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

exogenous growth factors to chronic wounds may be insufficient to induce cell proliferation and wound closure.

Chronic wound management frequently involves the debridement of necrotic tissue and application of a variety of topical growth factor gels, wound dressings, autologous skin grafting and skin equivalents. Most of the therapeutic methods available use biochemical agents that target the extracellular matrix (ECM) and growth factors/receptors. Although several other methods with different specific targets are used, the selection of these methods is dependent on the service providers' skill of wound assessment [31,32].

4. The JAK/STAT signaling pathway

The JAK/STAT signaling pathway is the primary signaling mechanism for a wide array of cytokines and growth factors. It consists of four JAK (JAK1, JAK2, JAK3 and Tyk2) and seven STAT (STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6) family members. This pathway is involved in the transmission of external cellular signals via specific receptors to the nucleus. The binding of a ligand to its receptor induces the phosphorylation of JAK and subsequent phosphorylation of the latent cytoplasmic STAT which is then translocated to the nucleus where it attaches to the promoter region on DNA for translation of the inducing signals. Many JAK/STAT ligands, including different growth factors, cytokines and chemokines, are involved in stimulating cell growth and development, proliferation, migration, cell survival and immunity [33], and these biological processes are precisely controlled essential cellular mechanisms for normal wound healing, embryonic development and immune response.

5. Role of JAK/STAT in chronic wound healing

Cytokines and growth factors play a critical role in the wound repair process by initiating the activation of numerous signaling pathways, including JAK/STAT. It involves cells such as fibroblasts, endothelial cells, keratinocytes, and macrophages. Pathological conditions including inflammatory diseases, and the development of chronic wounds, may arise due to the disruption of its regulation [34].

Wound repair experiments conducted in Drosophila showed that JAK/STAT signaling was activated and promoted regenerative cell proliferation in co-operation with Wingless (Wg) signaling [35]. Beigel *et al.,* [36] showed that oncostatin M (OSM), a member of the IL-6 cytokine family, induced tyrosine phosphorylation of STAT1 and STAT3 in a time-dependent manner in wounded intestinal epithelial cells, and reached a maximum after 10–30 min. They also found a 2-fold increase in STAT1 and STAT3, a 1.5-fold increase in STAT6, and a 16-fold increase in STAT5B. Up-regulation of the STAT genes, and activation of the STAT proteins, was directly linked to wound healing in intestinal epithelial cells in the same experimental models. Furthermore, the proliferation and differentiation of neural stem cells (NSCs) and neural progenitor cells (NPCs) in spinal cord injury (SCI) is co-ordinated through the JAK/STAT pathway. Wang et al., [37] investigated the significance of the JAK/STAT pathway in the differentiation of astrocytes that are associated with the formation of a glial scar and neuroprotection after SCI. The effects of the JAK/STAT pathway were time-dependent in reactive astrocytes, positive and protective in early phases while negative and inhibitory in the later chronic phase. In the nervous system the JAK/STAT pathway regulates the prevention and protection of neuron demyelination. The immune response in wound repair is a requisite for timeously and proper healing, and this response is modulated by IL-6 that has to bind to a specific receptor, IL-6Rα which does not contain kinase activity. IL-6Rα makes use of JAK1, JAK2, and TYK2 that recruits and phosphorylates the cytoplasmic domain at gp130 of the IL-6Rα [38].

SOCS proteins regulate the maximal response of JAK/STAT signaling and have an influence on the cytokines and growth factors, as well as the cells involved in the wound repair process [10]. Inhibitors of the JAK/STAT signaling pathway are currently used to treat autoimmune diseases, including psoriasis and rheumatoid arthritis. Therapeutic agents that target the inhibition of the JAK/STAT signaling pathway are a promising therapeutic method of treating hematopoietic malignancies, prostate cancers (PCa) and sarcomas [39]. SOCS have been connected with inflammatory diseases, and it has been found that in the absence of SOCS3, IL-6 acts as an immunosuppressive cytokine that reduces tumor necrosis factor (TNF) and selectively inhibits the activation of STAT3 signaling by IL-6. SOCS4 and 5 has also been linked to and has an effect on EGF signaling through the regulation of it receptor, EGFR. Feng and colleagues studied the gene expression pattern of seven SOCSs members in tissue collected from chronic venous leg ulcer patients. It was found that there was significantly higher mRNA levels of SOCS3 and 4 in chronic non-healing ulcers as compared to healing/healed ulcers [24].

