b76) | Increased levels79,81 | Granulation tissue formationReepithelializationMatrix formation and remodeling277 | Decreased levels[52](https://onlinelibrary.wiley.com/doi/full/10.1111/j.1524-475X.2008.00410.x#b52) |
| TGF‐β | PlateletsKeratinocytesMacrophagesLymphocytesFibroblasts[92](https://onlinelibrary.wiley.com/doi/full/10.1111/j.1524-475X.2008.00410.x#b92), [93](https://onlinelibrary.wiley.com/doi/full/10.1111/j.1524-475X.2008.00410.x#b93), [96](https://onlinelibrary.wiley.com/doi/full/10.1111/j.1524-475X.2008.00410.x#b96) | Increased levels[98](https://onlinelibrary.wiley.com/doi/full/10.1111/j.1524-475X.2008.00410.x#b98) | InflammationGranulation tissue formationReepithelializationMatrix formation and remodeling[81](https://onlinelibrary.wiley.com/doi/full/10.1111/j.1524-475X.2008.00410.x#b81), [101](https://onlinelibrary.wiley.com/doi/full/10.1111/j.1524-475X.2008.00410.x#b101), [107](https://onlinelibrary.wiley.com/doi/full/10.1111/j.1524-475X.2008.00410.x#b107) | Decreased levels[52](https://onlinelibrary.wiley.com/doi/full/10.1111/j.1524-475X.2008.00410.x#b52) |
| PDGF | PlateletsKeratinocytesMacrophagesEndothelial cellsFibroblasts[58](https://onlinelibrary.wiley.com/doi/full/10.1111/j.1524-475X.2008.00410.x#b58), [140](https://onlinelibrary.wiley.com/doi/full/10.1111/j.1524-475X.2008.00410.x#b140), [141](https://onlinelibrary.wiley.com/doi/full/10.1111/j.1524-475X.2008.00410.x#b141) | Increased levels[144](https://onlinelibrary.wiley.com/doi/full/10.1111/j.1524-475X.2008.00410.x#b144) | InflammationGranulation tissue formationReepithelializationMatrix formation and remodeling[141](https://onlinelibrary.wiley.com/doi/full/10.1111/j.1524-475X.2008.00410.x#b141), [142](https://onlinelibrary.wiley.com/doi/full/10.1111/j.1524-475X.2008.00410.x#b142), [146](https://onlinelibrary.wiley.com/doi/full/10.1111/j.1524-475X.2008.00410.x#b146), [153](https://onlinelibrary.wiley.com/doi/full/10.1111/j.1524-475X.2008.00410.x#b153) | Decreased levels[52](https://onlinelibrary.wiley.com/doi/full/10.1111/j.1524-475X.2008.00410.x#b52) |

Table from (Barrientos, Stojadinovic et al. 2008)

Question 3

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

Oxidative stress is two sided: Whereas excessive oxidant challenge causes damage to biomolecules, maintenance of a physiological level of oxidant challenge, termed oxidative eustress, is essential for governing life processes through redox signaling.(Sies, Berndt et al. 2017)

Oxidative stress reflects an imbalance between the systemic manifestation of reactive oxygen species and a biological system's ability to readily detoxify the reactive intermediates or to repair the resulting damage. Disturbances in the normal redox state of cells can cause toxic effects through the production of peroxides and free radicals that damage all components of the cell, including proteins, lipids, and DNA. Oxidative stress from oxidative metabolism causes base damage, as well as strand breaks in DNA. Base damage is mostly indirect and caused by reactive oxygen species (ROS) generated, e.g. O2− (superoxide radical), OH (hydroxyl radical) and H2O2 (hydrogen peroxide).(Birnboim 1986)

A large percentage of the population suffers from wound healing abnormalities, in particular aged individuals, patients with diabetes, and those treated with immunosuppressive drugs, chemo- or radiotherapy. The mechanisms underlying the impaired healing response are still poorly understood. Recent studies provided strong evidence for a role of oxidative stress in the pathogenesis of non-healing ulcers. Therefore, it is of major importance to identify and functionally characterize the factors involved in the generation and detoxification of reactive oxygen species (ROS). This will provide the basis for the development of new strategies for therapeutic intervention.(Schäfer and Werner 2008)

Redox-regulated processes are relevant to wound healing. A balance between bioavailable nitric oxide (NO) concentration and a level of oxidative and nitroxidative stress in wounds may be crucial in wound repair. The highly beneficial effect of bioavailable NO is attributed to scavenging of superoxide, which is the main component of oxidative stress. Also, the high level of NO can influence angiogenesis and endothelial/skeletal muscle cell remodeling and proliferation. However, under conditions of excessive and prolonged production of O in wounds, the supplementation of NO can be evolved in significant increase in nitroxidative stress due to production of peroxynitrite (ONOO ) and peroxynitrous acid (ONOOH). ONOOH can trigger a cascade of events leading to the generation of highly reactive and damaging radicals and oxidative species. These species (mainly CO , NO , NO, NO, OH ) can impose significant damage in biological milieu and impair the process of wound healing. Therefore, a general strategy for an acceleration of the wound healing process may include an intervention(s) leading to the decrease in oxidative stress (treatment with antioxidants and/or prevention of O generation by uncoupled constitutive nitric oxide synthase, cNOS) and delivery of NO (treatment with NO donors, cNOS gene therapy).(Soneja, Drews et al. 2005)

The generation of oxidative stress in wound maybe closely relate to inflammatory reaction. In the inflammatory stage of wound healing, oxidative stress induced the damage of tissue because of the imbalance of prooxidant and antioxidant. Conclusion: Oxidative stress should be considered in the inflammatory processes of wound healing and treatment of chronic wound. The treatment of antioxidation is a good strategy. If it is used in wound healing in time, it can be good to wound healing.( Yang, G.-Z & Wang *et al* 2007)

Molecular oxygen plays a central role in the pathogenesis and therapy of chronic wounds. When reactive oxygen species are overproduced, oxidative stress results, with detrimental cytotoxic effects causing delayed wound healing. Therefore, elimination of reactive oxygen species could be an important strategy to improve healing of chronic wounds. Currently first therapeutic strategies targeting reactive oxygen species by antioxidants are being introduced into the treatment of chronic wounds.(Dissemond, Goos et al. 2002)

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