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Mini Review

Skin-On-Chips for Drug Discovery of Chronic Wounds

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Abstract

Chronic wound is a big problem in a society faced with demographic change and aging. There is a great need for better wound treatment, in particular to cure diabetic foot ulcers, venous leg ulcers, and pressure ulcers. Approaches to increase the efficiency in developing therapeutics of chronic wounds are of great interest. This review summarizes the pathophysiology of complex chronic wounds and the current development of skin-on-chips technologies, and their applications for improved drug discovery and development.

Keywords: Wound healing; Chronic wound; Diabetic foot ulcers; Drug discovery; Organ-on-chips; Skin-on-chips

Abbreviations

COX-2: Cyclo-Oxygenase-2; ECM: Extracellular Matrix; EGFR: Epidermal Growth Factor Receptor; FGF-2: Basic Fibroblast Growth Factor; IL-6: Interleukin-6; IL-17: Interleukin-17; PDGF: Platelet-Derived Growth Factor; PPAR-γ: Peroxisome Proliferator Activated Receptor Gamma; ROS: Reactive Oxygen Species; TGF-β: Transforming Growth Factor Beta; TNF-α: Tumor Necrosis Factor-α; VEGF: Vascular Endothelial Growth Factor

Introduction

Diabetic foot ulcers, venous leg ulcers, and pressure ulcers contribute to majority of chronic wounds. The importance of improved wound healing measure is especially well demonstrated by the healing problems in diabetes. It is estimated that about 30% of all the costs for diabetes relates to wound care in USA. In addition, 2.4-4.5 million people have been reported to have chronic lower extremity ulcers in USA only. Pressure ulcers and leg ulcers, including venous ulcers, cost as high as $8 billion annually in USA, and are a significant cause of morbidity in aged population [1-3]. Although a slow wound repair is a self-limiting process and not a pathogenesis in itself, severe chronic wounds can also lead to chronic inflammatory diseases, fibrosis, and cancer, comprising stifling economic health care burdens.

The Challenges in the Treatment of Chronic Wound

Wound healing in clinical settings relies primarily on enabling the natural course of epidermal tissue regeneration [4]. In many cases, the involved processes and the progress of regeneration may be insufficient to save severely injured patients. Especially difficult are various types of chronic wounds, with diabetic wounds being the most severe type [5]. Current conventional treatment of chronic wound comprises mainly approaches with various types of dressings, bandages, and antibiotics. Several skin substitutes have reached the market place for second-line therapy of chronic ulcers, but they have not had the impact that was predicted [6]. In severe cases where the wounds do not heal, amputation is the only treatment option that is available. Therefore, there is a great need for better wound healing treatments, in particular to cure diabetic and other chronic wounds. Another challenge in clinics is the lack of available evidence demonstrating efficacy for the advanced wound care products. Personalized medicine based on a systematic evaluation of patients and their wound conditions comprise an attractive approach to accelerate and strengthen wound healing processes in the future.

The Factors Contributing to Delayed Wound Healing

The physiological healing process in acute wounds occurs as four tightly coordinated and overlapping phases haemostasis, inflammation, tissue formation (proliferation), and remodeling [7]. Immediately upon tissue injury, wounded vessels constrict rapidly and the coagulation cascade is activated to limit blood loss, leading to the formation of the clot, providing the provisional matrix for cellular migration and platelet aggregation. The inflammation stage follows haemostasis phase within the first few days after the injury, when inflammatory and immune cells are recruited from neighboring regions or from circulation to the wound site by complement, clotting components, and cytokines to clear the wound of cell debris and bacteria. The inflammatory and immune responses are accompanied with a coincident activation of surrounding tissue, which takes place over days to weeks, characterized by the replacement of the provisional fibrin/fibronectin matrix with newly formed granulation tissue. Following injury, fibroblasts and myofibroblasts are stimulated to migrate into the wound defect, proliferate and produce collagen and other matrix proteins to support further in growth of cells. Angiogenic capillary sprouts invade the provisional matrix and organize into a microvascular network throughout the newly formed granulation tissue. Upon injury, epithelial cells at the wound edge migrate to the wound surface, proliferate and differentiate to re-establishes coverage of the wound bed, a complex process termed re-epithlialization [8,9]. The final remodeling phase allow underlying contractile connective tissue shrinking in size and bring the wound margins closer together. With continued remodeling, the outgrowth of capillaries is halted and the density of macrophages and fibroblasts is reduced by apoptosis, finally leading to an a cellular, avascular scar [9].

Recent advances added significantly to our current understanding of the complex roles of pathophysiology of chronic

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Table 1: Pathophysiological components underling impaired wound healing.

Stage	Cell components	ECM	Soluble factors
Haemostasis phase	platelets activation	fibrinogen deposition and cleavage Fibrin clot formation	Complements TGF- β Chemokines
Inflammation phase	Innate immune cell activation (Eosinophil, Neutrophil, Macrophage) Adaptive immune cell activation (T-cell, B-cell) Fibroblast activation and transformation into myofibroblast Cell migration (reginal or systematic recruitment)	Activated fibroblasts produce ECM	ROS IL-6 IL-17 TGF-β TNF-α COX-2 PPAR-γ
Proliferation phase	Endothelial cell priming, activation and sprouting (angiogenesis) Fibroblast migration and proliferation Myofibroblast activation and wound contraction Epithelial cell migration and proliferation (Re-epithelialization) Epithelial to mesenchymal transition (EMT)	Collagen synthesis ECM deposition	FGF-2 VEGF PDGF EGFR
Remodelling phase	Vessel regression Cell degradation Scar maturation	Collagen fiber remodeling ECM degradation	MMPs

Table 2: The advantages and shortcomings of current skin-on-a-chip devices.

