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Skin wound healing in humans and mice: Challenges in translational research

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ABSTRACT

Despite the great progress in translational research concerning skin wound healing in the last few decades, no animal model fully predicts all clinical outcomes. The mouse is the most commonly used model, as it is easy to maintain and standardize, and is economically accessible. However, differences between murine and human skin repair, such as the contraction promoted by *panniculus carnosus* and the role of specific niches of skin stem cells, make it difficult to bridge the gap between preclinical and clinical studies. Therefore, this review highlights the particularities of each species concerning skin morphophysiology, immunology, and genetics, which is essential to properly interpret findings and translate them to medicine.

1. Introduction

Skin, the first protective barrier of all animals, has evolved and specialized differently among fish, reptiles, birds and mammals [1]. Epidermis, the outermost layer, consists of a stratified squamous epithelium of keratinocytes delimited by the basal membrane, and contains melanocytes and Langerhans and Merkel cells. Dermis, the internal layer that provides structural integrity, elasticity, and nutrition, is a connective tissue composed by fibroblasts and extracellular matrix enriched in collagen and elastic fibers [2–4], and also contains blood and lymphatic vessels, sebaceous glands, sweat glands, nerve endings, and hair follicles invaginated from epidermis [5–7].

As skin is constantly challenged by a wide variety of external factors, it is highly susceptible to trauma [8]. Complex intra and intercellular mechanisms are triggered after damage to recover tissue homeostasis [9,10]. In mammals, tissue repair reestablishes skin homeostasis, but not its complete functional activity [11]. The event cascades triggered after skin lesion and scar formation is very similar to those of myocardial infarction or spinal cord injury [10,12]. In this sense, and due to its accessibility, skin is one of the best models to study tissue repair mechanisms and to develop new strategies in regenerative medicine [9].

Despite the recent progress in stem cell field, no current experimental model fully predicts the outcomes of clinical trials [13,14]. Although *in vitro* models address repair pathways of specific cell populations, they do not recreate the complexity of the healing process [14,15]. Animal models are, therefore, essential to elucidate the physiological and pathological mechanisms of tissue repair [15,16].

Despite interspecies differences, the murine model has greatly contributed to understanding normal and pathological cutaneous repair. As skin repair in mice does not perfectly mirror that of humans, studies face challenges in bridging the gap between preclinical and clinical studies [9,17]. Knowing the particularities of each species is fundamental to properly interpret the results. Therefore, this review aims to compare human and murine skin wound healing to achieve adequate translation to medicine.

2. Mice as model for human skin wound healing

Mice (*Mus musculus*) is the most commonly used animal model, especially in studies of physiology and biochemistry, [9,13,15,18] since they are easy to handle and maintain, reproduce rapidly, and are economically accessible [15,18]. They can be standardized by age, sex, history and genetic predisposition, and allows the use of a

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relatively high number of animals for statistic validation [14]. Furthermore, genetically modified lineages have been developed to investigate the molecular pathways of healing and regeneration [15,16]. However, mice have small bodies, shorter life expectancy, and differences in physiology compared to humans [16,19]. They do not effectively reproduce the whole pathogenesis of certain human diseases, such as diabetes, and can develop obesity and hypertension due to *ad libitum* feeding [16,17].

In this context, the use of larger mammals that are physiologically closer to humans, such as pigs, have increased in translational studies [13,16]. Porcine skin structure and healing are similar to human. Certain pathological conditions not reproducible in other animals, such as hypertrophic scars, are well described in Red Duroc pigs [13,15]. On the other hand, pigs are expensive, genetically heterogeneous, and require manipulation training, especially concerning anesthetic, surgical, and post-surgical procedures [9,14,15]. Moreover, pigs are not well characterized at cellular and physiological levels when compared to mice, and specific swine reagents, such as antibodies and growth factors, are still not available [16]. Because of these, the vast majority of studies concerning skin wound healing is performed in mice.

3. Morphofunctional characteristics of human and murine skin

Skin healing is similar in humans and mice when considering the distinct and overlapping phases of highly complex cellular and molecular events: homeostasis, inflammation, proliferation, and remodeling, [9,10,20–22] summarized in Fig. 1. Much of the molecular processes are poorly understood and are possibly the reason why current therapies do not result in optimal repair [9,15].

