Journal of Tissue Viability xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Journal of Tissue Viability

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

Pharmacological control of inflammation in wound healing

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A B S T R A C T

Wound inflammation is a rapid and highly orchestrated process that significantly impacts the wound healing cascade. Consequent to injury, a series of events set off that include inflammatory, proliferation and maturation phases leading to wound closure and restoration of normal skin integrity. Stimuli causing stress to host immune system or induce inflammatory response include tissue damage and pathogenic microbial infection.Several evidences points towards the positive role of inflammation as it essential to fight against the attack of invading pathogens and to remove dead tissues from the site of injury. Besides its positive role, prolonged inflammation is injurious and may result in deregulated stages of the wound healing which may lead to excessive scarring. Achieving balance in inflammatory cascade is one of the challenging tasks for development of a wound healing drug.

This review mainly focuses on the pharmacological control of inflammation by agents which critically balance the inflammatory cascade. However, none of the agent is available in the healthcare market which exclusively plays a role in wound repair. In this review we shall explore different factors or agents affecting inflammation in wound healing. This information might be helpful in designing and development new process, technologies or drugs for better management of wound care. In addition, understanding the effect of inflammation on the outcome of the healing process will serve as a significant milestone in the area of pathological tissue repair.

1. Introduction

Inflammation is a highly synchronised process induced by tissue break or microbial infection. This process is characterised by host tissue destruction, multiple organ failure, sometime even death and is regarded as one of the crucial step of wound healing cascade [1]. Wound healing is an intricate network of overlapping biological processes to resolve tissue injuries. The prominent phases are haemostasis, inflammation, tissue proliferation and maturation that involve numerous different cell types, some from the local area, while others are recruited upon injury [2]. The ultimate goal of these processes is to eliminate the invading microorganisms, removal of damaged cells and tissue, and re-establishment of the skin barrier. Faulting in any of these steps may result in impaired healing. The present review discusses the role of inflammatory phase in cutaneous repair by looking toward the factors affecting it and various pharmacological approaches treating wound inflammation.

1.1. Inflammatory phase of wound healing (Fig. 1)

The inflammatory phase involves activation of the innate immune system, neutrophils and monocytes are the major cells that migrate rapidly into the wound site upon injury. It mainly consists of vascular permeability, active migration of blood cells, and the passage of plasma constituents into injurious tissue. Within few hours of injury cytokines and growth factors are released by neutrophils and macrophages. The recruited neutrophils begin the phagocytosis of infectious agents by releasing a large variety of highly active antimicrobial substances like reactive oxygen species (ROS), cationic peptides, eicosanoids, proteases and Myeloperoxidase (MPO) [3]. They also lead to debridement of devitalized tissue by secreting enzymes such as matrix metalloproteinases (MMPs). Approximately after 3 days of injury, monocytes are recruited to the injury site, where they differentiate into macrophages and support healing. Macrophage infiltration into the wound site is highly regulated by gradients of different chemotactic factors, including growth factors, proinflammatory cytokines, and chemokines [4]. Beside their immunological functions, macrophages are thought to play an essential role in a successful outcome of the healing response through the synthesis of numerous potent growth factors. In normal wound healing process, the inflammation phase usually lasts for 2–5 days.

1.2. Inflammation and impaired healing

Wound healing process aims to restore tissue integrity but there are

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https://doi.org/10.1016/j.jtv.2019.09.002
Received 1 January 2019; Received in revised form 2 August 2019; Accepted 13 September 2019

