Cytokine and Growth Factor Reviews xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Cytokine and Growth Factor Reviews

journal homepage: www.elsevier.com/locate/cytogfr

The JAK/STAT signaling pathway and photobiomodulation in chronic wound healing

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ARTICLE INFO

Keywords:
JAK/STAT
Wound healing
Cellular signals
Cytokines
Growth factors
Photobiomodulation

ABSTRACT

Wound healing is a physiological process that occurs in overlapping phases namely hemostasis, inflammation, proliferation, and remodeling. Chronic wounds fail to proceed through these reparative processes to achieve the functional integrity within the expected time. Wound healing relies upon growth factors and cytokines for the precise and accurate regulation of cellular responses. These are achieved through the use of complex growth factor/cytokine induced signaling pathways. The Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway transmits extracellular signals to the nucleus for the transcription of genes involved in proliferation and differentiation, to name but a few. Photobiomodulation (PBM) is an emerging area of interest within the scientific community and researchers are currently exploring its underlying mechanism and the associated signaling pathways involved. PBM is a light based therapy making use of low powered lasers or light emitting diodes (LEDs) to enhance tissue repair, and reduce pain and inflammation. Current conventional treatments for chronic wounds are frequently associated with failure and have limited therapeutic efficacy. Thus there is a need for efficient wound healing interventions and the identification and development of new treatments is required. In this review we summarize the involvement of JAK/STAT signaling and PBM in chronic wounds.

1. Background

Following tissue injury, a network of events starting with clot formation and going through inflammation, tissue regeneration and remodeling, and ending up with the reconstruction of the wound is initiated [1]. The repair process is sparked within seconds after wounding, usually by the release of cytokines, growth factors, and low molecular weight serum proteins released from the injured blood vessels and platelets [2]. Chronic wounds develop when acute wounds fail to progress through the normal stages of healing and these wounds include, but not limited to; venous leg [3], pressure [4] and diabetic [5] ulcers. Several factors contribute to the development of chronic wounds, and they share some common characteristics that include increased levels of pro-inflammatory cytokines, senescent non-responsive cells, reactive oxygen species (ROS), increased proteases, persistent infection, reduced cell and growth factor response, and stem cell dysfunction or deficiency [6]. Chronic wounds may also be attributed to deregulated cellular cytokine induced pathways [7].

The Janus kinase (JAK) signal transducer and activator of transcription (STAT) pathway is considered as one of the most important signaling pathways in cells that transduce signals for hormones, growth factors, and cytokines [8] and is involved in wound healing. It regulates cell proliferation, migration, differentiation and apoptosis [9]. However, this pathway requires intense cell control and its deregulation promotes chronic inflammation. The pathway is controlled by several mechanisms including tyrosine phosphatase, receptor antagonists, internalization and degradation of signal adaptor molecules, and inhibitors including suppressor of cytokine signaling (SOCS) proteins and

Abbreviations: AP, activator protein; ATP, adenosine triphosphate; Ca^{2+}, calcium ions; cAMP, cyclic adenosine monophosphate; Cox, cytochrome c oxidase; Cu, copper; Cyto c, cytochrome c; DNA, deoxyribonucleic acid; ECM, extracellular matrix; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; ERK, extracellular receptor kinase; Fe, iron; FGF, fibroblast growth factor; H, hydrogen; H_2O, water; H_2O_2, hydrogen peroxide; IkB, inhibitor of kappa B; IL, interleukins; JAK, janus kinase; JNK, c-Jun N-terminal kinase; K^+, potassium ions; LLLT, low level laser therapy; LEDs, light emitting diodes; MAPK, mitogen-activated protein kinase; MMPs, matrix metalloproteinases; mRNA, messenger ribonucleic acid; NIR, near-infrared; NO, nitric oxide; NPCs, neural progenitor cells; NPWT, negative pressure wound therapy; NSAIDs, non-steroidal anti-inflammatory drugs; NSCs, neural stem cells; NFkB, nuclear factor kappa B; OSM, oncostatin M; Ox, oxidised; PBM, photobiomodulation; PCa, prostate cancers; PDGF, platelet derived growth factor; pH, potential of hydrogen; PIAS, protein inhibitors of activated STATs; Red, reduced; RNA, ribonucleic acid; ROS, reactive oxygen species; SCI, spinal cord injury; SOCS, suppressor of cytokine signaling; SP, surfactant protein; STAT, signal transducers and activators of transcription; TGF-β, transforming growth factor beta; TNF, tumor necrosis factor; TIMP, tissue inhibitors of metalloproteinase; TYK2, tyrosine kinase 2; Upd, unpaired; VEGF, vascular endothelial growth factor; Wg, wingless

