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Review article

Learning from regeneration research organisms: The circuitous road to scar free wound healing

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ABSTRACT

The skin is the largest organ in the body and plays multiple essential roles ranging from regulating temperature, preventing infection and ultimately defining who we are physically. It is a highly dynamic organ that constantly replaces the outermost cells throughout life. However, when faced with a major injury, human skin cannot restore a significant lesion to its original functionality, instead a reparative scar is formed. In contrast to this, many other species have the unique ability to regenerate full thickness skin without formation of scar tissue. Here we review recent advances in the field that shed light on how the skin cells in regenerative species react to injury to prevent scar formation versus scar forming humans.

1. Introduction

Open wounds or scar tissue caused due to genetic skin diseases or as a result of traumatic burn or blast injuries have a devastating effect on people's lives and pose a huge financial burden. Serious skin disorders count among the most devastating health conditions and most difficult treatment challenges. These arise both from genetic diseases and from injuries, such as the often debilitating long-term suffering of the > 500,000 serious burn victims who are hospitalized every year in the US alone. Today's top treatments, including major skin grafts, still struggle to overcome the key natural limitations of human skin's relatively basic repair processes. While these generally restore structural integrity, they often result in extensive scarring that not only causes disfigurement and accompanying psychological trauma, but also significant loss of functionality, including impaired sensitivity and increased susceptibility to infection.

The development of more effective skin therapies may in the future benefit greatly from emerging new understanding of the remarkable healing abilities exhibited by species that naturally regenerate scar-free.

In recent years regeneration research organisms that are able to regenerate skin without the formation of permanent scar tissue have provided interesting new insights into the mechanism of scar-free wound healing. These research organisms include classic developmental organisms such as *Danio rerio, Xenopus* genus, and urodele amphibians such as *Ambystoma mexicanum*. Additionally, newly emerging research organisms including the African spiny mouse, *Acomys* spp., and the crustacean *Paryhale* add to the repertoire of research organisms that expand our understanding of the conserved and divergent mechanisms different species employ to functionally regenerate complex tissue.

This review will discuss mammalian skin development and it's response to injury. We will review recent findings in skin regeneration from research organisms and commonalities of the scar-free wound healing process will be discussed.

2. Mammalian skin development

2.1. Epidermis formation and homeostatic replacement

Embryos develop three distinct lineages, the endoderm, ectoderm, and mesoderm. During embryonic development, the skin arises from two different germ layers. The epidermal cells (those lying above the basal lamina); develop from non-neural ectoderm (Nassar and Blanpain, 2012; Sotiropoulou and Blanpain, 2012). In contrast, dermal cells (those lying below the basal lamina), develop from the mesoderm (Fuchs, 2016). Cells of the ectoderm lineage have the potential to become either the nervous system, tooth enamel, or epithelium (Fuchs, 2016). Wnt signaling during the early stages of development plays an important role in determining cell fate (Grigoryan et al., 2008; Nassar and Blanpain, 2012; Sotiropoulou and Blanpain, 2012). Cells that receive Wnt signals will not respond to fibroblast growth factors (FGFs) (Fuchs, 2016; Grigoryan et al., 2008). In the absence of FGF signaling, these ectoderm lineage cells produce bone morphogenic proteins (BMPs), and the BMP signaling cascade ultimately results in these cells becoming epidermis (Clayton et al., 2007; Fuchs, 2016; Grigoryan et al., 2008; Jensen et al., 1995;

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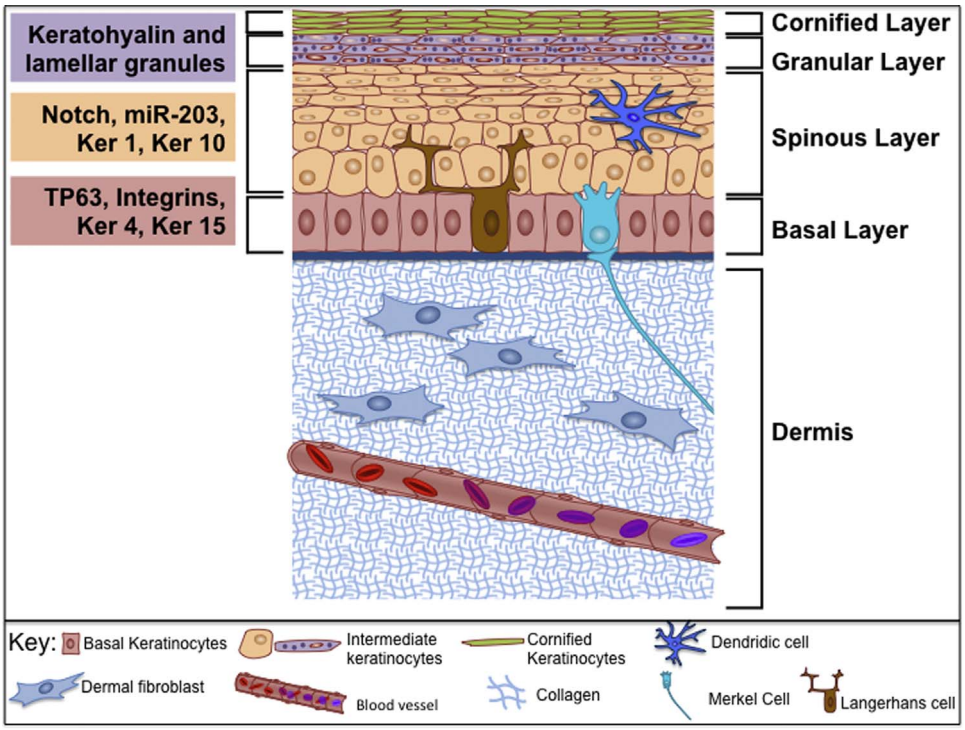

