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Hair Follicle Stem Cells: the Signaling Hub of the Skin

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Abstract

Hair follicle stem cells (HFSCs) are recognized as multipotential stem cells with exceptional proliferative capacity. Their regulatory effect on skin homeostasis is orchestrated through intricate signaling pathways, including Wnt/β-catenin, transforming growth factor-β/bone morphogenetic protein (TGFβ/BMP), Notch, and Hedgehog. Concurrently, HFSCs inhabit the bulge region of the outer root sheath of the hair follicle (HF), serving as the epicenter for skin-organizing signaling during homeostasis, engaging in dynamic interactions with other functionally specialized niche cells. This comprehensive review delineates the nuanced interplay of both cell-intrinsic and cell-extrinsic mechanisms governing HFSCs within the skin. The aspiration is that this synthesis of knowledge will contribute meaningfully to the theoretical foundations underpinning further investigations into skin disorders.

Keywords: HFSCs, Wnt/β-catenin, Skin homeostasis, LLLT

Introduction

HFSCs represent a distinct category of stem cells localized within HF, characterized by unique biological attributes and functionalities primarily implicated in the growth, development, and regeneration of hair. Notably, HFSCs are not only pivotal for fostering hair growth but also play a crucial role in the reparative processes of skin wounds [1-3]. Substantial evidence supports the assertion that HFSCs assume a central position within multiple skin components surrounding tissue HF thereby functioning as key tissue centers during adult skin homeostasis. Diverse signaling pathways, including Wnt/β-catenin, TGF-β/BMP, Notch, among others, intricately participate in the regulatory milieu governing the activities of HFSCs. These signaling pathways exert a profound impact on the self-renewal, differentiation, and cellular fate determinations of HFSCs.

HFSCs are strategically positioned within specific zones of the HF, notably within the coat sheath (outer root sheath) and the hair papilla (hair bulb) [4]. These anatomical regions are deemed critical for the viability and functionality of HFSCs. Possessing the remarkable capability for self-renewal and differentiation into diverse cell lineages, HFSCs emerge as pivotal contributors to the intricate orchestration of hair growth, instigating the generation of new hair cells that propel the continuous cycle of hair growth and renewal. Within the hair growth cycle, HFSCs actively partake in the regulation of distinct phases, encompassing the growth period (Anagen), regression period (Catagen), and rest period (Telogen) [5]. Notably, during the growth phase, HFSCs undergo active differentiation, instigating the robust growth of hair.

The skin, being the largest organ in the human body, undergoes meticulous regulation of homeostasis orchestrated by its diverse niches. Among these, HFSCs emerge as a crucial subset of stem cells, playing a pivotal role in sustaining skin homeostasis through intricate interactions with various ecological niches, including vasculature, nerves, and the extracellular matrix (ECM). In our discussion today, we delve

into the signaling pathways associated with HFSCs and explore the dynamic crosstalk between HFSCs and other niches, aiming to deepen our understanding of the multifaceted functions of HFSCs within the intricate landscape of the skin.

Signaling Pathways

Epidermal homeostasis is intricately governed by the regulatory influence of HFSCs within the skin. This regulatory role is contingent upon a sophisticated network characterized by the interplay of multiple signaling pathways, including but not limited to the Wnt/β-catenin, TGFβ/BMP, Notch, and Hedgehog pathways, as illustrated in **Figure 1**.

The Wnt/β-catenin signaling pathway constitutes a pivotal cell signaling cascade, assuming a critical role in diverse biological processes encompassing embryonic development, the preservation of tissue homeostasis, and the determination of cellular fate [6]. Wnt proteins, a category of secreted signaling molecules, engage Frizzled (Fz) receptors on the cellular membrane, instigating downstream signaling events. In the absence of Wnt ligands, a destruction complex comprising Axin, adenomatous polyposis coli (APC), and glycogen synthase kinase 3β (GSK-3β) phosphorylates β-catenin, marking it for subsequent degradation by the proteasome. This mechanism maintains a basal intracellular β-catenin level. Upon Wnt ligand binding to its receptor, inhibition of the destruction complex occurs, preventing β-catenin phosphorylation and degradation. Consequently, β-catenin accumulates in the cytoplasm, translocating to the nucleus. Within the nucleus, β-catenin associates with T cell factor/lymphocyte enhancer, thereby activating target genes. The target genes modulated by β-catenin, subsequent to its nuclear translocation, participate in the orchestration of various cellular processes, encompassing but not limited to cell proliferation, differentiation, and survival [7]. A significant interrelationship is evident between the Wnt/β-catenin signaling pathway and HFSCs, exercising a crucial regulatory impact on the initiation, proliferation, and differentiation of HFSCs. The activation of the Wnt/β-catenin pathway emerges as a compelling force propelling HFSCs into the Anagen phase. Throughout this phase, the Wnt signaling pathway intricately directs the stabilization of β-catenin, enabling its translocation into the nucleus, where it orchestrates the activation of a repertoire of genes intricately linked to the process of HF growth [7,8]. Noteworthy in the Wnt/β-catenin pathway are Wnt proteins that assume a critical role in the activation of HFSCs. For instance, Wnt7b, whose protein expression initiates during the initial growth period, has been demonstrated to be indispensable for the activation of HFSCs,