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http://dx.doi.org/10.1016/j.cytogfr.2017.10.001
Received 5 September 2017; Received in revised form 29 September 2017; Accepted 2 October 2017

protein inhibitors of activated STATs (PIAS) [10].

Current treatments for chronic wounds are frequently challenging, lengthy, costly and associated with failure to heal and relapse, and is associated with a financial burden and decreased patient lifestyle. The complexity of chronic wounds have a long-term impact on the patient's quality of life, morbidity and mortality [11]. The acceleration of wound repair reduces morbidity including scar formation, and this results in reduced financial expenses and the improvement in patient's quality of life [12]. The use of antibiotics for bacterial infection, dressings to supplement the wound matrix, topical and intradermal delivery of growth factors, skin grafting and bioengineered skin equivalents and negative pressure wound therapy (NPWT) are some of the treatments currently used for chronic wounds [4]. Most of the successful treatment choices for chronic wounds focus on identifying and managing the contributing factors present in each patient [12].

Studies suggest that photobiomodulation (PBM), otherwise frequently referred to as low level laser therapy (LLLT), another treatment used for chronic wound healing, enhances tissue repair. However, the absence of strong evidence to this effect restricts its clinical use [13]. PBM involves the application of non-ionizing optical radiation, typically from lasers and light emitting diodes (LEDs), in the visible red and near-infrared (NIR) electromagnetic spectrum. The photon energy is absorbed by endogenous chromophores within the cells which produce photochemical events leading to physiological changes and therapeutic effects, including the release of growth factors [14]. *In vitro*, PBM stimulates cellular migration, proliferation, viability and growth factor production in wounded cells. However, the signaling pathways involved in these observations are not well understood. More investigations to understand the cellular and molecular mechanisms, including pathways involved in the repair process following PBM, is crucial for the generation of therapeutic modalities for chronic wound healing complications. This review focus on the mechanisms of the JAK/STAT signaling pathway and the effects of PBM in chronic wound healing.

2. Normal wound healing

Wound healing is aimed at reversing the loss of structural integrity and is achieved through four spatial overlapping phases: hemostasis, inflammation, proliferation, and remodeling. Platelets, keratinocytes, immune cells, micro-vascular cells, and fibroblasts play important roles to restore tissue integrity [4,15]. The repair process is initiated within seconds following injury with the formation of a clot. Besides its control against invading micro-organisms and blood loss, the clot provides a matrix for infiltrating cells and become a reservoir for growth factors that regulate the later stages of wound healing. Inflammatory cells migrate into and invade the wound matrix promoting the inflammatory response. They produce a variety of ROS and proteinases used in defense against invading micro-organisms, followed by phagocytic activity on cellular debris [16]. These inflammatory cells are also a source of cytokines and growth factors that regulate cell proliferation and remodeling of the wound. The inflammatory phase typically overlaps with the proliferation phase of wound healing.