Impact	Skin-on-a-chip
Benefits	- Well suited for detailed studies of material-bio interactions and evaluation of therapeutic efficacy in a more physiological context - The chips can incorporate primary cell isolated from patients or cells differentiated from induced pluripotent cells such as skin fibroblasts to mimick human chronic wound pathophysiology. This enables the evaluation of individual responses to therapies - Relevant *in vitro* models for evaluating biomaterial interactions with human tissues, as well as testing pharmacokinetics and pharmacodynamics and efficacy of new therapeutics - Avoid the problem in mouse models as mouse skin lack of sweat glands - Useful to study biocompatibility, toxicity and therapeutic efficacy over the whole period of wound healing - Suitable for high resolution imaging and detailed analysis of the interaction between biomaterial scaffoldand cells, cellular structures and biological barriers - Very useful for predicting patient response to new compounds and new biomaterials, which has been traditionally challenging
Limitations	- Slow manufacturing process - Expensive - Demandingskills and special biofabrication facilities - The functionality of the tissue, as well as the environmental components need to be constantly monitored - challenges for detecting cellular responses to external stimuli, monitoring the 3D microenvironment

wounds. Although the underlying pathologies among various types of chronic wounds differ, some common features shared by these wounds include prolonged drug-resistant bacterial infections, persistent or chronic inflammation, and the inability of dermal and/or epidermal cells to proliferate, differentiate and migrate upon regenerative stimuli. In Table 1, we have listed the pathophysiological components that underlie impaired healing. Therefore, targeting these pathophysiological factors represents a powerful therapeutic of chronic ulcers and inflammatory diseases.

Traditional *in vitro* models of wound healing are based on static culture systems of fibroblasts and keratinocytes that only emulate human epidermis [10]. The complicated structure of the skin cannot be mimicked in the absence of multiple epithelial cell layers, a lack of epithelial-mesenchymal interactions, the absence of other skin structures (hair follicles, immune cells, melanocytes, Merkel cell complexes, blood vessels, nerve fibers, etc), characteristics that are present in native tissues [7,11]. Researchers in a wide variety of industrial, clinical and academic fields are anticipating the development of *in vitro* skin models capable of simulating critical and common skin diseases. For instance, constructing new types of skin injury model system represents one cogent application of new therapy screening.

Skin-on-chips are micro fluidic cell culture devices combined with novel micro- and nano scale technologies [12,13]. Recent advances in tissue engineering, biomaterials and micro fluidics have led to the development of micro scale functional units of such models also referred to as 'organs on a chip'. Extensive recent reviews summarized the enabling technologies for on-chip tissue models that may tailor cellular and tissue microenvironments with high spatiotemporal control over the environmental cues to regulate cellular behavior [14-18]. As an example, technology advances in the engineering and micro fabrication of "skin-on-chips" enable integrating cells, signals, and scaffolding material to recapitulate skin structure and functions [19]. These chips can mimic the full thickness wounds that involve the loss of both the epidermal and dermal layers of the skin [20]. Keratinocytes, fibroblasts, endothelial cells, as well as inflammatory cells can be cultured in these devices. Cell shape, cell-cell contact, cell-ECM interactions, and cell-soluble factor components can be regulated on the chips to mimic the human-specific pathophysiological context [21,22].

As no ideal wound therapy has been identified till date, the novel tissue-engineering approaches are showing tremendous promise to replace animal test for drug screening, drug development and personalized medicine to treat various types of chronic wounds [18,23-25]. For instance, a bilayer skin composite model consisting of a collagen lattice with dermal fibroblasts, covered with epidermal keratinocytes, is not only for mechanistic discovery, but also being evaluated in clinical trials for the treatment of burns and in patients with epidermolysis bullosa [22]. In a recent study, a micro fluidic human skin-on-a-chip device was developed consisting of three layers to mimic the epidermis, dermis and vessels in the skin. Each

layer was separated from the others by transparent and porous membranes, allowing dynamic interlayer communication among human epidermal, dermal and endothelial cells [26]. Interestingly, this skin chip was used to evaluate the efficacy and toxicity of therapeutic drug of skin disease [26]. Therefore, high-throughput experiments can be expected to be performed on the skin-on-a-chip platform with controlled mechanical, chemical and electrical stimuli and enable identification of new therapeutic targets of chronic wounds *in vitro* [27,28]. The advantages and shortcomings of current skin-on-a-chip devices are listed in Table 2.

The Future

This review covers several aspects of the wound pathophysiology, the current development of skin-on-chips technologies, and their applications for improved drug discovery and development. With further advances in tissue engineering, biomaterials and micro fluidics, developing functional skin on a chip is becoming a more realistic goal for various diagnostics and drug screening applications. Finally, we highlight future opportunities within the field. It is import to provide innovative and tailored solutions to the integration of biological, materials science, and pharmacological processes on skin-on-a-chip model system. Development of new manufacturing technologies, such as 3D printing and integrated quality control will pave the way for more individualized drug discovery. Furthermore, the system will enable the generation of personalized data by using patient derived induced pluripotent stem cells. Based on the pathophysiology of complex chronic wounds, engineering more complex skin-on-a-chip systems are required to incorporate not only the diseased cells but also the diseased 3D microenvironment, together with the development of potent readout assays (such as imaging) for evaluation of drug efficacy and toxicity at different time points of wound development. Additional advances in real-time, remote sensing, in situ monitoring of the microenvironment and cellular and/or metabolic responses, and intelligence will lead to a revolution of next generation of skin-on-a-chip devices in diagnosis and treatment of tissue repair and regeneration in wound healing.

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