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Review article

Wounds, burns, trauma, and injury

Marianne Frieri [a,*], Krishan Kumar [b,1], Anthony Boutin [c,1]

[a] Division of Allergy Immunology, Department of Medicine, Nassau University Medical Center, 2201 Hempstead Turnpike, East Meadow, NY 11554, United States
[b] Division of Pediatric, Department of Emergency Medicine, Nassau University Medical Center, 2201 Hempstead Turnpike, East Meadow, NY 11554, United States
[c] Adult Emergency Medicine, Department of Emergency Medicine, Nassau University Medical Center, 2201 Hempstead Turnpike, East Meadow, NY 11554, United States

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ABSTRACT

The purpose of this review paper is to discuss many areas related to wounds, photobiomodulation, reactive oxygen species, biofilms, neutrophils in wounds, other cells and growth factors in wounds, T cells in wounds, additional role of stem cell in wounds, mast cells in wounds, trauma and injury, surgical management, burns, trauma and injury, cytokines and trauma.

Contents

1. Introduction

1.1. Wounds

In wound healing, fibroblasts collagen and matrix deposition are important for healing, however this material can contribute to remodeling of organs with substantial morbidity and mortality [1]. Certain receptors can lead to fibroblast activation, collagen

* Corresponding author. Fax: +1 516 572 5609.
E-mail addresses: mfrieri@numc.edu (M. Frieri), kkumar@numc.edu (K. Kumar), aboutin@numc.edu (A. Boutin).
[1] Fax: +1 516 572 5465.

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synthesis and adenosines, a small molecule extracellularly generated from adenine nucleotides from direct stimulation, hypoxia, or injury can act via a family of classical seven-pass G protein-coupled protein receptors as discussed in a recent article [1]. Signaling pathways are involved with adenosine receptors and in wound healing as described in a recent article [1]. Adenosine and its receptors play important roles in both production of matrix and neovascularization, critical areas for wound healing and tissue repair. These receptors are A_{2A} and A_{2B}, with generation of cAMP and activation of downstream targets such as protein kinase A and exchange protein activated by cAMP or EPAC, a family of guanine nucleotide exchange factors can cause activation of fibroblast and also collagen synthesis [1]. Adenosine signaling contributes to fibrosis and may have opposite effects in a variety of different organs. Thus, drug development that selectively target these receptors and signaling pathways will disrupt fibrosis pathogenesis and slow or arrest the progression of important underlying disorders.

In a recent article these authors reported on the development of an image-based multi-scale mechanical model that predicts the short-term structural reorganization of a fibrin gel by fibroblasts [2]. Regional differences in short-term structural remodeling and cell migration were observed for two gel boundary conditions. A pilot experiment indicated that these small differences in the short-term remodeling of the fibrin gel translated into substantial differences in long-term remodeling for collagen production [2]. The multi-scale models predicted some regional differences in remodeling and qualitatively similar reorganization patterns for the two boundary conditions. However, other aspects of the model, magnitudes and rates of deformation of gel did not match the experiments. These discrepancies between model and experiment can be important for challenging model assumptions and devising new experiments enhancing the understanding of how this multi-scale system functions. Thus, these efforts can improve the predictions of remodeling, dermal wound healing and reduction of patient scarring. These models could be used to recommend patient-specific mechanical-based treatment dependent on s wound geometry, location, age, and health [2].

A study aimed to develop optimal amikacin dosing for the empirical treatment of Gram-negative bacterial sepsis in pediatric patients with burn injuries [3]. Optimal amikacin dosing regimens for the empirical treatment of Gram-negative bacterial sepsis in pediatric patients with burn injuries were developed [3]. The authors stated amikacin pharmacokinetics are altered in patients with burn injuries, including a significant increase in clearance and the volume of distribution in simulations, increased doses ($\geq$25 mg/kg) led to improved PD target attainment rates. Further clinical evaluation of this proposed dosing regimen is warranted to assess clinical and microbiological outcomes in pediatric patients with burn wound sepsis [3].

1.2. Photobiomodulation

Treatments for many wounds can be recalcitrant and an area of photobiomodulation involves inducing wound healing by illuminating wounds with light emitting diodes or lasers [4]. Photobiomodulation is used on different animal models, in vitro studies, and clinically. Wound healing is induced by many different wavelengths and powers with no optimal set of parameters [4]. Simultaneous multiple wavelength illumination according to data suggest it is more efficacious than single wavelengths, and the optimal single and multiple wavelengths must be better defined to induce more reliable and extensive healing of different wound types. These authors focused on studies in which specific wavelengths could induce wound healing and on their mechanisms [4].

1.3. Reactive oxygen species

Photobiomodulation is defined as a nonthermal process involving endogenous chromophores that are able to elicit photophysical and photochemical events at various scales, resulting in beneficial photobiological responses. There appears to be enough anecdotal scientific literature for the use of light in wound care from sterilization, desiccation, promotion of healing and effective treatment for a number of conditions, including inflammation [5]. In terms of the mechanism of photobiomodulation, interaction of light and biological tissues can lead to generation of transient and extremely reactive chemical intermediates, or reactive oxygen species (ROS), in both extracellular and intracellular compartments [5].

The different materials, sizes, shapes, and structures have different responses. This paper investigated the successful treatments made with nanoparticles and some general health effects. A review of the literature revealed an inflammatory response and an increased production of ROS, common immune responses to nanomaterial use. The mechanisms by which the inflammatory response and ROS production was discussed [6].

Quinones are electron proton carriers that play a primary role in the aerobic metabolism of virtually every cell. Quinones undergo highly regulated redox reactions in the mitochondria, Golgi apparatus, plasma membrane and endoplasmic reticulum. Important consequences of these electron transfer reactions are the production of and protection against ROS. Quinones have been extensively studied for both their cytotoxic as well as cellular protective properties and they have been particularly useful in rational drug design [7].

A severe burn is associated with release of inflammatory mediators which ultimately cause local and distant pathophysiological effects [8]. Mediators including ROS and reactive nitrogen species (RNS) are increased in affected tissue, which are implicated in pathophysiological events observed in burn patients [8]. However following a burn, there is an enormous production of ROS which is harmful and implicated in inflammation, SIRS, immunosuppression, infection and sepsis, tissue damage and multiple organ failure. Thus, clinical response to burn is dependent on the balance between production of free radicals and its detoxification. Supplementation of antioxidants in human and animal models has proven benefit in decreasing distant organ failure suggesting a cause and effect relationship. Oxidative damage is one of the mechanisms responsible for the local and distant pathophysiological events observed after burn, and therefore anti-oxidant therapy might be beneficial in minimizing injury in burned patients [8].

2. Biofilms

A beneficial effect of low-level laser therapy in promoting wound healing in both animal and human studies has been demonstrated [9]. This recent review identified literature reporting on low-level laser therapy alone, without photodynamic agents, as an antimicrobial/antibiofilm technology and determined its effects on wound healing [9]. The authors stated efforts need to be addressed to standardize phototherapy and develop suitable in vitro and in vivo biofilm models to test low-level laser therapy efficacy in promoting biofilm eradication and wound healing [9].

Biofilms due to *Staphylococcus aureus* and exotoxins that act as superantigens have been implicated to play an important pathological role in the incidence, maintenance, and ongoing burden of chronic rhinosinusitis as well as in wounds [10]. A better understanding of the interplay between bacterial factors, host factors, and the environment will facilitate better management. This literature review focused on these factors and highlights