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Review

Insulin and wound healing

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ABSTRACT

Skin is a dynamic and complex organ that relies on the interaction of different cell types, biomacromolecules and signaling molecules. Injury triggers a cascade of events designed to quickly restore skin integrity. Depending on the size and severity of the wound, extensive physiological and metabolic changes can occur, resulting in impaired wound healing and increased morbidity resulting in higher rates of death. While wound dressings provide a temporary barrier, they are inherently incapable of significantly restoring metabolic upsets, post-burn insulin resistance, and impaired wound healing in patients with extensive burns. Exogenous insulin application has therefore been investigated as a potential therapeutic intervention for nearly a century to improve wound recovery. This review will highlight the important achievements that demonstrate insulin's ability to stimulate cellular migration and burn wound recovery, as well as providing a perspective on future therapeutic applications and research directions.

Contents

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1. Burns and treatment

Burns are one of the most frequent skin injuries resulting from excess exposure to heat, caustic chemicals, solar, lumpectomy/mastectomy, or radiation [1]. Depending on the surface area and depth of a burn, healing times can vary significantly [2]. Most burns are treated using a dressing placed over the wound to isolate it from the environment. In more severe cases however, skin grafts, reconstructive surgery, or amputation may be required [3]. Rehabilitation following a burn can be difficult, painful, and time consuming. Burn wound treatments must therefore be initiated at the earliest possible opportunity to improve recovery and reduce the burden on healthcare resources.

Presently, burn treatments encompass a wide range of approaches depending on the condition of the burn. The majority of partial thickness burn wounds can be treated with a range of dressings including silver impregnated hydrocolloids to more traditional based materials such as white petrolatum coated gauze dressings [4]. These materials help prevent entry of foreign debris, maintain a moist wound healing environment and absorb excess exudate from the wound [5,6]. These materials are also widely available, affordable, convenient, and remain stable for extended periods, making them a gold standard in treatment [7]. Gauze dressings however, have no inherent capacity to promote wound healing beyond the natural rate of healing, and can destroy *de novo* tissue during dressing removal [8]. Therefore, new dressing technologies have been explored to overcome this limitation and to improve patient recovery.

In advanced trauma centers, more advanced materials and therapeutics can be applied to aid burn wound healing when significant reconstruction is required. Biologicals can be referred to as both the biopharmaceutical, or the dressing itself. Biological wound dressings for example, consist of human, porcine, or cadaver tissue which is pre-treated to produce an acellular scaffold, mimicking the native dermis and basement membrane. The use of biological dressings may however, give rise to rejection, transmit diseases, and are typically a temporary solution [9]. Application of growth factors in wound healing treatments has subsequently been tested as a method of promoting faster recovery by stimulating skin cells to migrate and proliferate more rapidly than naturally [10]. Historically, growth factors such as epidermal growth factor (EGF) and transforming growth factor beta (TGF-β) have been tested both in the laboratory and in the clinic with varying degrees of success [11,12]. Unfortunately, biological dressings and growth factors are difficult to store for extended periods, come at a high cost, and are usually complex to manipulate, thereby limiting their widespread clinical and commercial success.

Alternatively, insulin has been reported to promote wound healing, but in contrast to other growth factors, is lower in cost, available in a highly pure crystalline form, and is compatible with most common biomaterials used in wound dressings and drug delivery devices. Integration of insulin within a burn wound dressing would therefore be a potentially effective method of promoting wound healing, while reducing cost. Within the following review, the application of insulin both topically and systemically has been discussed in a historical context to highlight how insulin could be used in future wound dressings, and clinical approaches, while highlighting areas for further improving our understanding of insulin mediated healing.

2. Therapeutic biologicals in wound healing

Biologicals are a class of recombinant medicines that include monoclonal antibodies, nucleic acids, and small or large molecular weight proteins [13–15]. Approximately 150 recombinant biopharmaceuticals have been approved by the Food and Drug Administration (FDA) and the list of submissions and approvals continues to grow [16]. Recombinant peptides are an increasingly important therapeutic intervention against a variety of medical conditions including diabetic, oncologic, cardiovascular, immunosuppressive and gastroenterological diseases [17–21]. Growth factors are a subclass of biologicals that have the ability to stimulate, or inhibit cellular division, differentiation, migration, or gene expression in cells [22]. Growth factors can act in an autocrine, paracrine or endocrine fashion depending on the target receptor [23]. Once released, growth factors will either bind to their respective receptor, or become consumed by proteolytic enzymes resulting in degradation and inactivation. The action of growth factors is therefore strong and usually short-lived.

Biomedical researchers have examined the potential use of growth factors, especially in the field of wound healing [24]. Exhaustively investigated growth factors have included epidermal growth factor (EGF) [25], transforming growth factor beta (TGF-β) [26], and platelet derived growth factor (PDGF) [27]. Delivery of a growth factor to the wound allows the regenerative healing mechanisms to be initiated faster, as opposed to being released naturally by cells and tissues within the wound bed.

Unfortunately, the high cost of producing purified growth factors has prevented their integration into burn wound dressings. Beginning in the 1970s, growth factors were first harvested by processing tissue and/or blood samples from animals and humans [28]. Tissues would undergo mechanical and chemical treatments to yield small quantities of semi-pure growth factors. This approach was laborious and ineffective in sustaining large scale production. As molecular techniques advanced, recombinant technologies utilizing bacteria and yeast made it easier and safer to increase production [29]. As a result, the mean cost of growth factors such as EGF, TGF-β and other highly specialized growth factors can be upwards of $1500–10,000 USD per mg. Growth factor application in wound healing technologies has therefore been confined largely to experimental settings, and not commercial markets.