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Advances in electrospun skin substitutes

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ABSTRACT

In recent years, nanotechnology has received much attention in regenerative medicine, partly owing to the production of nanoscale structures that mimic the collagen fibrils of the native extracellular matrix. Electrospinning is a widely used technique to produce micro-nanofibers due its versatility, low cost and easy use that has been assuming an increasingly prominent position in the tissue engineering field. Electrospun systems have been especially investigated for wound dressings in skin regeneration given the intrinsic suitability of fibrous structures for that purpose. Several efforts have been made to combine distinct design strategies, synthetic and/or natural materials, fiber orientations and incorporation of substances (e.g. drugs, peptides, growth factors or other biomolecules) to develop an optimized electrospun wound dressing mimicking the native skin. This paper presents a comprehensive review on current and advanced electrospinning strategies for skin regeneration. Recent advances have been mainly focused on the materials used rather than on sophisticated fabrication strategies to generate biomimetic and complex constructs that resemble the mechanical and structural properties of the skin. The technological limitations of conventional strategies, such as random, aligned and core-shell technologies, and their poor mimicking of the native tissue are discussed. Advanced strategies, such as hybrid structures, cell and *in situ* electrospinning, are highlighted in the way they may contribute to circumvent the limitations of conventional strategies, through the combination of different technologies and approaches. The main research challenges and future trends of electrospinning for skin regeneration are discussed in the light of *in vitro* but mainly *in vivo* evidence.

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1. Introduction

The first shield between the external environment and the human body is the skin. This tissue plays a crucial role in body protection and, when damaged at full-size, the human life could be in risk [1,2]. According to the World Health Organization (WHO) it is estimated that every year 265,000 deaths occurs caused by burns and, annually about 6 million people were burned requiring medical attention [3–6]. The average length of stay in the hospital is 8.4 days, thus resulting in a considerable social and economic burden for the health care systems worldwide. Therefore, innovative strategies are required to promote skin tissue regeneration, despite the encouraging recent developments in wound dressings and tissue engineering-based products [7]. Electrospun meshes have been gaining increasing attention through the combination of materials and processing strategies of great potential for skin regeneration [8]. Wound dressings prepared from electrospun nanofibers have been claimed to present exceptional properties compared to conventional dressings, such as similarity to architecture of the natural extracellular matrix (ECM), improved promotion of hemostasis, absorption of wound exudates, permeability, conformability to the wound, and avoidance of scar induction [9]. New processing strategies are thus being explored in which natural and synthetic materials are combined with new design approaches allowing the incorporation of substances that turn not electrospinnable materials into electrospinnable ones. In this review skin regeneration strategies will be revised with a focus on electrospinning methodologies and materials.

2. Skin tissue and wound healing process

The human body comprises several organs each one with specific functions, dimensions and shapes. The largest vital organ in the body is the skin that represents 7% of the total body weight and has the main function of protecting the human being against the external environment. It also helps protecting the body against excessive water loss, against attacks from chemicals and other harmful substances, and ultraviolet radiation [1,8,10–12]. In spite of the protective function of the skin, this tissue plays other important functions namely: (i) control of body temperature, by secreting sweat through the sweat glands, thereby lowering the temperature; (ii) sensory, through different receptors able to detect touch, pain, pressure and temperature; and (iii) synthesis of vitamin D (after exposure to sunlight), a precursor of calcitriol hormone that is converted in the liver and kidneys and plays an important role in the calcium absorption in the small intestine [10,13]. Although the skin works as a barrier it is not totally impermeable: some substances are transferred across the skin, such as sweat, drugs and biomolecules [10,14].

Skin functions are carried out by specialized cells and structures found in the two main skin layers, epidermis and dermis (Fig. 1). Besides these two layers, beneath the dermis there is the hypodermis that provides support to the dermis [10,15]. The epidermis, the outermost skin layer, is around 120 μm thick and is composed by numerous cells closely linked in different stages of differentiation, which form the stratified squamous epithelium [10]. The epidermis is avascular (nourished through diffusion from the dermis), consists of 4 different types of cells (keratinocytes, melanocytes, Langerhans cells and merkels cells) and presents 5 distinct cell layers (stratum basale, spinosum, granolosum, lucidum and corneum) [16,17]. The dermis layer is composed by a complex mesh of ECM material that provides structure and resilience to the skin. The thickness of this layer varies according to the body region but is in average of 2 mm [10,17]. The dermis is composed by a nanometer-sized network of structural proteins (collagen, which provides strength and flexibility, and elastin, which provides elasticity), blood and lymph vessels, and specialized cells (mast cells that help in the healing process and protect against pathogenic organisms, and fibroblasts that produce collagen and elastin). This ECM network is engaged in a ground substance that is mostly composed by glycosaminoglycans and plays an important role in hydration and in maintaining moisture levels in the skin [10,14]. The ECM is also highly dynamic, being constantly synthesized and re-organized by the cellular components, but in turn also having a prominent role in directing cellular behaviour through direct and indirect signaling. For instance, ECM molecules control cell adhesion through specific cell binding sites, cell migration through

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