In chronic wounds, it is required that the JAK/STAT pathway be upregulated, especially in cases when its normal functioning has been compromised, specifically in an environment of senescent cells and reduced growth factor/receptor potency. Binding of EGF to EGFR induces receptor dimerization and tyrosine auto-phosphorylation, and activation of the JAK/STAT pathway, leading to cell proliferation and migration. The analysis of activated EGFR by EGF and ERK 1/2 by TGF-β1 demonstrated a loss or reduced signaling capacity in senescent fibroblast cells. EGFR down-regulation by miR-7 affects ERK signaling, subsequently affecting the functional pathways for cellular proliferation, migration, differentiation and wound healing [40].

6. Photobiomodulation (PBM) and wound healing

PBM is an approach in which exposure of cells or tissue to low-level laser light or LEDs enhances cellular activities leading to therapeutic effects [41]. This technique typically involves the use of visible red and NIR light over the site of injury to activate the healing process and relieve pain, without sensation or side effects. It is commonly used in treating many defects including chronic wounds, such as in the case of chronic diabetic ulcers. The effects of PBM are non-thermal and the photon energy delivered to tissue and cells produces insignificant temperature changes on the exposed site [42]. PBM thus acts by inducing a photochemical reaction within cells. PBM is believed to produce a shift in the cell redox potential usually towards the direction of greater oxidation, and cells in different growth conditions manifest definite redox states, rendering variable effects of PBM. Cells with a reduced redox state, i.e. low intracellular pH, respond favorably to PBM, while those in a normal and favorable state have a reduced response, or do not respond at all [43]. The cell redox state mediates regulatory pathways within the cell and its changes influence the initiation of several intracellular regulatory signaling pathways for protein synthesis, activation of enzymes and cell metabolism [44].

Photo-acceptors, or chromophores, within the cells absorb the photon energy which stimulates cell metabolism through the activation or deactivation of enzymes which later activates downstream molecules, including DNA and RNA for signal translation. Photons are absorbed by mitochondrial cytochrome c oxidase (Cox) that leads to the excitement of electrons that induce reactions for electron transfer, leading to the release of nitric oxide (NO), increased intracellular ROS and increased production of adenosine triphosphate (ATP) [45]. This in turn creates alterations in cellular redox potential, pH levels, calcium ions (Ca^{2+}), potassium ions (K^{+}), and cyclic adenosine monophosphate (cAMP), which all play an important role in signal transduction, and induce several transcription factors (activator protein-1, AP-1, and Nuclear Factor Kappa B, NFkB). This in turn leads to an increase of cell proliferation and migration, production and secretion of growth factors and cytokines, and extra cellular matrix accumulation (Fig. 1) [46]. The increased ATP levels provide energy for the cell to activate normal metabolic functions in compromised cells. Effects of this action have been observed at a biological level. The absorbed energy can be relayed

