Journal of Dermatological Science 66 (2012) 3–11

Contents lists available at SciVerse ScienceDirect

Journal of Dermatological Science

journal homepage: www.elsevier.com/jds

Invited review article

Multi-layered environmental regulation on the homeostasis of stem cells: The saga of hair growth and alopecia

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ARTICLE INFO

Article history:
Received 6 January 2012
Received in revised form 20 February 2012
Accepted 21 February 2012

Keywords:
Regeneration
Niche
Macro-environment
Stem cell
Bmp
Sfrp
Dkk
Hair
Alopecia
Adipose cell

ABSTRACT

Stem cells are fascinating because of their potential in regenerative medicine. Stem cell homeostasis has been thought to be mainly regulated by signals from their adjacent micro-environment named the "stem cell niche". However, recent studies reveal that there can be multiple layers of environmental controls. Here we review these environmental controls using the paradigm of hair stem cells, because to observe and analyze the growth of hair is easier due to their characteristic cyclic regeneration pattern. The length of hair fibers is regulated by the duration of the growth period. In the hair follicles, hair stem cells located in the follicle bulge interact with signals from the dermal papilla. Outside of the follicle, activation of hair stem cells has been shown to be modulated by molecules released from the intra-dermal adipose tissue as well as body hormone status, immune function, neural activities, and aging. The general physiological status of an individual is further influenced by circadian rhythms and changing seasons. The interactive networks of these environmental factors provide new understanding on how stem cell homeostasis is regulated, inspiring new insights for regenerative medicine. Therapies do not necessarily have to be achieved by using stem cells themselves which may constitute a higher risk but by modulating stem cell activity through targeting one or multiple layers of their micro- and macro-environments.

Contents

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0923-1811/$36.00 © 2012 Published by Elsevier Ireland Ltd on behalf of Japanese Society for Investigative Dermatology.
doi:10.1016/j.jdermsci.2012.02.007

1. Introduction

Stem cells are fascinating because of their unique potential to differentiate into different cell types and regenerate tissues and organs. This has great promise for the dreams of therapeutic possibility in degenerative disorders. From embryonic stem cells, they differentiate into all derivatives of the three primary germ layers: ectoderm, endoderm, and mesoderm that form different organs. In the adult, some adult organs still contain dormant multipotent or unipotent somatic stem cells which can be activated under changing physiological conditions or in response to injury. How this activation can be regulated is the key to the success of regenerative medicine.

The regeneration time, period, and potential of each organ stem cell varied from one to another (Fig. 1). In some organs, such as the hair follicle, gut and bone marrow, the stem cells can divide frequently and regularly to replenish the exhausted or damaged cells by either natural course or injury throughout the whole life. However, in other organs, such as pancreas and heart, they are not activated spontaneously until a special situation occurs. Stem cells were first thought to be regulated by the micro-environment, called stem cell niche. More recent studies revealed that the stem cell homeostasis can also be modulated by the so called extra-niche macro-environments (Fig. 2). In the skin, there is intradermal adipose tissue. Then there are systemic factors at the level of an individual which include input from hormones, immune and nervous systems, and aging. Stem cell activity is also modulated by the external environment which includes circadian rhythms and seasonal changes (Fig. 4). Different mammals have different robustness in their ability to grow and regenerate hairs (Fig. 5). There have been many reviews on the micro-environment of stem cells. In this review, we will focus on developing the concept on how the macro-environment affects stem cell activation. We mainly use hair stem cells for discussion, but will refer to other organ stem cells as well.

2. Stem cell niche in adult organs

The concept of "niche" is known to be a specialized microenvironment where stem cells reside, which was first proposed by Schofield [1]. The niche not only emits signals to maintain the homeostasis of stem cells but also functions as a shelter to filter extrinsic stimuli that induce apoptosis, differentiation and so on. It is more difficult to identify the stem cell niche in mammalian tissues due to their complicated anatomic structures as compared to *Drosophila* and *Caenorhabditis elegans*. However, using lineage tracing methods by uptake and long-term retention of bromodeoxyuridine (BrdU) or incorporation of fluorescently labeled histone 2B during DNA synthesis, slow cycling or so called "label-retaining" stem cells and their niche could be identified within mammalian tissues.