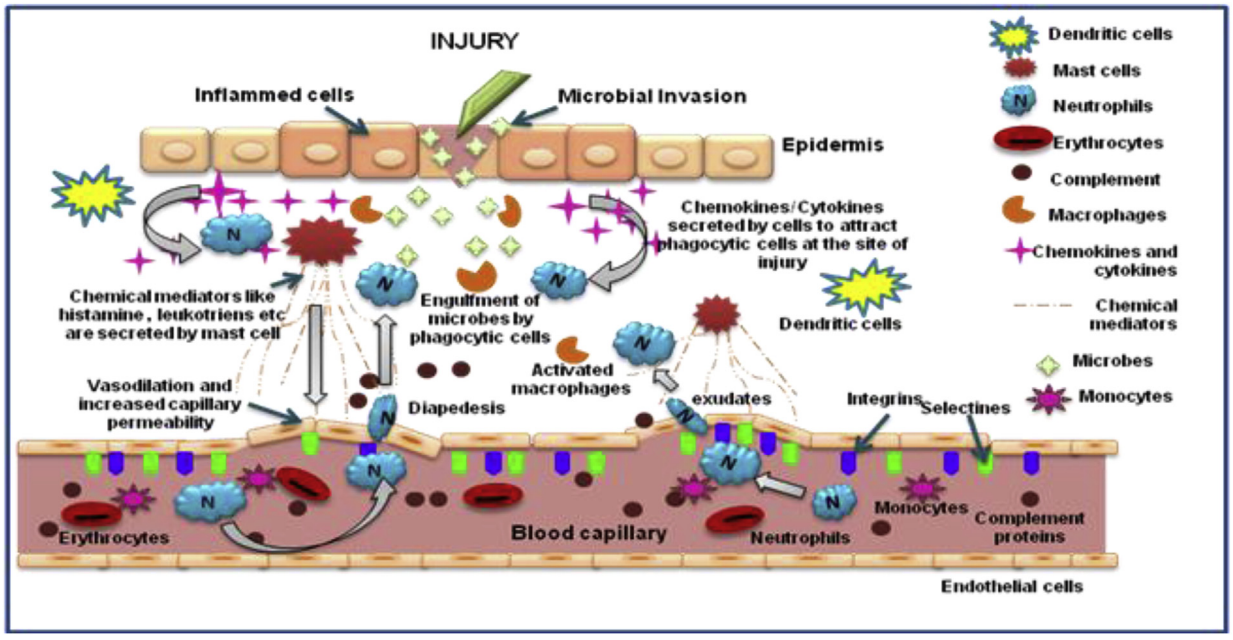

Fig. 1. Injury mediated inflammatory phase involving various cells and cellular factors.

some cases where the wounds heal slowly and fail to progress through the typically sequenced stages of repair resulting in a chronic inflammatory state that lead to the generation of chronic wounds which possess distinct characteristics like high bacterial load, imbalanced growth factor, inflammatory mediator and proteolytic enzymes that favour tissue degradation over repair. Unbalanced proteolytic activity is one of the major consequences of the persistent inflammatory response at the wound site. The characteristic of such chronic wounds are abundant neutrophils, macrophages, upregulated Matrix metalloproteins (MMPs) and prooxidant microenvironment [5].

1.3. Pharmacological approach towards inflammation (Fig. 2)

Drug facilitates wound healing by affecting different stages of tissue repair starting from inflammation to maturation phases. The effect of medication may be either appealing or interfering depending on its mode of action, dosage, and route of administration in relation to the specific phase of the wound healing process. Various treatment modalities used to treat wound inflammation are as follows:

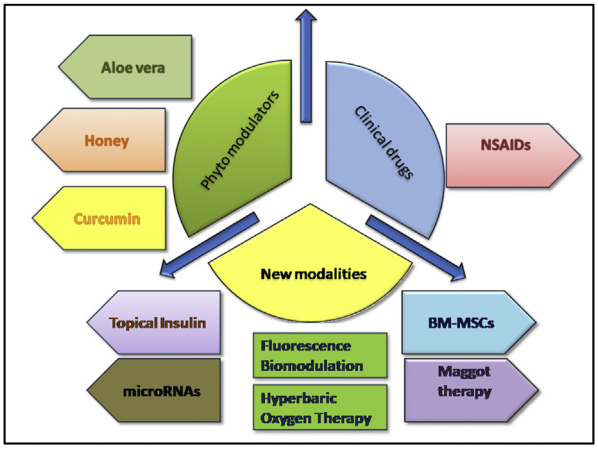

Fig. 2. Pharmacological control of inflammation.

1.3.1. Phyto-modulators

Plants based secondary metabolites or other product possess ability to modulate the inflammation by acting on cells, growth factors and cytokines involved in the wound healing that culminate in to enhanced angiogenesis, fibroplasias and epithelization [6]. Despite challenges on identification and purity of active molecules, a number of clinical studies are available with the herbal products. The few promising phytomedicine are briefly discussed for their ability to control the inflammation during wound repair.

1.3.1.1. Aloe vera products. Mucilagenous gel present in the leaves of the plant has been used from ancient times for anti-inflammatory and wound healing property. The mechanism of action for promotion in wound healing is based on inhibition in production of reactive oxygen production, protagladins, cytokines and enhanced proliferation of fibroblast and keratinocytes [7]. The carbohydrates content of the gel activates the macrophages and other immune cells that participate in inflammation process. Aloe vera solution showed improvement in second degree burn wound rat model through modulation of leukocytes adhesion and cytokines levels. Several animal models exhibited in relieving the severity of acute inflammation by Alove vera. The products like cream, gel and impregnated dressing are tested for acute and chronic wounds in animals [8].