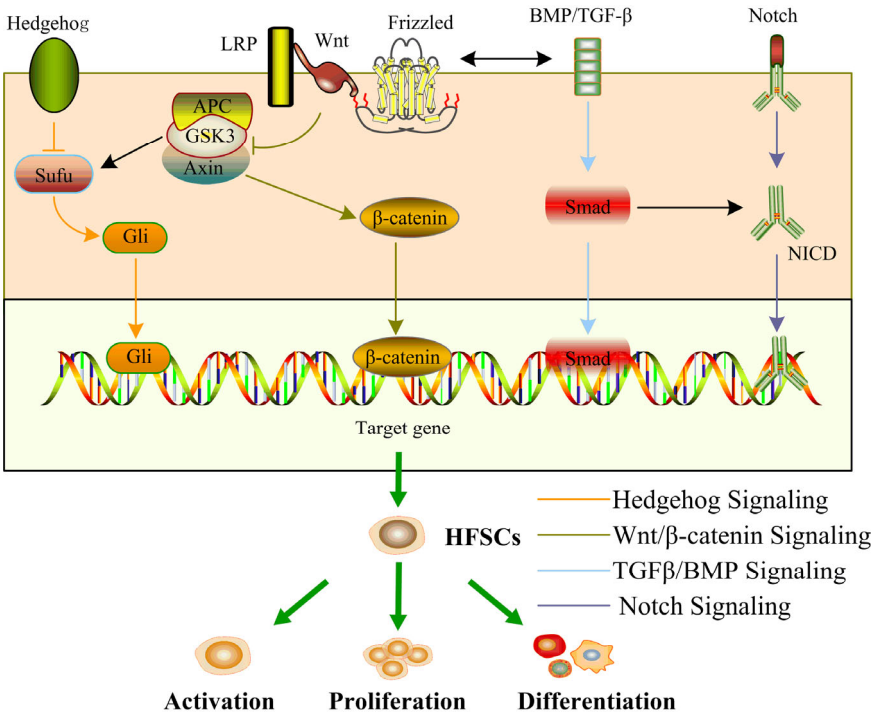

Figure 1. Signaling pathways network of HFSCs. Wnt/β-catenin, TGFβ/BMP, Notch, and Hedgehog signaling pathways form a signaling network to jointly activate HFSCs, promoting their proliferation and differentiation. The black arrowheads show the interaction of signaling pathways.

as its postnatal knockout halts this activation process [9,10]. Conversely, experimental overexpression of Wnt10b, a distinct member of the Wnt protein family, has been demonstrated to induce the transition of HF from the quiescent phase to the growth phase [11]. Contrarily, the targeted knockdown of Wnt10b impedes the initiation of HF into the Anagen phase [12]. HFSCs, as multipotent stem cells, manifest the capability for differentiation into a myriad of cell types, encompassing adipocytes, chondrocytes, neurons, or smooth muscle cells [13-18]. Shen et al. documented the central involvement of β-catenin in the initiation of HFSCs differentiation through the activation of the nuclear gene c-myc [19]. In summary, the intricate regulation of HFSCs by the Wnt/β-catenin signaling pathway constitutes a complex and pivotal process, bearing significant implications for various facets of HF dynamics.