Different organs have different strategies to regulate their stem cells. In the skin, multi-potent hair stem cells reside in the bulge area which is located below the sebaceous gland. Hair stem cells receive cues from the dermal papilla, a population of specialized mesenchymal cells surrounded by hair matrix cells, to activate into transit-amplifying (TA) cells migrating downward to replenish matrix cells. After a couple of divisions, TA cells differentiate to form a new hair shaft. Alternatively, hair stem cells can accept signals from wounded skin to become epidermal progenitor cells and replace inter-follicular epidermis (Fig. 1A).

Hematopoietic stem cells (HSCs) are regulated by two types of niches, endosteal osteoblastic and vascular niches, which are located in bone marrow. These two niches share structural and functional mediators but exert different functions in modulating HSCs. The endosteum plays a more stimulatory role under conditions of stress to trigger the proliferation of HSCs, however, central vascular regions play a homeostatic role during steady state conditions [2] (Fig. 1B).

Intestinal stem cells (ISCs), which are located at the 4th or 5th position from the bottom of the crypt, the Paneth cell, could give rise to four different lineages of cells: columnar enterocytes, mucin-producing goblet cells, Paneth cells, and entero-endocrine cells [3]. The niche, mesenchymal cells, which can release signals to regulate ISCs is located adjacent to the crypt epithelium by the separation of basal lamina (Fig. 1C).

Neural stem cells (NSCs), the astrocytes (B), are located in the sub-ventricular zone (SVZ), which is separated from the lateral ventricle (LV) by ependymal cells (E). NSCs can differentiate into TA cells (C) and then produce neuroblast cells (A). The extracellular matrix (ECM) rich basal lamina (BL) which directly contacts NSCs serves as the niche [4] (Fig. 1D) for these stem cells.

Spermatogenesis progresses uniformly over the inner surface of the tubules or the seminiferous epithelium, which is composed of the basement membrane, sertoli and peritubular myoid cells. Specialized sertoli cells, blood vessels, basement membranes, myoid cells and interstitium are thought to function as the niche to maintain the homeostasis of undifferentiated spermatogonia or germline stem cells (GSCs) [5,6] (Fig. 1E).

In the muscle, satellite cells inhabiting a region under the basal lamina of myofibers are thought to be stem cells due to their self-renewal and myogenic differentiation capabilities (Fig. 1F). Upon injury, progenitor cells will be produced by activated satellite cells and migrate from beneath the basal lamina [7]. Host muscle fibers, basal lamina and the microvasculature are the three major components of the satellite cell niche that modify the function of muscle stem cells [8].

3. Intra-follicle regulation of hair stem cells

The hair follicle is a unique organ that undergoes cyclic bouts of degeneration and regeneration throughout life. A hair follicle cycles through anagen (growth), catagen (involution) and telogen (resting) phases and then re-enters anagen. At the base of this cycle is the ability of hair follicle stem cells to briefly exit their quiescent status to generate transient amplifying progeny which differentiate into different hair components, but maintain a cluster of stem cells. Thus hair follicles can undergo episodic regeneration physiologically or in response to injury. When they regenerate physiologically, hair follicles take the opportunity to generate new hair phenotypes to adapt themselves better to the environment [9]. It is generally believed that a niche microenvironment is important in the control of stem cell homeostasis in various systems [10]. Because of these properties, the hair has become a mainstream model for researches in stem cell biology as it represents rejuvenating power [11].

To keep the hair stem cells under quiescent status, bulge, the microenvironment, expresses BMPs and Wnt inhibitors, including DKK, Wif, and sFRP to suppress cell growth and differentiation. Upon anagen initiation, Wnt signals secreted by the dermal papilla will stabilize the β-catenin which acts on hair stem cells directly within the bulge to reduce the activation threshold. For hair stem cell activation, Wnts are not sufficient on their own. The dermal papilla will produce some other signals, including fibroblast growth factor (FGF) which could coordinate with β-catenin to support hair stem cells to overcome the gate for activation. Interactions between the bulge and dermal papilla form an intrafollicular regulation network to govern the homeostasis of hair stem cells [12–14].

4. Extra-follicle macro-environment and stem cell regulation

The hair growth pattern in rats behaves as a wave composed of periodical anagen spreading through the ventral side of the