Review

The Modulatable Stem Cell Niche: Tissue Interactions during Hair and Feather Follicle Regeneration

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Abstract

Hair and feathers are unique because (1) their stem cells are contained within a follicle structure, (2) they undergo cyclic regeneration repetitively throughout life, (3) regeneration occurs physiologically in healthy individuals and (4) regeneration is also induced in response to injury. Precise control of this cyclic regeneration process is essential for maintaining the homeostasis of living organisms. While stem cells are regulated by the intra-follicle-adjacent micro-environmental niche, this niche is also modulated dynamically by extra-follicular macro-environmental signals, allowing stem cells to adapt to a larger changing environment and physiological needs. Here we review several examples of macro-environments that communicate with the follicles: intradermal adipose tissue, innate immune system, sex hormones, aging, circadian rhythm and seasonal rhythms. Related diseases are also discussed. Unveiling the mechanisms of how stem cell niches are modulated provides clues for regenerative medicine. Given that stem cells are hard to manipulate, focusing translational therapeutic applications at the environments appears to be a more practical approach.

Specialized stem cells residing in most tissues and organs possess the capacity for self-renewal, as well as for multi-potent differentiation to maintain organ function and organismal health. In some tissues, such as the skin and intestines, stem cells remain in a prolonged quiescent state. However, in most tissues, stem cells may be transiently activated when needed during physiological organ regeneration or in response to injury [1,2]. Therefore, it seems that our ability to overcome degenerative disorders and aging problems is not just a dream but is a reachable goal if we can identify and harvest stem cells in various tissues. However, stem cells are relatively rare and are difficult to distinguish from their neighbors with current molecular markers. Rather than isolating and transplanting stem cells, one could simply augment natural mechanisms to activate resident stem cells within the tissue of interest. To date, it has not been easy to regulate stem cell activity, even though they are controlled in part by their specialized shelter, the so-called niche [3–5]. Using a variety of approaches, it has become apparent that regulating stem cell activity is more complicated than previously imagined; thus, it will take a concerted effort to resolve this puzzle.

The skin as a model organ

The skin is a multi-layered epidermis overlying the dermis that rests upon adipose tissue. One of the main functions of skin is to form a barrier to prevent loss of fluids. It also serves to prevent infection using an immune system composed of Langerhans cells in the epidermis and macrophages, mast cells and lymphocytes within the dermis. The skin is highly vascularized and innervated. Hair follicles and sweat glands are mini-organs that reside within the skin (Fig. 1). Thus, the skin is a complex organ that serves many functions that are essential to life.

The hair follicle stem cell model

The hair follicle is a great model in which to study stem cell biology because it is one of the few organs that can regenerate cyclically throughout life. The cyclic process goes through phases of anagen (growth phase), catagen (involution phase) and telogen (resting phase) (Fig. 2). This cycle allows hair stem cells to briefly exit their quiescent status to generate transient amplifying progeny and differentiate into different portions of the hair follicles. Hair stem cells located in the bulge area can be activated by physiological processes or in response to injury.

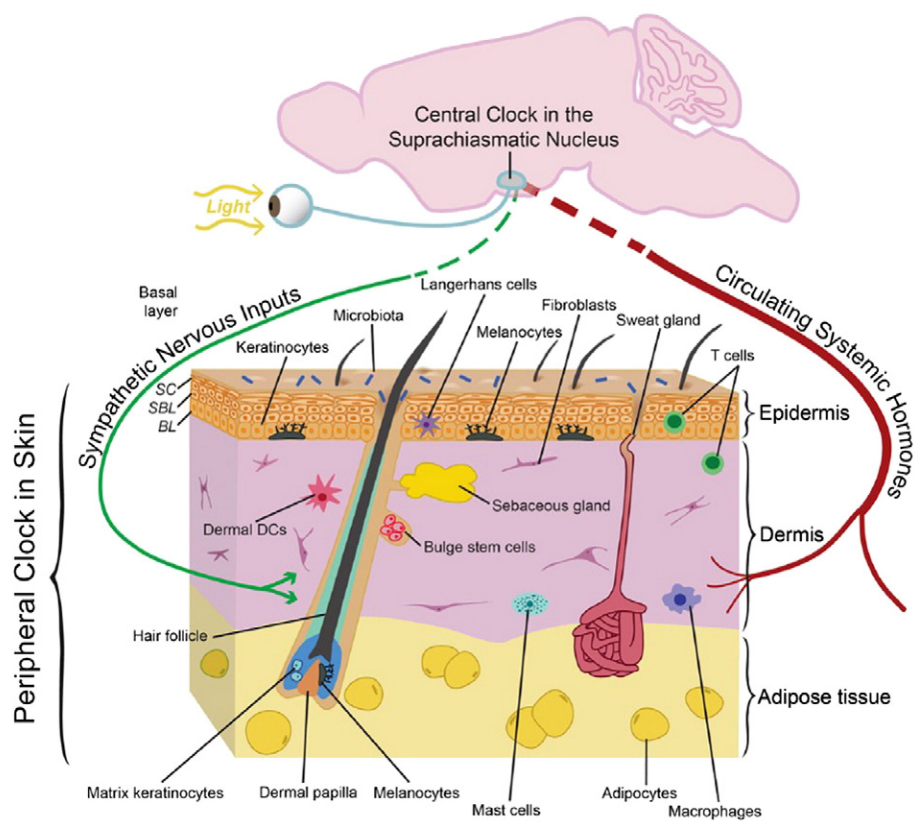

Fig. 1. Skin structure with many different tissue components within and input from the external environment. The epidermis is composed of three layers. (1) Epidermis, the outermost layer, is mainly composed by keratinocytes. It prevents water loss and functions as a barrier to infection through immune cells, like Langerhans cells, residing within. (2) Dermis, the middle layer of the skin, contains three major cell types, fibroblasts, adipocytes and immune cells, including macrophages, mast cells and lymphocytes. (3) Adipocytes reside within the subcutaneous layer. Melanocytes, the pigment-producing cells, are also located within epidermis and color the skin and hairs. In humans, melanocytes appear in both hair follicles and inter-follicular epidermis; however, in mouse, melanocytes can only be found within hair follicles and become activated during hair regeneration. Hair follicles, which regenerate cyclically throughout life and sweat glands, the skin cooling system, are two other important mini-organs inhabiting the skin. The skin is also richly vascularized and innervated; cells within these structures likely have their own circadian clock that could modify their functions including sensory responses, heat regulation and oxygenation. There is evidence for an active circadian clock in all cell types of the skin, and it is highly likely that distinct functions are modulated in different cell types. It is also known that circadian clock activity in skin is coordinated by the suprachiasmatic nucleus, presumably through neuronal and hormonal mediators, although this remains to be defined in skin. (Adopted from Plikus *et al.* [55].)