1.3.1.2. Honey. Ancient uses of honey are reported for wound healing. Different varieties of honey have been investigated for their wound healing properties. Recently Manuka honey has shown promising potential for wound repair due to antibacterial and anti-inflammatory properties [9]. In general, honey affects the process of healing at the wound site by providing moist environment, removes bacteria and cell debris, import nutrients, oxygen and increase the proliferation of fibroblast and endothelial cells. Honey has been effectively accelerated the healing of acute and chronic wound. The anti-inflammatory action of the honey is due to inhibition of many factors like ROS formation, complement pathway, leukocytes infiltration, COX-2, iNOS and MMP-9 [10]. A number of clinical trials have shown decrease in symptoms of inflammation through the application of honey on the wound [11].

1.3.1.3. Curcumin. It possesses anti-inflammatory and antioxidant

properties responsible for faster and better wound healing especially in diabetic rats [12]. Topical curcumin has found effective in chronic and nasal wounds. Nanoformulation of curcumin accelerate wound repair by activation of fibroblast migration by activation want signalling and inhibited inflammation by decreased level of monocyte chemoattractant protein-1 by fibroblasts [13]. Curcumin affects the level of cytokines and growth factors thereby controlling the process of inflammation in enhancing the cutaneous repair. Its mode of action include decreased expression of TNF-α, IL-1β, and MMP-9, and increased levels of the anti-inflammatory cytokine IL-10 and antioxidant enzymes at the wound site [14].

Apart from the above phyto-modulators certain other plants were also recommended for wound healing due to their anti-inflammatory properties.

1.3.2. Clinical drugs

1.3.2.1. Non-steroidal anti-inflammatory drugs (NSAIDs). These drugs are widely used to control the inflammation. They possess anti inflammatory, antipyretic, analgesic and thrombotic properties due to inhibition of cyclooxygenases 1 and 2 (COX-1 and COX-2) [15]. These drugs are the first choices for the treatment of pain, soft tissue injuries, osteoarthritis, gout, and inflammatory disorders with an estimated usage of > 30 million per day [16]. Their mode of action is to decrease prostaglandin production by inhibiting cyclooxygenase, lipooxygenase transformations of arachidonic acid along with inhibition of oxygen radical and suppression of neutrophils migration. Numerous studies indicate the negative effect of NSAIDs on wound healing due to decreased keratinization, epithelisation, angiogenesis and granulation. Furthermore, they may inhibit the 12-HHT/BLT2 pathway in the skin affecting the wound repair [17]. However, short-term usage of these drugs accelerated the healing of combat related extremity wounds through altering the levels of inflammatory cytokines [18]. Aspirin has shown positive effect on healing of chronic wounds by inhibiting inflammatory pathways through upregulation of anti-inflammatory molecules responsible for repair.

1.3.2.1.1. Cyclooxygenase (COX) inhibitors. These inhibitors stall the expression of COX enzymes responsible for synthesis of prostaglandin that induces the inflammation. Cyclooxegnase has two isoforms, COX-1 and COX-2 which impact the course of inflammation through induction by growth factors, cytokines, and hormones [19]. COX-1 is ubiquitously presents in most of the cells, however COX-2 is a inducible form located on fibroblast, macrophages and other immune cells and predominantly upregulated during inflammation. Numerous inhibitors were made for COX-2 to control the cytotoxic effects of inflammation. COX-1 Inhibitors render adverse effect to gastrointestinal mucosa where as COX-2 was found to be safe The use of COX inhibitors are routinely used after post operative procedure to transiently relive the inflammation and allow wound closure.

The prominent COX-2 Inhibitor drug approved by Food and Drug administration, USA is Celecoxib which is antiinflammatory and recommended for use in varieties of arthritis pain and in familial adenomatous polyposis (FAP). It is available in capsule form under brand name Celebrex. Celecoxib has shown improvement in animal pressure ulcer model through inhibition in wound TGF Beta-1 leading to fast wound repair progression and reduced scarring [20]. It has decreased in seroma formation and suppressed the interlekin-1 in a mastectomy model of rats. Similarly topical treatment of celecoxib with full thickness incision mice model showed inhibition in inflammatory responses like neutrophil infiltration and activation, protoaglandin-2 activity and TGF-b1 protein levels. Enhanced Bone marrow stem cells mediated wound repair was observed by celecoxib through promotion of engraftment and re-epithelialization.

The notable limitation of COX-2 inhibitors is vascular disorders like myocardial infarction (MI) or heart attack, non-fatal stroke, and death [21].

