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

**CYTOKINE SIGNALLING**

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 (Sino biological).

The immune system depends on cytokine signalling 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 signalling helps 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 (Sino biological).

**Cytokine signalling 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 Janus kinases (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 phosphorylation of a carboxy-terminal site mediates homo- or heterodimerization through the SH2 domains, triggering movement to the nucleus and DNA binding.

Its role in wound healing

1. Regulates/induces collagen synthesis and degradation induces polymorphonuclear cell (PMN)margination and cytotoxicity, Provides some metabolic substrates and Increases vascular permeability and homeostasis (Rumalla *et al*., 2001 ; Feiken *et al*., 1995 ; Dinarello and Moldawer, 2001).
2. Induces PMN and macrophage activation and cytotoxicity, Induces collagenase activity, as well as preventing collagen synthesis and Crosslinking (Rumalla *et al*., 2001; Dinarello and Moldawer, 2001).
3. Induces keratinocyte, neutrophil, and fibroblast chemotaxis, as well as neutrophil activation Induces collagen synthesis and degradation Enhances endothelial cell proinflammatory cytokine expression (Rumalla et al., 2001; Dinarello and Moldawer, 2001 ; Loppnow *et al.,* 1998 ;Fong *et al.,*1989).
4. Upregulates fibroblast metabolism and increases fibroblast infiltration (Rumalla *et al*., 2001; Dinarello and Moldawer, 2001).
5. Induces fibroblast proliferation , Enhances proteoglycan and collagen synthesis Inhibits TNF-, IL-1, and IL-6 expression (Rumalla *et al*., 2001; Dinarello and Moldawer, 2001).
6. Up-regulates arginase expression Induces fibroblast proliferation Enhances hepatic acute-phase protein synthesis Protects endothelial cells from ischemic injury (Rumalla *et al*., 2001; Dinarello and Moldawer, 2001).
7. Increases PMN and macrophage activation and chemotaxis Induces keratinocyte maturation and margination (Rumalla *et al*., 2001; Dinarello and Moldawer, 2001).
8. **When is wound healing referred to as impaired? And why?**

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.

A wound is a disruption of the normal structure and function of the skin and underlying soft tissue (Orr and Taylor, 2003). Acute wounds in normal, healthy individuals heal through an orderly sequence of physiologic events.

The overlapping intricacy of the wound healing pathway serves to prevent a single primary factor from disrupting the process. As examples, local tissue ischemia and neuropathy can impair chemotaxis during the hemostasis and inflammatory stages, tissue necrosis and infection alter the balance of inflammation and compete for oxygen, and uncontrolled periwound edema and wound instability disrupt myofibroblast activity, collagen deposition, and cross-linking. Impaired wound healing often occurs in the setting of multiple, smaller contributing issues to stall the healing process; however, infection or ischemia alone can impair wound healing.

When the healing process is stalled, a chronic wound may develop, and this is more likely to occur in patients with underlying medical disorders. Chronic ulceration commonly affects the lower extremities with a prevalence that ranges between 0.18 and 1.3 percent in the adult population ( Lipscomb and Ling, 2003 ; Diegelmann and Evans,2004 ; Leibovich and Ross, 1975 ; Mor-Vaknin *et al*.,2003 ). The most common nonhealing wounds affecting the lower extremities are associated with chronic venous insufficiency, peripheral artery disease, and diabetes mellitus (Orr and Taylor, 2003 ; Lipscomb and Ling, 2003 ; Armstrong *et al*.,1998 ; Morbach *et al., 2012* ; Mills *et al*., 2014).

Some factors that causes impaired wound healing; Diabetes, Smoking, Alcohol consumption, Malnutrition,stress, etc



The effects of stress on wound healing. Stress-impaired wound healing is mediated primarily through the hypothalamic-pituitary-adrenal, sympathetic-adrenal medullary axes, and psychological-response-induced unhealthy behaviors (Guo and DiPietro, 2010).

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

Oxidative stress is defined in general as excess formation and or insufficient removal of highly reactive molecules such as reactive oxygen species (ROS) and reactive nitrogen species (RNS) (Maritim et al., 2003).

Oxidative processes are fundamental to biological reactions and in any living organism there is a constant production of what are collectively referred to as reactive oxygen species (ROS), these includes free radicals , atoms, or ,molecules containing one or more unpaired electron. However, oxidative stress also has a useful role in physiologic adaptation and in the regulation of intracellular signal transduction. Therefore, a more useful definition of oxidative stress may be “a state where oxidative force exceeds the antioxidant systems due to loss of the balance between them” (Yoshikawa and Naito, 2000). Oxidative stress occurs when there is either increased production of oxidative species or when there is a depletion of antioxidants (Vervaart and Knight, 1996)

Oxidative stress also contributes to tissue injury following irradiation and hyperoxia, as well as in diabetes.

The reactive species produced in oxidative stress can cause direct damage to the DNA and are therefore mutagenic, and it may also suppress apoptosis and promote proliferation, invasiveness and metastasis (Halliwell, 2007). Infection by Helicobacter pylori which increases the production of reactive oxygen and nitrogen species in human stomach is also thought to be important in the development of gastric cancer (Handa *et* al., 2011)

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