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Assignment Title: WOUND HEALING

Course Title: Introduction to Histopathology

Course Code: ANA 404

Question 1.

Write on cytokine signalling and its role in wound healing.

Answer:

1-In wound healing, a variety of mediators have been identified throughout the years. The mediators discussed here comprise growth factors, cytokines and chemokines. These mediators act via multiple (specific) receptors to facilitate wound closure. As research in the last years has led to many new findings, there is a need to give an overview on what is known, and on what might possibly play a role as a molecular target for future wound therapy.

Wound healing is an integrated and complex process involving a large number of regulatory molecules, including pro inflammatory cytokines and growth factors, and an orchestrated tissue response. Dysregulation in cytokine or growth factor expression dramatically alters the normal

wound healing process, and blocking the inappropriate production of specific pro inflammatory cytokines or supplementing the milieu with increased quantities of growth factors has demonstrated the central role played by these mediators. Both protein-based and DNA-based (gene transfer) therapies are currently under clinical development as tools to improve the healing process. Although there has been some success with these approaches in both experimental models and in patients, only through a better understanding of the complexity and diversity of the wound healing process, as well as an improved comprehension of the time-dependent and concentration-dependent responses to individual pro inflammatory cytokines or growth factors, will further development in the therapeutic treatment of healing wounds be attained.

Role of cytokines in wound healing

Cytokines are critical to a myriad of fundamental homeostatic and pathophysiological processes such as fever, wound healing, inflammation, tissue repair and fibrosis. They play important roles in regulating cell function such as proliferation, migration, and matrix synthesis. It is the balance or the net effect of the complex interplay between these mediators, which appears to play a major role in regulating the initiation, progression and resolution of wounds. Wound healing involves a

complex process including induction of acute inflammation by the initial injury, followed by parenchymal and mesenchymal cell proliferation, migration, and activation with production and deposition of extracellular matrix. Failure to resolve or abnormal wound healing results in fibrosis. The latter process involves similar cellular interactions via complex cytokine networks, which result in extensive remodeling with heightened extracellular matrix production and their abnormal deposition in the tissue. Various cytokines, both promoting and inhibiting fibrogenesis, have been implicated in the pathogenesis of fibrosis and wound healing. Recent progress in understanding the mechanisms underlying the pathogenesis of fibrosis leads us to expect that inhibitors of pro-fibrogenic cytokines and growth factors may be useful as novel therapeutic agents in controlling undesirable fibrosis. In this review, the role of cytokines in wound healing and fibrosis will be summarized and highlighted with more detailed discussion reserved for the possible points of therapeutic attack in pulmonary fibrosis. In this review, the major cytokines that are in current clinical use will be also discussed. In addition, advances in the application of novel cytokines and anti-cytokines for accelerating wound healing and attenuating fibrosis both at the experimental and the clinical trial levels will be discussed.

Question 2.

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

In **wounds** where oxygenation is not restored, **healing** is **impaired**. Temporary hypoxia after **injury** triggers **wound healing**, but prolonged or chronic hypoxia delays **wound healing**(Bishop, 2008; Rodriguez *et al*., 2008). In acute **wounds**, hypoxia serves as a signal that stimulates many aspects of the **wound-healing** process.

The wound-healing process consists of four highly integrated and overlapping phases: hemostasis, inflammation, proliferation, and tissue remodeling or resolution (Gosain and DiPietro, 2004). These phases and their bio physiological functions must occur in the proper sequence, at a specific time, and continue for a specific duration at an optimal intensity (Table 1; Mathieu et al., 2006). There are many factors that can affect wound healing which interfere with one or more phases in this process, thus causing improper or impaired tissue repair.

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

Oxidative stress plays an important role in the development of all kinds of diseases. Currently, to demonstrate the relationship between oxidative stress and wound healing.

Oxidative stress is a condition which is the imbalance of pro oxidant and antioxidants, abnormally high levels of free radicals and/or the decline of antioxidant defense mechanisms. Excessive oxidative stress could lead to damage of tissue, which played an important role in the development of many kinds of diseases.

1-Free radical relatively increased during oxidative stress. Normally free radical was necessary for defense of organism and there was a balance between its produce and scavenge.

2- Oxidative stress was closely associated with reactive oxygen species. Reactive oxygen species could play an important role in physiology in some extent, also it led to damage of tissue or cells when organism could not defend excessive reactive oxygen species.

43-Excessive reactive oxygen species and its degradation product generated during the healing of cutaneous wound. Oxidation increased in acute and chronic wound. After wound oxidative stress generates, antioxidation increased in chronic wound, which indirectly reflected the increasing of oxidative stress and compensation and defense of tissue to oxidative stress.