1.3.3. New modalities

1.3.3.1. microRNAs. MicroRNAs (miRs) are small noncoding RNA molecules of about 22 nucleotide long which regulate various cellular and physiological processes in health and disease like proliferation, differentiation, apoptosis, RNA silencing and post-transcriptional regulation of gene expression [22] by binding to the 3′-untranslated regions (3′-UTR) of target messenger RNA (mRNA). MiR-152, miR-143, miR-126, miR-21, miR-27a, miR-214, miR-16, miR-203, miR-125b, miR-34a, miR-205, miR-27b, miR-30b, miR-125a, miR-191 and miR-200 were highly expressed in the skin. Various studies have shown the uprugulation or downlregulation of different mi-RNAs in various phases of wound healing implicating their possible role in wound repair [23]. MicroRNAs can regulate the process of inflammation by targeting the mRNAs of mediators involved in the wound healing process. MiR-155, miR-140 and miR-16, miR-105miR-21, miR-125b, miR-223, miR-203, miR-146a,b are found to be anti-inflammatory and pro-inflammatory respectively [24]. Inhibition of MiR-155 has found to effective in mice chronic foot ulcers model through restoration of fibroblast growth factor-7 and decreased wound inflammation [25]. MiR-25 and miR-21 mainly participate in proliferative phase by regulating the AKT pathways in keratinocytes. MiR-424 promotes angiogenesis in vitro and *in vivo* rodent models. Studies on MiR-31 indicate its role in angiogenesis, proliferation and inflammation. MiR-142 has been identified as inflammation related marker required for neutrophilic chemotaxis via inhibition of small GTPase translation. MiR-223 shown to be promising target in infected wounds as it suppress suppresses IL-6 expression leading to hamper in neutrophil activation necessary for removal of microbes resulting in to faster wound closure. Human diabetic ulcers skin and leptin receptor-deficient (db/db) diabetic mice have shown reduced level of microRNA-132 (miR-132) however, local application in db/db mice enhance wound closure due to higher proliferation of keratinocytes nd suppressed inflammation [26]. Based on the identification of MicroRNAs, gene therapy for chronic wounds may be possible however challenges are appropriate delivery systems, extracellular and intracellular factors.

Major drawback of this therapy is that a single miRNA can silence a number of different proteins due to which specificity of treatment becomes a problem. Also, before introduction into clinical practice, dosage concerns should be addressed, as overdose of miRNA can result into non-specific immune responses, and toxicities. Therefore, normal applications of miRNAs at proper physiological concentrations in *in vivo* are preferred.

1.3.3.2. Bone-marrow-derived mesenchymal stem cells (BM-MSCs). Mesenchymal stromal cells exhibit strong potential for cutaneous wound healing due to differentiation, easy harvesting and low immunogenicity [27]. Owing to multi lineage differentiation, immunomodulator and proangiogenic properties, MSCs have come out as promising treatment of acute and chronic wounds. They impart faster healing via higher cell migration, angiogenesis, epithelialization, and granulation tissue formation. Additionally they secrete chemoattractant for macrophages and keratinocytes. Preclinical and clinical studies with MSCs have clearly exhibited the improvement in wound healing [28]. Intraperitoneal and intraregional administration of MSCs in mice full thickness wound model showed accelerated healing. Topical BMCs application through fibrin spray to acute surgical wounds and chronic lower-extremity wounds significantly decreased the wound. Experiments also demonstrated the administration of mouse bone marrow-derived allogeneic MSCs was found more effective in wound healing and cutaneous regeneration than acelullar derivatives in Non -Obese Diabetic mice [29].

Most severe side effect of cell therapy is possibility of malignant transformation in long-term culture. Transplant of biological material also carries risks of transmitting infectious agents.

1.3.3.3. Medical maggot therapy. It is known that Maggot debridement

therapy (MBT) uses live disinfected maggots that are placed into the non healing wounds to disinfect the wounds and to clean out the necrotic tissue within the wound. Studies suggested that the maggot excretions/secretions can reduce superoxide generation and also lowers the release of myeloperoxidase (MPO) from stimulated neutrophils [30]. MBT influences angiogenesis, inflammation and cell migration and possesses debridement, antibacterial and stimulator properties for wound healing. It stimulates healing in diabetic foot ulceration by changing monocytes activity by decreasing the level of proinflammatory cytokines (IL-12p40, TNF-α, and MIF) whereas elevating the level of anti-inflammatory cytokine IL-10 [31]. Therapy showed augmented healing in infectious wounds by inhitibiting bacterial growth. Dried secretions of maggots in rat models increased wound capillary density and VEGF-A mRNA protein expression. Plenty of reports are available about application of MBT in diabetic, venous extremity ulcers, arterial extremity ulcers and pressure ulcers. US FDA has approved Maggot as Medical device for physicians.