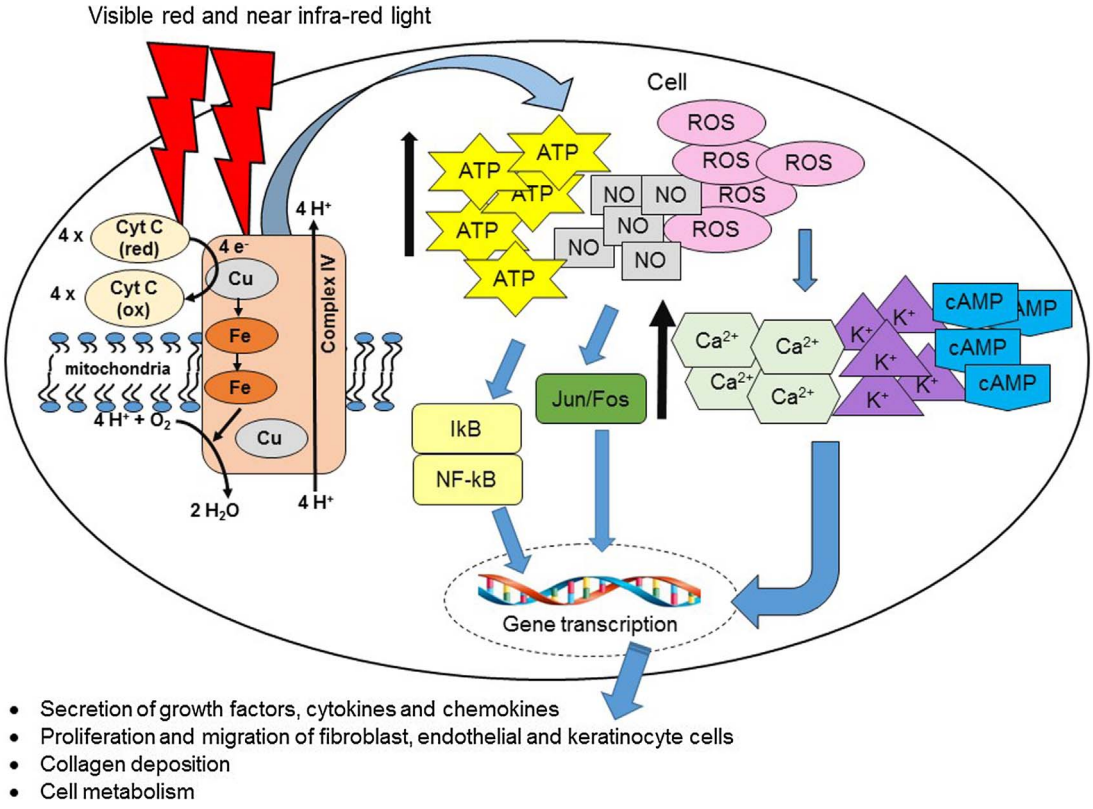

Fig. 1. Cell molecular mechanisms following photobiomodulation in chronic wounds.

to other surrounding molecules, enhancing chemical reactions in neighboring tissue. The production of biological energy in cells in the form of ATP is critical for the wound repair process as its increase leads to the stimulation of enzymes that activate a multitude of intracellular signals [47], including JAK/STAT. Cheng-Yi Liu et al., [48] elucidated that the response of cellular signal transduction pathways to PBM are as a result of the biochemical interaction within the cellular micro-environment. It is believed that a group of cell signaling pathways are modulated after PBM. However, as to which signal pathway is modulated is not yet resolved.

PBM is dose dependent, and at an optimal dose there is stimulation of cellular activity (cell migration and proliferation) essential for wound healing processes, with increased mitochondrial ATP production and anti-inflammatory effects [49]. Gagnon et al., [50] found that PBM accelerated cellular migration and proliferation at doses of 0.1, 0.2, and 1.2 J/cm^2 and that exposure to 10 J/cm^2 reduced cell proliferation and migration. Houreld and Abrahamse [51] also showed this effect when diabetic wounded cells were irradiated at a wavelength of 632.8 nm at a dose of 5 or 16 J/cm^2, with cells responding better to a dose of 5 J/cm^2. Piva et al., [52] found that PBM has anti-inflammatory effects in the wound healing process by reducing chemical mediators, cytokines, and inflammatory cell migration, and increases growth factors. Gkogkos et al., [53] evaluated the effect of PBM on human gingival fibroblasts on the proliferation and secretion of growth factors, specifically EGF, bFGF, and VEGF. They observed that all laser-irradiation doses used increased cell proliferation 48 h post-irradiation in a dose dependent manner, reaching statistical significance ($p = 0.03$) in the cells that received 15.8 J/cm^2. On the other hand, all laser doses that were used increased the secretion of EGF at 48 h and a significant secretion ($p = 0.04$) was observed in cells receiving 2.6 J/cm^2. Peplow et al., [54] performed a review of the PBM experimental investigations done on human and animal cultured cells to assess its effects on the expression of genes and the production of cytokines and growth factors. Their findings comprehensively demonstrate that laser irradiation has the ability to induce the expression of genes and the production of various cytokines and growth factors in cultured cells. Hamblin and Demidova [43] described another study that implicated PBM in the increase in growth factor levels, with a significant increase in the release of bFGF. Khoo et al., [55] observed a significant increase in FGF expression in cultured fibroblasts from diabetic mice following PBM at 810 nm with a dose of 1 J/cm^2. In one of their investigations, Landau et al., [56] found that within the irradiated group 90% of patients having diabetic ulcers healed and the reduction of wound size was 89%. The average wound closure time was 7.14–11.16 weeks, while in the placebo group wound healing was 33% and the reduction of wound size was 54%. The average wound closure time was 11.5 weeks. Kajagar et al., [57] also found a significant reduction in ulcer area in irradiated patients compared to the non-irradiated group.