4-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 pro-oxidant and antioxidant. Conclusion: Oxidative stress should be considered in the inflammatory processes of wound healing and treatment of chronic wound. The treatment of antioxidants on is a good strategy. If it is used in wound healing in time, it can be good to wound healing.

Oxidative stress is a phenomenon caused by an imbalance between production and accumulation of oxygen reactive species (ROS) in cells and tissues and the ability of a biological system to detoxify these reactive products. ROS can play, and in fact they do it, several physiological roles (i.e., cell signaling), and they are normally generated as by-products of oxygen metabolism; despite this, environmental

stressors (i.e., UV, ionizing radiations, pollutants, and heavy metals) and xenobiotics (i.e., antiblastic drugs) contribute to greatly increase ROS production, therefore causing the imbalance that leads to cell and tissue damage (oxidative stress). Several antioxidants have been exploited in recent years for their actual or supposed beneficial effect against oxidative stress, such as vitamin E, flavonoids, and polyphenols. While we tend to describe oxidative stress just as harmful for human body, it is true as well that it is exploited as a therapeutic approach to treat clinical conditions such as cancer, with a certain degree of clinical success

If not strictly controlled, oxidative stress can be responsible for the induction of several diseases, both chronic and degenerative, as well as speeding up body aging process and cause acute pathologies (i.e., trauma and stroke).

Cancer and Oxidative Stress

Cancer onset in humans is a complex process, which requires both cellular and molecular alterations mediated by endogenous and/or exogenous triggers. It is already well known that oxidative DNA damage is one of those stimuli responsible for cancer development [valko.M,2004)]. Cancer can be driven and/or promoted by chromosomal abnormalities and oncogene activation determined by oxidative stress. Hydrolyzed DNA bases are common by-products of DNA oxidation and

are considered one of the most relevant events in chemical carcinogenesis [Halliwell B,2007]. The formation of such kind of adducts impairs normal cell growth by altering the physiological transcriptomic profile and causing gene mutations. Oxidative stress can also cause a variegated amount of modifications against DNA structure, for example, base and sugar lesions, DNA-protein cross-links, strand breaks, and base-free sites. For instance, tobacco smoking, environmental pollutants, and chronic inflammation are sources of oxidative DNA damage that could contribute to tumor onset. Oxidative stress resulting from lifestyle reasons can also play an important role in cancer development, as suggested by the strong correlation between dietary fat consumption (a factor that exposes the organism at greater risk of lipid peroxidation) and death rates from different types of cancer [Young I.2001]

. Cardiovascular Disease and Oxidative Stress

Cardiovascular diseases (CVDs) are clinical entities with a multifactorial etiology, generally associated with a very large amount of risk factors, the most broadly recognized of which are hypercholesterolaemia, hypertension, smoking habit, diabetes, unbalanced diet, stress, and sedentary life [Bahorun T.,2006] During the last years, research data pointed out that oxidative stress should be considered either a primary or

a secondary cause for many CVDs [. Pacher P,2007] Oxidative stress acts mainly as a trigger of atherosclerosis. It is well known that atheromatous plaque formation results from an early endothelial inflammation, which in turn leads to ROS generation by macrophages recruited in situ. Circulating LDL are then oxidized by reactive oxygen species, thus leading to foam cell formation and lipid accumulation. The result of these events is the formation of an atherosclerotic plaque. Both in vivo and ex vivo studies provided evidences supporting the role of oxidative stress in atherosclerosis, ischemia, hypertension, cardiomyopathy, cardiac hypertrophy, and congestive heart failure [Ceriello A, *et al,*2008].

Neurological Disease and Oxidative Stress

Oxidative stress has been linked to several neurological diseases (i.e., Parkinson's disease, Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), multiple sclerosis, depression, and memory loss) [Halliwell B,2001]. In AD, several experimental and clinical researches showed that oxidative damage plays a pivotal role in neuron loss and progression to dementia . β-amyloid, a toxic peptide often found present in AD patients' brain, is produced by free radical action and it is known to be at least in part responsible for neurodegeneration observed during AD onset and progression [Christen Y,2000].

Respiratory Disease and Oxidative Stress

Several researches pointed out that lung diseases such as asthma and chronic obstructive pulmonary disease (COPD), determined by systemic and local chronic inflammation, are linked to oxidative stress. Oxidants are known to enhance inflammation via the activation of different kinases involving pathways and transcription factors like NF-kappa B and AP-1 [MacNee W.2001].

Rheumatoid Arthritis and Oxidative Stress

Rheumatoid arthritis is a chronic inflammatory disorder affecting the joints and surrounding tissues, characterized by macrophages and activated T cell infiltration [Mahajan A,2004] Free radicals at the site of inflammation play a relevant role in both initiation and progression of this syndrome, as demonstrated by the increased isoprostane and prostaglandin levels in synovial fluid of affected patients [Magajan,A,2004].

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