Molecular Perspectives of Wound Healing—Cellular Models*

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The skin is the largest and heaviest organ and the most vital protective mechanism against foreign organism invasion and physical injury. It consists of two layers, the dermis and epidermis, both of which include different types of cells, including keratinocytes, melanocytes, and Langerhans and Merkel cells, as well as collagen and elastic fibers, in which fibroblasts, macrophages, mast cells, and white blood cells are embedded. Pathology affecting the integrity of the skin is diverse and numerous conditions contribute to wound formation in skin. Most of these diseased states can, however, be treated successfully using laser irradiation or phototherapy. Skin injury and subsequent repair of the tissue is a complex pathophysiological process known as wound healing which involves a sequence of overlapping processes such as homeostasis, inflammation, angiogenesis, granulation tissue formation, extracellular matrix deposition, remodeling, and scarring.1,2,3

Dysregulation in the underlying mechanisms of these coordinated processes and between participating cellular systems may lead to abnormal wound repair. The extent to which altered regulation of normal wound healing takes place manifests itself in the classification of two types of wounds: acute and chronic. Acute wounds heal so that connective tissues are repaired, the wound completely epithelializes by regeneration, and a return to normal anatomical structure and function is observed. In chronic wounds, however, the normal biochemical mechanism underlying the healing process is disrupted. Although the causes of chronic wound formation and maintenance are varied, the three most common causes include diabetes, pressure ulcers, and venous stasis. These non-healing, pathologically inflamed wounds represent a significant cause of morbidity and mortality for a large portion of the world population. In addition, the psychosocioeconomic cost to countries is significant and this has contributed to the development of novel therapeutic approaches.4,5

Although phototherapy and its numerous clinical applications are well documented, the importance of the underlying biochemical mechanisms have only been studied and afforded attention over the last ten to fifteen years. Understanding the basic mechanisms, pathways, and cascades and identifying the biochemical factors that orchestrate and regulate these mechanisms have lead to the development of novel therapeutic targets for wound healing. Compelling evidence exists in animal studies as well as human clinical studies demonstrating the effectiveness of laser phototherapy for the treatment of chronic wounds.6,7

The scientific basis for this success can only be found in studying wound healing at a cellular and molecular level and providing sound scientific proof of the contribution that laser therapy can make to wound healing. Tissue and cell culture techniques have proven to be highly effective in identifying the compounds participating in and regulating the cellular mechanisms contributing to successful wound healing. The ability to isolate different cell types and maintain them in isolation has allowed identification and contribution of regulatory factors and mechanisms of control of independent cell types. Governed by sequential participation of a variety of cell types, the up- and down-regulation of many signaling molecules, as well as the interaction of a variety of enzyme catalyzed pathways, have been elucidated in cells in culture.3

The effectiveness of laser therapy for the treatment of wounds can be illustrated in cell model systems simulating pathophysiological conditions associated with diseased states such as diabetes. Diabetic, wounded, acidic, hypoxic, and ischemic conditions can be induced in tissue and cell culture models, allowing research to be conducted at a cellular and molecular level.8 In our studies, we have confirmed that although a central scratch method only wounds 5–10% of the surface cells, it is sufficient to successfully induce a wound environment in vitro.9 Work conducted in our laboratory is aimed at establishing dose response curves to demonstrate the effect of laser irradiation in a number of cell types by changing laser parameters such as fluence and wavelength.10,11 Additionally, the frequency of irradiation at different intervals has been varied.12 The aim of the work has always been to design research studies which are scientifically sound and publishable in order to establish evidence of the effect of laser phototherapy.13 Research demonstrating cellular and molecular responses to low intensity laser irradiation has used biochemical tests that are sensitive enough to distinguish changes between normal, wounded, diabetic wounded, acidic, and hypoxic human fibroblast cells in culture after exposure.9,13

Using established techniques including inverted microscopy, ELISAs, spectrophotometry, luminometry, immunofluorescent

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live imaging, RT-PCR, comet assays, and flow cytometry, our research in cell models shows changes in ATP viability, caspase 3/7 activity, proliferation, cytotoxicity, DNA integrity, reactive oxygen species (ROS), nitric oxide (NO) production, the pro-inflammatory cytokines TNF-α and IL-1β, and apoptosis when irradiated and compared with normal cells.14,15,16,17,18 These changes are always a function of the fluence and wavelength, and the duration of effect may vary.10 Irrefutable evidence from our own as well as many other reputable laboratories has been published demonstrating the significant beneficial effects on cells that laser irradiation induces. In vitro models may not only be used to study wound healing but also cellular responses related to other pathological conditions such as heart attack, stroke, diabetes, and biological or biochemical changes in response to treatment such as laser phototherapy.9,10

While the ideal study design to obtain firsthand evidence of the effects of low intensity laser irradiation on the healing process has to be clinical research conducted in patients suffering from chronic wounds, the use of cellular models has contributed extensively to our understanding of the intricate biochemical mechanisms underlying different diseased states. The more recent development of two and three dimensional tissue culture models will further contribute to the elucidation of the exact mechanisms that are activated at the cellular and molecular level to allow successful treatment of diseased conditions. Diabetes is the greatest contributing factor to the growing problem of chronic wounds, affecting approximately 170 million people worldwide, with projections indicating a doubling effect by 2030.19 Laser therapy is a treatment choice that appeals to patients with difficult wounds, and significant strides have been made in establishing it as a scientifically sound treatment modality. The extensive clinical evidence that has been published, together with the more recent identification and mapping of cellular factors that play a key role in the up-regulation of wound healing as a result of laser irradiation, has contributed to the future of laser therapy as one of the most promising treatment modalities.

References


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