The proliferative phase is characterized by re-epithelialization. The proliferation and migration of fibroblast cells into the wound matrix is essential. New blood vessels are formed within the wound through angiogenesis, and at the same time nerves sprout from the edges of the wound. A large number of growth factors and cytokines including transforming growth factor beta (TGF-β), platelet derived growth factor (PDGF), epidermal growth factor (EGF), fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), and several pro-inflammatory cytokines, including interleukins (IL) play critical roles during the repair process [17,18]. The mobilization for re-epithelialization is regulated by family members of EGF and FGF. In the final phase of wound healing, remodeling, there is development of mechanically incomplete scar tissue which lacks normal skin appendages like hair follicles, sweat glands and sebaceous glands [4,19,20].

The co-ordination by growth factors, cytokines and low molecular weight serum proteins released into the wound matrix from platelets and the serum of severed blood vessels induce signals that promote cell proliferation, migration and differentiation. These downstream events are achieved through complex growth factor/cytokine induced signaling pathways. Chronic wounds develop due to a variety of factors including the underlying pathophysiological mechanisms that interfere with the response to injury. Co-morbidities such as obesity, diabetes and malnutrition; medications including steroids and non-steroidal anti-inflammatory drugs (NSAIDs); cancer treatments in the form of chemotherapy and radiation; and controversial habits such as smoking and alcohol abuse may contribute to the development of chronic wounds [8].

3. Chronic wound healing

Chronic wounds begin as small traumatic injuries that would normally heal within a few days, however due to dysfunctional healing pathways, specifically in patients with underlying pathologies, including diabetes, these wounds fail to heal. Chronic wounds are defined as wounds which have failed to proceed through the normal reparative process to achieve functional tissue integrity within an expected period, usually 3 months [21]. Often, these wounds stall and become stuck in the inflammatory phase, with failure to progress. Approximately 1–2% of the world's population has or will experience chronic wounds, a prevalence which is expected to dramatically increase over time due to an aging population and the increased occurrence of various health-related disorders, such as vascular diseases and diabetes [22]. Chronic, non-healing wounds embody major global clinical and surgical challenges and cost governments and health care systems millions of dollars annually. Out of 22 skin diseases analyzed, non-healing chronic ulcers and wounds were responsible for US$9.7 billion of the US$29.1 billion total spent in the United States alone in 2004 [23,24]. It is a well-known fact that non-healing ulcers located in the lower extremities of diabetic patients are responsible for a large percentage of amputations, and have a considerable effect on the patient's quality of life. Roughly 90% of all non-traumatic amputations are due to the presence of underlying pathologic disorders such as diabetes [25].

Despite differences in etiology, chronic wounds share common features, including increased levels of pro-inflammatory cytokines, proteases, ROS, and senescent cells, as well as the existence of persistent infection, and a deficiency of stem cells that are often also dysfunctional [6]. The impairment of wound healing is also associated with an altered pattern of cytokines and growth factors, evidenced by reduced bio-availability in the chronic wound milieu. The development of impaired wound healing is due to combined extrinsic and intrinsic wound factors. Neuropathy, which renders patients insensitive to repeated trauma or mechanical stress applied to the skin, and ischemia, due to macro- and micro-vascular diseases, represent some of the extrinsic factors of impaired wound healing.

The chronic wound bed is also known to contain many proteases which are thought to be in part responsible for the inability of ulcers to heal [26]. Matrix metalloproteinases (MMPs) determine and coordinate wound remodeling and are regulated by tissue inhibitors of metalloproteinase (TIMP). Literature reports on the high levels of MMPs and decreased levels of TIMPs in chronic wounds, and that cells within these wounds undergo functional changes including impaired proliferation and migration. Senescent fibroblast cells from chronic ulcers have a reduced efficiency for proliferation, differentiation, migration, cell membrane transport, signal transduction, and growth factor production [27]. Therefore, adjunctive treatments that would activate this critical ratio favoring the non-senescent cell line can enhance the healing rate [28]. Literature elucidates that a decreased response to growth factors including EGF, bFGF, and PDGF, appears not to be due to the reduced number of cellular receptors, but rather due to non-functional intracellular signaling [29,30]. Therefore, even the application of