The activation of TGF-β/BMP signaling pathway can elicit a spectrum of cellular responses, encompassing cell proliferation, differentiation, apoptosis, as well as the synthesis of the ECM [20,21]. TGF-β and BMP represent two closely related classes of cytokines functioning as signaling molecules that mediate cellular communication. These cytokines initiate signaling by binding to their respective receptors, culminating in the phosphorylation of Smad proteins and the formation of an activated Smad protein complex. This complex translocates into the nucleus, where it engages with other transcription factors to intricately regulate the transcription of specific genes. Analogously, the TGF-β/BMP signaling pathway assumes a pivotal role in the development, growth, and regulation of HFSCs. Within the context of this signaling pathway, the nuclear interaction between TGF-β/BMP and Smad proteins serves as a facilitator for the induction of transcription of pertinent target genes [22-26]. This transcriptional activity functions as a regulatory mechanism, delicately modulating the proliferation and differentiation of HFSCs. The collective evidence underscores the pivotal role of the TGF-β/BMP signaling pathway in shaping the dynamics of HFSCs in a consistent manner. Notably, the BMP antagonist, Noggin, emerges as an instrumental factor in the regulation of HFSCs. BMP-4 intricately interacts with Noggin to finely modulate the differentiation of HFSCs, guiding them towards the development of sebaceous glands, sweat glands, and epidermal cells through the overexpression of lymphoid enhancer-binding factor (LEF) molecules [27]. Concurrently, the TGF-β/BMP signaling pathway demonstrates regulatory control over the Wnt/β-catenin signaling pathway by promoting the upregulation of Dickkopf3 (DKK3) molecules [28,29]. This intricate interplay underscores the nuanced regulatory mechanisms involved in orchestrating the activities of HFSCs.

The Notch signaling pathway represents a highly conserved mechanism of cellular signaling [30]. The interaction between the Notch receptor and its ligand serves as a regulatory mechanism governing cell proliferation, differentiation, and fate decisions [31,32]. The Notch signaling pathway has the capacity to promote the differentiation of HFSCs into HF cells while concurrently inhibiting their differentiation into epidermal cells through the Notch/RBP-J mechanism [33,34]. The Notch signaling pathway additionally functions as a downstream pathway of Wnt/β-catenin signaling, activating the transcription of target genes such as hair and split enhancers (Hes), runt-associated transcription factors (Runx), and Notch inhibitory membrane proteins (Numb) [35]. Yet another conserved mechanism of cellular signaling, the Hedgehog signaling pathway, is imperative for the activation of β-catenin activity [36]. All these signaling pathways intricately interact, forming a finely tuned regulatory network to govern the activities of HFSCs.

Cell-extrinsic Mechanisms

As a crucial ecological niche within the skin, HFSCs possess the capacity to interact with other niches, contributing to the maintenance of skin homeostasis and regulate hair growth, as illustrated in **Figure 2**. The normal functioning of HFSCs necessitates an adequate vascular supply. The circulatory system plays a crucial role in supporting the growth and differentiation of HFSCs by furnishing them with essential elements such as oxygen, nutrients, and various growth factors [37]. The lymphatic system plays a pivotal role in removing tissue waste and supporting immune surveillance for HFSCs [38]. Simultaneously, upon activation of HFSCs, there is a transient increase in lymphatic vessel caliber, accompanied by the dissociation of lymphatic capillaries in close proximity to HFSCs [39,40]. However, during quiescence, lymphatic capillaries closely associate with HFSCs [39]. Hence, there exist dynamic changes in the association between lymphatic capillaries and HFSCs. Collectively, the vasculature assumes a pivotal role in the health and functionality of HFSCs. This interaction encompasses not only the provision of nutrients and oxygen but also involves cell signaling, niche maintenance, and participation in the healing process. Therefore, ensuring an adequate blood supply may prove crucial for the maintenance of HF health and the prevention of hair loss.

Nerves and neurons communicating with various tissue stem cells, including hematopoietic stem cells [41], intestinal stem cells [42-44] and muscle stem cells [35,45,46], have been extensively documented. HFSCs are no exception to this phenomenon. HFSCs are not only regulated by the niche in wound healing through sensory nerves but are also activated by sympathetic nerves [35,48-50]. Similarly, HFSCs express neurotrophic factors to modulate their neural niche [51]. The regulation of HFSCs by the nervous system constitutes a complex network, encompassing various aspects such as neuroendocrine regulation, neurovascular regulation, and neural-immune interactions. A more profound understanding of these interactions is crucial for comprehending mechanisms underlying hair loss, advancing treatment strategies, and preserving overall hair health.

