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LEVEL: 400

DEPARTMENT: ANATOMY

ANA 404 ASSIGNMENT

COURSE TITLE: INTRODUCTION TO HISTOPATHOLOGY

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QUESYIONS: Write on cytokine signaling and its role in wound healing.

When is wound healing referred to as ‘impaired’? And why?

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

CYTOKINE SIGNALLING AND ITS ROLE IN WOUND HEALING

The term cytokine (Greek *–cyto*, cell, and *–kinos*, movement) was proposed by Stanley Cohen in 1974 and refers to peptides, proteins, and glycoproteins which play a role in controlling the survival/death of cells, their growth and differentiation as well as the effector functions in tissues and immune cells. cytokines are important molecules for cell communication. . (Gregory A. *et.al*., 2013)

Intracrine actions: intracellular action by regulation of intracellular events within the cytoplasm and/or nucleus.

Autocrine: action produced within the cell through surface cell receptors.

Intercrine: communication between cells. This type of cell interaction can be classified into:

- Paracrine: signaling produced by soluble mediators through neighboring cells.
- Matricrine: cytokines are immobilized in the extracellular matrix (ECM) by its binding to proteoglycans, and they are then stored in an inactive form. These cytokines will be released by the action of proteases such as Metalloproteinases (MMPs) by a mechanism know as Protease-triggered

matricrine (PTM). Glycocalyx, which is made of glycoprotein carbohydrate-motifs with proteoglycan on its surface, could play the same role.

- Cytokine secretion by exchange of membrane fragments between cells through mechanisms such as trogocytosis, formation of tunneling nanotubes (TNTs) and release, secretion, and transportation of microvesicles (MVs)/Exosomes.
- Juxtacrine: neighboring adjacent cells send signals through membrane-anchored mediators. The classic example is the action of the endothelium on smooth muscle of the tunica media of certain vessels. Some cytokines have the ability to bind to extracellular matrix soluble proteoglycans or to proteoglycan-cell surfaces (for example, CD44, Glypicans, Syndecans, Betaglycan/TGFBR3, inter alia), where this mechanism serves as a reservoir, or as an enabler of these mediators to act on specific receptors in a juxtracrine manner.
- Endocrine: this refers to the distal or systemic action which depends on secreted cytokine and its transportation within the blood. (Gregory A. *et.al*., 2013)

Proinflammatory cytokines, particularly IL-1 and interleukin-6, and TNF-α are up-regulated during the inflammatory phase of wound healing (Singer

AJ and Clark RA, 1999). IL-1 is produced by neutrophils, monocytes, macrophages, and keratinocytes. Upon wound healing it is immediately released by keratinocytes. In addition to having a paracrine effect, it also works in an autocrine fashion increasing keratinocyte migration and proliferation (Raja *et.al.*, 2007).

IL-1 induces the expression of K6 and K16 in migrating keratinocytes.(Freedberg *et.al*., 2001) In addition, IL-1 activates fibroblasts and increases the secretion of FGF-7 (Stefan B. *et.al*., 2008)

- IL-6 is produced by neutrophils and monocytes and has been shown to be important in initiating the healing response. Its expression is increased after wounding and tends to persist in older wounds.(Greorg *et.al.*, 2000). It has a mitogenic and proliferative effect on keratinocytes and is chemoattractive to neutrophils (Stefan B. *et.al*., 2008)

- Much like IL-1, TNF-α can induce the production of FGF-7, suggesting that it can indirectly promote reepithelialization (Brauchie M.*et.al*., 1994). Alone, TNF-α has been shown to inhibit wound reepithelialization. The effects of exogenous TNF-α are dependent on concentration and duration of exposure emphasizing the importance of balancing the proinflammatory signals controlling wound healing. TNF-α, at low levels, can promote wound

healing by indirectly stimulating inflammation and increasing macrophage produced growth factors. However, at higher levels, especially for prolonged periods of time, TNF-α has a detrimental effect on healing. TNF-α suppresses synthesis of ECM proteins and TIMPs while increasing synthesis of MMPs (MMP-1, MMP-2, MMP-3, MMP-9, MMP-13, and MT1-MMP) (Agren *et.al.,* 1992)In addition, elevated levels of IL-1β have a similar response to that of TNF-α. Both TNF-α and IL-1β have been shown to perpetuate each others expression and therefore amplify this signal (Mast and Schultz 1996).