In summary, numerous *in vitro* and *in vivo* studies suggest that PBM facilitates healing by inducing the stimulation of cell proliferation and motility, and increases angiogenesis, collagen synthesis, and release of growth-factors [58]. These effects are traditionally induced through well-coordinated signaling pathways. Santabárbara-Ruiz et al., [59] established that ROS is generated during cell death and is disseminated to the neighboring cells. The disseminated ROS trigger p38 and stimulate c-Jun N-terminal kinase (JNK). The stimulated JNK and p38 effects the manifestation of the cytokines Unpaired (Upd), and this activates the JAK/STAT signaling pathway. These outcomes reveal that ROS/JNK/p38/Upd stress pathway, through JAK/STAT signaling, rebuilds tissue homeostasis, and that this pathway is not only initiated following cell death but also following physical damage. Increased ROS following PBM possibly effects the JAK/STAT signaling pathway that may lead to downstream cell proliferation, migration and growth factor production. Park et al., [60] established that p38 Mitogen-activated protein kinase (MAPK), ERK1/2, and STAT proteins are activated via oxidative stress, signifying that inhibition of surfactant protein (SP)-A and SP-B gene expression by hydrogen peroxide (H_2O_2) is linked to MAPK and JAK/STAT signaling pathway. Activation of these pathways

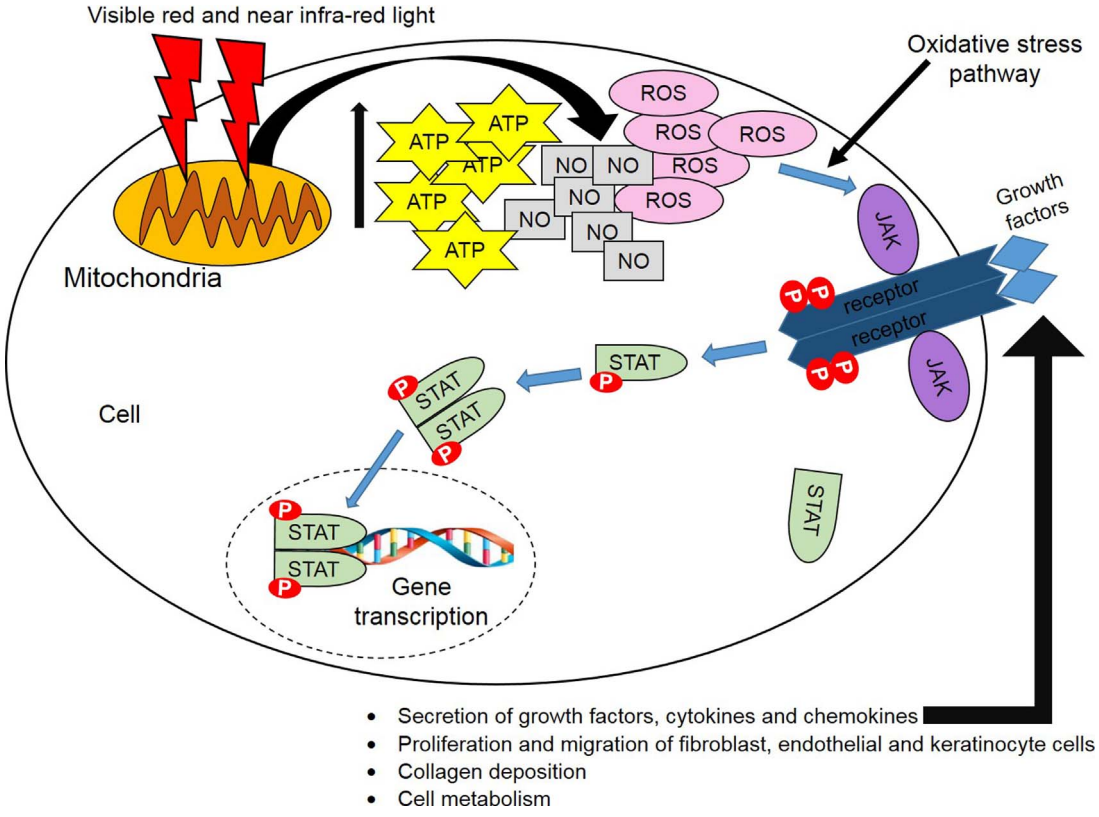

Fig. 2. Photobiomodulation and the presumed activation of cellular proliferation and migration via the JAK/STAT signaling pathway in chronic wounds.