Major drawbacks of MBT are pain and discomfort to patients.

1.3.3.4. Topical insulin. Insulin is a peptide hormone with diverse physiological functions. The role of insulin in wound healing has been reported over considerable past. It has been found that the insulin receptor, IRS-1, IRS-2, ERK and Akt are significantly expressed in the damaged wound than the intact skin indicating potential role of insulin signalling pathway in wound repair [32]. Insulin showed the anti-inflammatory ability due to higher the IL-4, IL-13, Il-10 chemokines and lower IFN-ϒ production. It also exhibited inactivation of TNF-α mediated inflammatory pathway during fat metabolism. Overall antiinflammatory properties of Insulin are based on metabolic and synthesis pathways that are responsible for cell proliferation, survival, angiogenesis, migration and anti-inflammation. Application of topical insulin has effectively promoted wound healing thermal, incisional and chronic animal models. Low cost and potential wound healing ability makes promising usage of insulin in dressing, bioadhesive and hydrogels. Topical insulin dressing promotes wound healing in the patients with diabetic foot ulcer in comparison to conventional dressing [33].

1.3.3.5. Fluorescence biomodulation. It is a kind of laser therapy where red and near infra read lights are used for reduction of inflammation and promotion of wound healing. Anti-inflammatory effect of FBM has been shown in various animal models like acute traumatic brain injury, autoimmune encephalomyelitis, and lung inflammation. Superpulsed laser has attenuated the inflammation through decreased TNF-α, NF-kB, and up-regulated levels of VEGF, FGFR-1, HSP-60, HSP-90, HIF-1α and matrix metalloproteinases-2 and 9 and enhanced wound healing in burn wound model of rat [34]. A mulicentric, prospective and uncontrolled clinical trial with chronic ulcer patients undergoing FB treatment showed remarkable recovery with significant wound closure. FB seems to be attractive therapy to treat acute and chronic wounds [35]. The mechanisms of FB for the stimulation of wound healing are reduction microbial load, down regulation of proinflammatory cytokines, induction of cell proliferation, stimulation of angiogenesis, increased collagen production and minimum scar formation.

1.3.3.6. Hyperbaric oxygen therapy. Oxygen impairment leads to hamper the wound healing phases. It is known to activate immune cells, cytokine, and modulate the inflammatory and bactericidal mediators. Hyperbaric oxygen therapy (HBOT) refers to clinical usage of pure oxygen at greater pressure and being used in chronic non healing wounds like diabtetic. It is specifically effective for those chronic wounds having poor blood supply and tissue oxygen availability. HBOT has shown to recover the muscle injury by oxygenation, reduction in inflammation and regeneration through macrophage and satellite cell activation. This therapy recovered non healing chronic wound patients through stimulation of wound healing by increasing levels of VEGF, IL-6 and downregulating endothelin-1 [36]. In soft tissue injuries and bone infections, HBOT showed inhibition in growth of microorganisms thus improving leukocyte and macrophage function for efficient wound healing. It has shown mucosal healing in refractory ulcerative colitis patients by stimulation of colon stem cells. Some detrimental effects of HBOT are claustrophobia, reversible myopia, mild to severe pain due to barotrauma [37].

2. Conclusion

The inflammatory response is a series of well coordinated cellular events leading to wound repair. It can play both beneficial and deleterious roles in cutaneous repair. The present review discusses the role of inflammation in wound healing and various pharmacological approaches towards wound inflammation leading to tissue repair. To attain proper tissue homeostasis during healing, a perfect balance between various leukocyte cell subsets and numerous pro and anti inflammatory mediators is necessary. Thus, level of inflammation can reveal both healing time and repair quality. In contrast, robust inflammation is responsible for delayed wound healing in chronic wounds. This probably reflects both “good” and “bad” aspects of the inflammatory response.

Moreover, phagocytic actions of neutrophils are important for proper macrophage function and tissue repair. Therefore, we suggest that suppression of inflammation in wound may not be always advantageous as it may increase the risk of infection. We believe that despite of various advances in wound care there is no unfailing solution available that can overcome the various complexities in wound healing and its management.

Attempts are required to develop technologies facilitating complete wound healing. Novel therapies may focus on attaining a balance of inflammatory phase in healing cascade by attenuating the detrimental effects of inflammation while preserving its beneficial aspects which will facilitate tissue repair.

Acknowledgement

The authors are thankful to Director, Institute of Nuclear Medicine & Allied Sciences (INMAS), Defence Research & Development Organization, India, for providing necessary facility in writing this review

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