Levels of TNF-α and IL-1β are elevated in chronic wounds (Singer AJ and Clark RA, 1999). In addition, infection that is common in chronic wounds further contributes to prolonged inflammation. Furthermore, nonhealing wounds also exhibit elevated levels of interstitial collagenases, gelatinases, and stromelysins that have been shown to be induced by TNF-α and IL-1β. It has, therefore, been hypothesized that in chronic wounds, chronic inflammation causes inflammatory cells to secrete TNF-α and IL-1β that synergistically increase production of MMPs while reducing synthesis of TIMPs. It is increased MMP activity that degrades the ECM inhibiting cell migration and collagen deposition. MMPs also break down growth factors and their target cell receptors (Stefan B. *et.al*., 2008).

When is wound healing referred to as impaired and why?

The wound-healing process consists of four highly integrated and overlapping phases: hemostasis, inflammation, proliferation, and tissue remodeling or resolution (Gosain and DiPietro, 2004).Wounds that exhibit impaired healing, including delayed acute wounds and chronic wounds, generally have failed to progress through the normal stages of healing. Such wounds frequently enter a state of pathologic inflammation due to a postponed, incomplete, or uncoordinated healing process (S. Guo and L.A di pietro, 2010).

Multiple factors can cause impaired wound healing by affecting one or more phases of the process and are categorized into local and systemic factors. The influences of these factors are not mutually exclusive. Single or multiple factors may play a role in any one or more individual phases, contributing to the overall outcome of the healing process. For example, Oxygen which is important for cell metabolism, especially energy production by means of ATP, and is critical for nearly all wound-healing processes and lack of oxygen can cause impaired healing. Due to vascular disruption and high oxygen consumption by metabolically active cells, the microenvironment of the early wound is depleted of oxygen and is quite hypoxic. Several systemic conditions, including advancing age and diabetes, can

create impaired vascular flow, thus setting the stage for poor tissue oxygenation. In the context of healing, this overlay of poor perfusion creates a hypoxic wound (Tandara and Mustoe, 2004).

In wounds where oxygenation is not restored, healing is impaired.

In other words, why wound healing gets impaired is because of some local and systemic factors that may be present when a person has a wound.

Oxidative stress in the development and progression of impaired wound healing.

During the process of wound healing, various inflammatory cells like neutrophils, macrophages (phagocytes), endothelial cells and fibroblasts produce superoxide. Activated neutrophils and macrophages produce large amounts of superoxide and its derivatives via the phagocytic isoform of NADPH oxidases. Thrombin, PDGF and tissue necrosis factor (TNF-) stimulate release of superoxide from endothelial cells whereas interleukin (IL-1), TNF- and platelet activation factor (PAF) stimulate superoxide release from fibroblasts (Droge, 2002). Superoxide is the main component of ROS. Superoxide can rapidly dismutate to H2O2 and O2 by constitutive and inducible superoxide dismutases (SOD). H2O2 can also be detoxified by catalases to H2O and O2.

Various damaging effects of reactive oxygen species/ reactive nitrogen species (ROS/RNS) which brings about oxidative stress can be seen in chronic wounds. An overproduction of ROS/RNS results in inactivation of epidermal enzymatic antioxidants, despite increased enzymatic antioxidant expression in the wound and significantly depletes nonenzymatic antioxidant levels in wound tissues. This results in sustained elevation and survival of ROS/RNS in chronic wounds (James *et.al.,* 2001) . Sustained oxidative and nitroxidative stress prolongs the inflammation in chronic wounds as both ROS and RNS stimulate neutrophil and macrophage chemotaxis and migration and also induce the expression of adhesion molecules in the capillaries. Direct cellular effects of ROS/RNS include impaired migratory, proliferative and extracellular matrix (ECM) synthetic properties of dermal fibroblasts and keratinocytes (moseley *et.al.,* 2004).

High oxidative stress can inhibit the migration and proliferation of keratinocytes, especially hydrogen peroxide when given in micromolar concentrations which has been shown to inhibit these processes (Goel *et.al.,* 1997). Oxidative stress can be implicated to increase protease activity by increasing syndecan expression (Kemp *et.al*., 2003).

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