may lead to increased cytokine and growth factor production, and the released growth factors would eventually be ligands for the producing and surrounding cells that would enhance cellular activities that lead to wound healing. Thus, the possibility that PBM stimulates proliferation and motility through the JAK/STAT pathway cannot be ignored (Fig. 2). No study has been conducted to investigate the effect of PBM on the JAK/STAT signaling pathway in chronic wounds. Although PBM is fully utilized in various sectors of health as a therapeutic modality, it still remains a controversial mode of treatment since cellular mechanisms following exposure to low level light are still not well understood.

7. Future directions

Effective wound repair is a challenging and lasting issue for clinicians and the affected patients. Several strategies are used to improve and accelerate the repair process. One such strategy has involved targeting the signaling pathways by using therapeutic agents to accelerate wound healing and reduce scarring. Wound healing normally relies upon suitable concentrations of growth factors and cytokines so that cell responses are precisely and accurately regulated. Successful preclinical studies have been reported on the use of TGF-β signaling pathway targeted therapeutic agents in wound healing [61]. Available literature suggests that JAK/STAT signaling pathways play important roles in wound healing and that PBM effects cell proliferation, differentiation, migration and production of growth factors. Therapeutic agents that can target this pathway, and the use of PBM to revive senescent cells and the production of growth factors, may contribute to the enhancement and acceleration of the repair process in chronic wounds.

8. Conclusion

Any compromise to a variety of the mechanisms involved in wound healing, such as the inhibition of growth factors and cytokines, and disruption to the JAK/STAT pathway, may affect normal wound healing and the efficacy of some of the best wound treatments currently available. There is rapid progress to understand various factors that affect and accelerate wound healing, specifically chronic wounds associated with diabetes. The JAK/STAT signaling pathway is critical in chronic wound healing, and is among the principal signaling pathways used by growth factors and cytokines. Chronic wounds, including diabetic ulcers, are affected by reduced cell numbers, growth factors and receptors, and ECM activity. Senescent cells lose the ability to divide and grow, and these activities are regulated by cytokines and growth factors via signaling pathways. Methods that revive senescent cells, including cytokine production, and receptor and signaling pathway activation, can result in effective cell proliferation, migration and wound closure. Further investigations into cellular and molecular mechanisms and signaling pathways involved in chronic wound healing, and methods of activating senescent cells through various treatments such as PBM is therefore imperative.

PBM induces cell proliferation, migration and the production of growth factors in diabetic wounded and other stressed cells, yet the cellular and molecular mechanisms following PBM are still not well understood. It is plausible that PBM activates cell proliferation and migration of senescent cells by activating the signaling pathways that may include the JAK/STAT pathway. More research on the molecular mechanisms, including signaling pathways, following PBM is indeed necessary for this therapeutic modality to be widely used and accepted. There is also a need to explore the possibility of a multifaceted treatment approach involving PBM in combination with other conventional wound treatments as this may further advance chronic wound repair.

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and material

Not applicable

Competing interests

The authors declare that there is no conflict of interest regarding the publication of this paper.

Funding

This review manuscript is supported by the South African Research Chairs Initiative of the Department of Science and Technology and National Research Foundation of South Africa (Grant No 98337), as well as grants received from the University of Johannesburg (URC), the African Laser Centre (ALC), the National Research Foundation (NRF), and the CSIR (Council for Scientific and Industrial Research) − NLC (National Laser Centre) Laser Rental Pool Programme.

Authors' contributions

SWJ prepared the article. NNH conceptualized the idea for the research, and was involved in drafting the manuscript and revising it critically for intellectual content, and is the postgraduate supervisor of lead author. HA provided professional guidance and supplied editorial input and is a co-supervisor of the lead author. All authors read and approved the final manuscript.

Acknowledgements

Not applicable.

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