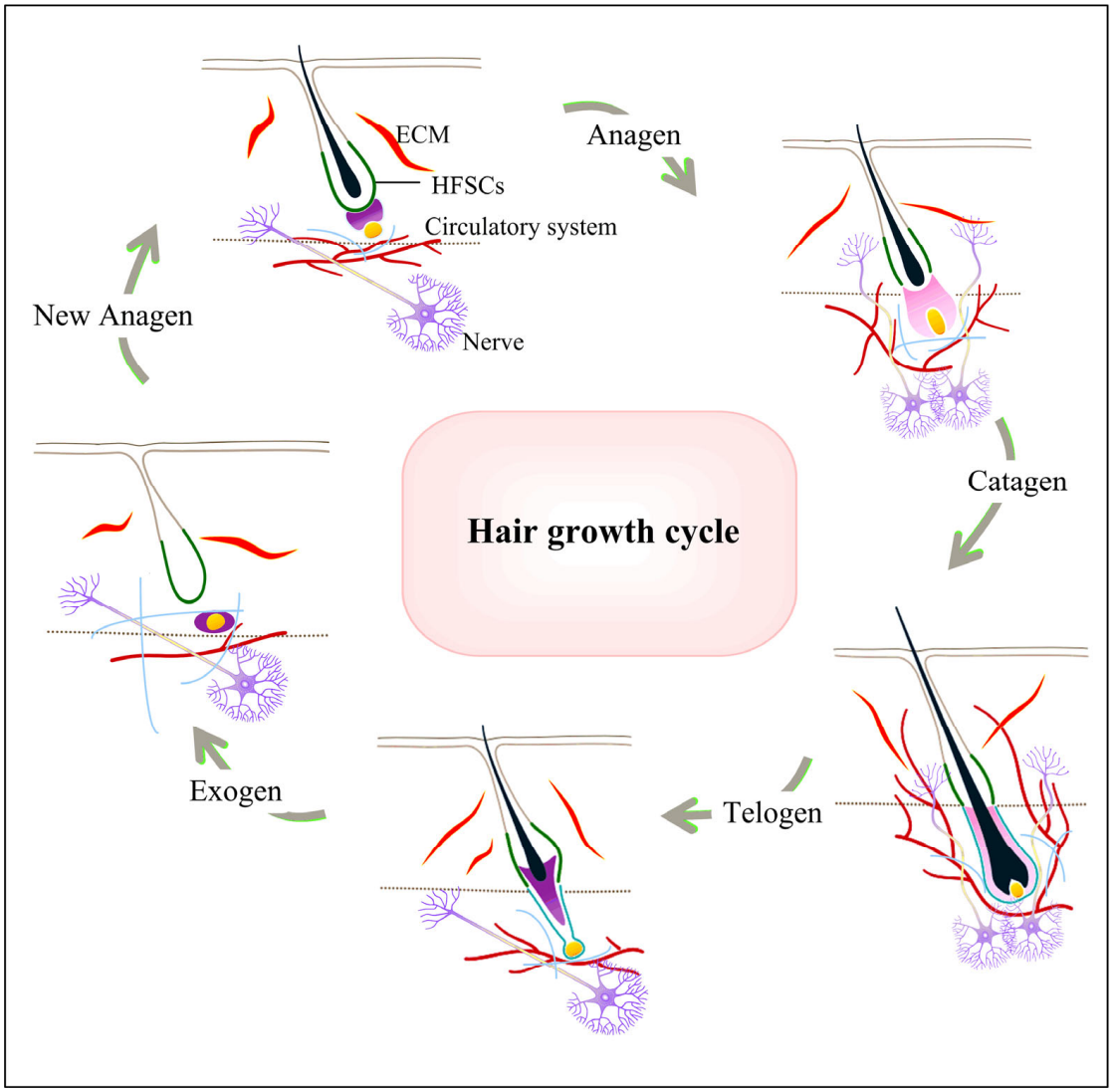

Figure 2. HFSCs with other niches during the hair growth cycle. The hair growth cycle includes Anagen, Catagen, Telogen, Exogen, and then it can begin a new Anagen. In different periods, the interaction of HFSCs with nerve and circulatory system is different. When the HF undergoes hair growth cycle, the nerve and circulatory system also make periodic changes. As the HFSC is activated, the HF enters Anagen. The subcutaneous vasculature structures that normally oriented horizontally and fill the vessels below the hair ula disperse and become more vertical. Meanwhile, angiogenesis occurs in the cutaneous vasculature, which can provide both oxygen and nutrients. In Telogen, the present vasculature becomes horizontal again, forming a dense vascular structure and maintaining this structure until the onset of the next Anagen. HF innervation and the density of cutaneous peripheral nerves increase during the growth phase and decrease during the degenerative phase and maintaining to next Anagen. The ECM itself is the true ecological niche of the HFSCs, and ECM from hair epithelium, the ECM proteins are mediators of various components in the HFSC microenvironment.