Although human and murine skin has the same layers of cells in the dermis and epidermis, they greatly differ in thickness and number (Fig. 2). Human skin is relatively thick (over 100 μm), firm, and adhered to the underlying tissues, whereas murine skin is thinner (less than 25 μm) and loose [15,17,18]. Human epidermis is composed of 5 to 10 cell layers, whereas murine skin contains only

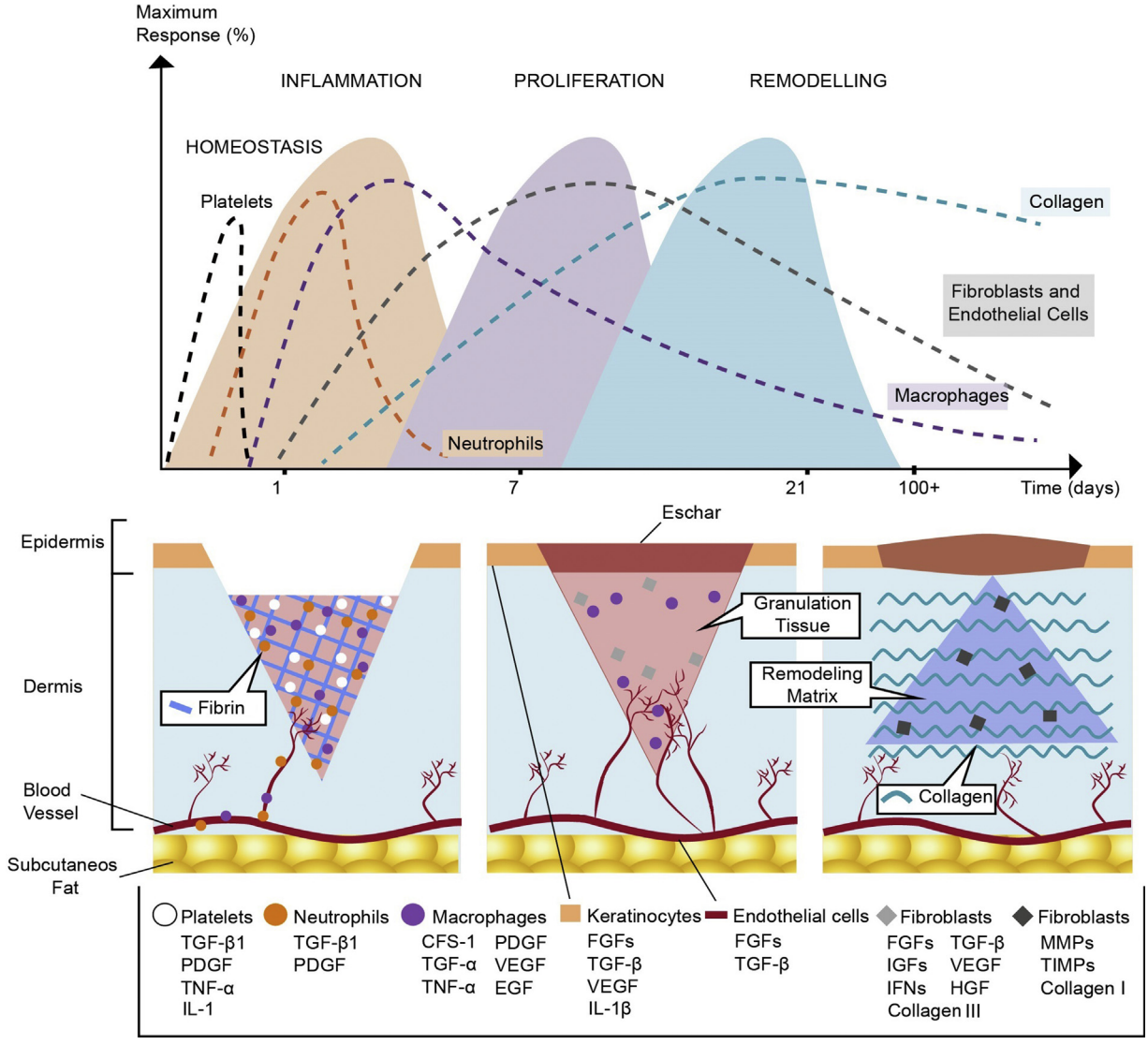

Fig. 1. Skin wound healing.
In the upper panel, the phases of tissue repair (homeostasis, inflammation, proliferation and remodeling) are shown over time. Dotted lines show involvement of platelets, collagen, and cells during the process. The bottom panel highlights cell-secreted proteins involved in healing. Abbreviations: TGF-β: transforming growth factor β; PDGF: platelet-derived growth factor, TNF-α: tumor necrosis factor α, IL-1: interleukin 1, CSF-1: colony stimulating factor 1, TGF-α: transforming growth factor α, VEGF: vascular endothelial growth factor, EGF: Epidermal growth factor, IGFs: insulin-like growth factor, IFNs: interferons, HGFs: hepatocyte growth factor, FGFs: fibroblast growth factor, MMPs: metalloproteinases, TIMPs: metalloproteinase inhibitors.

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