Fig. 1. Schematic diagram of mature mammalian skin. Skin consists of several layers of keratinocytes (indicated on the right) that differentiate as cells proceed from the basal layer to the cornified layer. As keratinocytes move through these layers of skin, their morphology and gene expression profiles also change (indicated on the left). Basal keratinocytes are the least differentiated cells and will express, TP63, several integrins, Keratin 4 and Keratin 15. Once keratinocytes are in the spinous layer, expression of Notch, miR-203, Keratin 1 and Keratin 10 will occur. After keratinocytes proceed through the granular layer, marked by keratohyalin and lamellar granules, keratinocytes will extrude all organelles and become cornified skeletons that form a ridged keratin network to form a barrier.

Kurata et al., 2004; Lechler and Fuchs, 2005; Poulson and Lechler, 2010; Sotiropoulou and Blanpain, 2012; Strachan and Ghadially, 2008). Eventually, the epidermis will be comprised of four different cell types: the most predominant epidermal cell type is the keratinocyte, which constitutes 80–90% of the cellular epidermis (Fig. 1; Nassar and Blanpain, 2012). The main function of keratinocytes is to form a barrier against the external environment. The mature skin contains, melanocytes, Langerhans cells and Merkel cells (Fig. 1). Each of these cell types has an important function within the skin. For example, the neural crest derived melanocytes produce melanin that affords protection from UV damage (Bin et al., 2016). Langerhans cells are a type of dendritic cell immune cell that protects against infection (Berberich et al., 2003). Lastly, the Merkel cells, are involved in the sense of touch by making contacts with sensory nerve endings (Fig. 1) (Sorenson and Clark Brelje, 2014).

During embryonic development the epidermis forms as a single cell layer of multipotent cells that express Tumor protein p63 (TP63 or p63), a gene necessary to maintain the epidermal progenitor population (Koster et al., 2004; Mikkola, 2007; Pozzi et al., 2009; Testoni et al., 2006; Westfall and Pietenpol, 2004). As development progresses, the $p63^{+}$ epidermal basal progenitors undergo a spindle shift to create one daughter in the basal layer and one daughter in the suprabasal, differentiating layer (Candi et al., 2006; Koster et al., 2004; Mikkola, 2007; Pozzi et al., 2009). The basal daughter continues to express p63, while the suprabasal daughter loses p63 expression in coordination with Notch signaling-dependent differentiation (Okuyama et al., 2007; Tadeu and Horsley, 2013; Truong and Khavari, 2007). Recent research has shown that p63 is post-transcriptionally regulated by miR-203 and that this leads to reduced p63 expression during differentiation (Lena et al., 2008). MiR-203 expression increases in the suprabasal daughter cell, leading to a decreasing abundance of p63; thereby promoting differentiation (Truong and Khavari, 2007).

p63 plays a pivotal role in epidermal development but also has a key role in regulating keratinocyte homeostasis in mature skin (Borrelli et al., 2010; Kouwenhoven et al., 2015; McDade and McCance, 2010; Pozzi et al., 2009; Testoni et al., 2006; Truong et al., 2006). Depletion of p63 in keratinocytes results in decreased proliferation and a subsequent loss of stratified epithelium (Truong et al., 2006). As proliferative progenitors differentiate and migrate away from the basal lamina to become spinous suprabasal cells, a number of transcriptional changes occur which ultimately lead to stratified epithelium. For example, expression of Notch receptors, Keratin 1, and Keratin 10 are increased during this process, with a concordant loss of expression of Keratin 5 and Keratin 14 (Fig. 1). Once cells reach the granular layer, keratinocytes start producing both keratohyalin and lamellar granules (Fuchs, 2016). The final step of terminal differentiation is the extrusion of cellular organelles (including the nucleus) to leave a cornified framework that provides structure and protection (Fuchs, 2016).

In humans, the process outlined in the preceding paragraph takes approximately four weeks (Schoenwolf et al., 2014). This developmental cycle (termed homeostatic replacement) is not restricted to embryonic development and occurs throughout life. In mouse studies of skin development there are currently two models proposed for how homeostatic maintenance of the skin occurs: the hierarchical model and the stochastic model (Alcolea and Jones, 2014; Jensen et al., 1999; Yan and Owens, 2008; Yang et al., 2015). The hierarchical model suggest that divisions by basal progenitor cells will generate rapidly dividing transity amplfligying cells, which then give rise to differentiated cells. While the stochastic model suggest that all basal cells have equal proliferative capacity, and proliferation can yield three different outcomes: 1. basal cell self renewal and one differentiated daughter cell, 2. two basal progenitors, 3. two differentiated daughter cells. The combination of genetic tools and in vivo imaging is currently helping to delineate between the two proposed models (Clayton et al., 2007; Doupe and Jones, 2013; Mascre et al., 2012; Rompolas et al., 2016).