The ECM, comprising components such as collagen, integrins, proteoglycans, and other structural macromolecules, serves as a tissue scaffold that offers crucial structural support. It plays a pivotal role in cell adhesion, migration, and cell signaling [52]. The mutual crosstalk between stem cells and the ECM represents a prominent and current research focus. The ECM stands as a pivotal component within the HF niche, furnishing essential support for the growth and differentiation requisite for HFSCs [14,52-54]. The ECM encompasses a diverse array of proteins, polysaccharides, and other biomolecules. These components collectively construct a microenvironment essential for the survival and optimal functioning of HFSCs [14,53-57].

All in all, the interaction between HFSCs and other skin niches forms an integrated regulatory network. This interaction occurs through various means, including the exchange of nutrients, exudates, signaling molecules, etc.

Treatment of Hair Loss

The periodic growth of HF is orchestrated by HFSCs, which assume a pivotal role in the treatment of hair loss. Research data indicates that HFSCs can drive HF regeneration through interventions such as drugs, laser therapy, and cell transplantation.

Minoxidil initially emerged as a medication for hypertension in the 1970s; however, its use revealed instances of hair regeneration and generalized hirsutism in bald patients [58]. Over time, 2% and 5% formulations of minoxidil have been employed for the treatment of hair loss. Mori and Uno observed a significant reduction in the Telogen phase in rats treated with minoxidil compared to the untreated group [59]. Simultaneously, it was discovered that minoxidil could markedly upregulate vascular endothelial growth factor in dermal papillary cells, a phenomenon typically robustly expressed during the Anagen phase [60]. The effects of minoxidil can vary from person to person, with some individuals experiencing a significant slowdown in the hair loss process and promotion of new hair growth. However, not everyone responds in the same way, and common side effects, such as irritant contact dermatitis with typical symptoms of itching and desquamation, may occur in some individuals.

Low-level laser therapy (LLLT) is a biological intervention relying on low-intensity laser irradiation, employing a single type of non-thermal radiation with wavelengths in the red to near-infrared range of the electromagnetic spectrum [61]. LLLT is most commonly employed in clinical settings for various purposes, including irradiation of injured sites to promote wound healing, remodeling, or reduce inflammation. It is utilized for inducing nerve cells to relieve analgesia, reducing lymph node edema and inflammation, as well as promoting muscle relaxation and alleviating pain [62-64]. In the 1960s, Endre Mester discovered that a low-power ruby laser (694 nm) enhanced hair growth in the shaved area of the back [65]. The introduction of LLLT marked the first demonstration of its beneficial effects on hair growth, opening up new avenues for the treatment of hair loss [66]. Subsequently, an increasing number of studies have revealed the efficacy of LLLT in the context of hair loss. In 2007 and 2011, the U.S. Food and Drug Administration (FDA) granted approval for LLLT as a safe treatment for male and female-pattern alopecia, respectively [67]. In 2021, Jin et al. discovered that LLLT mitigates hair loss through the activation of HFSCs [68]. They found that LLLT can stimulate the activation of quiescent HFSCs and alleviate HF atrophy. This is achieved through the induction of reactive oxygen species (ROS), which activate the PI3K/AKT/GSK-3β signaling pathway, thereby inhibiting the proteasomal degradation of β-catenin in the HFSC. On the other hand, LLLT accelerates microvascular blood flow, leading to increased blood oxygen content, thereby promoting HF regeneration [69]. LLLT not only has the capacity to regulate the signaling pathways of HFSCs but also exerts an effect on the ecological niche of HFSCs.

Cell transplantation emerges as a therapeutic approach for hair loss, involving the implantation of HF or other cell sources into the scalp to stimulate the growth of new hair. Hair loss can be addressed through either the direct transplantation of HF or by fostering their regeneration with transplanted stem cells. Research findings suggest that neural stem cells directly regulate the HF niche, inducing core growth factors to promote hair regeneration through the TGF-β and BMP signaling pathway [70]. Despite the numerous available treatments for hair loss, the underlying mechanisms warrant further investigation.

Conclusion

The term "niche" denotes the specific position or role occupied by an organism for its survival and lifestyle. This encompasses biological functions, behaviors, adaptation strategies, and interactions with the surrounding environment and other organisms. Within the context of skin biology, HFSCs function as a pivotal signaling center. They are not only subject to regulation by a diverse array of signaling pathways but also engage in intricate interactions with other elements, forming an extensive network mediation center crucial for maintaining skin homeostasis.

In summary, the investigation of signaling pathways and the niche environment surrounding HFSCs holds promise for identifying effective strategies in addressing skin diseases, potentially serving as a target for conditions such as alopecia in the near future. This scholarly discourse underscores the potential translational impact of understanding HFSCs and their niche in the realm of skin health.

Conflicts of Interest

None.

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