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Lgr5$^+$ Stem Cells and Potential Treatments for Hair Loss

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Abstract. Hair follicle regeneration represents a very dynamic and tightly regulated biological process that requires the interaction of the stem cells and their specific niche. The Lgr5+ hair follicle stem cells (HFSCs) are considered to be among the most proliferative stem cell subpopulations that are vital in the initiation and homeostasis of the hair follicle cycling. This paper has explained in specifics the distribution, the biological functions and significance of Lgr5+ HFSCs as the stem cell markers. The key aspect of such a regulatory mechanism is the Wnt/β-catenin pathway, which maintains constant regulation of lineage differentiation, stem cell stimulation, and hair follicle developmental morphogenesis in developmental and wound healing processes. Wnt/β-catenin signaling functions are examined at major developmental events of organogenesis, cytodifferentiation, cyclical regeneration and hair follicle induction. This underscores its deep penetration of interactions with other signaling pathways, such as Shh, BMP, Notch, and EDA/EDAR/NF-κB. There are also the effects of the Wnt dysregulation. Lack of adequate signaling may result in inactivation of stem cells, follicular miniaturization, and eventual loss of hair. On the other hand, uncontrolled or overactivity may lead to the enhancement of the risk of abnormal growth of the epithelia, irregular follicle schedules and tumors associated with hair follicles. Lastly, new therapies to Wnt signaling and the Lgr5+ HFSC are addressed, such as peptide-based, small molecule modulators, physical therapy adjuncts, and stem cell-based regenerative therapies. All these findings highlight the importance of modulating Wnt/β-catenin with accuracy and precision to ensure that hair loss can be treated safely and effectively.

Keywords: Lgr5 stem cell, Hair follicle, Hair loss, Regeneration

1. Introduction

We can broadly sort stem cells into pluripotent stem cells and adult stem cells. They both possess high self - renewal ability and contribute to the creation of functional tissues. Generally speaking, adult stem cells are limited to generating specialized cell types in their resident tissues or organs. On the other hand, pluripotent stem cells can differentiate into almost all cell lineages in the body. By means of tightly controlled self - renewal and differentiation, stem cells take on a central role in tissue regeneration and the upkeep of physiological homeostasis [1].

The hair follicle, a highly specialized skin appendage, is an example of a well - characterized model of adult stem cell function. It goes through a repeated and strictly regulated process called the

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hair cycle, which has three main stages. Among them, the anagen phase is the period of active hair growth. It usually lasts about three years and includes over 85% of the hairs on the human scalp. The catagen phase is a phase of transition or regression that lasts two to three weeks. The resting phase, known as telogen, is the third stage. It makes up 10% - 15% of the scalp's hairs and lasts some 3 months. Hairs start to shed in telogen as a result of the appearance of new - growing anagen hair [2].

The management of the hair cycle and total hair density mainly depends on HFSCs. When in the telogen phase, a large proportion of HFSCs in the bulge region remain dormant, whereas the primed HFSCs of the hair germ are more ready to be switched on. When these cells get activated, the formation of the hair shaft and its supporting structures is done by transient amplifying cells, starting the anagen phase. As the follicle turns to the catagen phase and afterwards the telogen phase, these HFSCs go back to a latent state, keeping a supply of regenerative cells for the next cycle. Maladies in HFSCs' function can bring on hair thinning and a lessening of hair density [3]. These days, hair loss has become a more and more common problem among people. While it appears to be an unimportant problem, it can have a serious negative effect on a person's mental self, ultimately causing psychological distress and disturbance. The common feelings of people suffering from hair loss are self - awareness, embarrassment, desperation, and jealousy [4]. This points out the value of investigating and finding potential treatments for this problem.

Multiple signaling pathways control HFSC behavior. The Wnt/β-catenin pathway is of great importance in hair follicle development and growth. The hair follicle cycle requires this signaling cascade all the time. In particular, it's very important for driving the shift from the quiescent resting stage to the active growth phase [5]. In addition, the Wnt - responsive gene Lgr5 has been shown to be a characteristic marker of hair follicle stem cells, as its expression is abundant among actively cycling cells [6]. So, this paper sets out to investigate the contribution of $Lgr5^+$ stem cells to hair growth and how Wnt signaling regulates them. It also looks into how dysregulation leads to hair - loss problems and how they might be addressed in future therapies.

2. HFSCs and Lgr5

2.1. Distribution of $Lgr5^+$ stem cells

During the hair growth phase, certain special cells are mainly located in the lower bulge region and also within the secondary hair germ area. The bulge niche refers to the specific compartment of the hair follicle, which is found below the isthmus and infundibulum parts, corresponding to where the tiny muscle connects to the follicle structure [7]. At the very base of the hair follicle lies a particular group of cells, which are highly specialized and provide important regulatory information to nearby stem cell populations. These two structures stay very close physically, a feature that has became essential for starting and maintaining hair growth. These base cells don't express the same markers, but instead send out signals that affect the special cells. This process is known as niche signaling, and the most well-known pathway involved is the Wnt pathway [8].

2.2. Biological functions of $Lgr5^+$ stem cells

$Lgr5^+$ cells are a specific group of hair follicle stem cells, or HFSCs, known for being very good at multiplying and really helping the follicle grow back. Functionally speaking, these particular cells serve as an early-acting HFSC population when the hair moves from resting phase to growth phase, specifically responding to signals from the dermal papilla part and also the area around the follicle. Their starting up within the secondary hair germ area basically helps make a fully grown new hair

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follicle and shows the beginning of the growth stage. That is to say, $Lgr5^+$ HFSCs create intermediate multiplying cells during the main growth part of the hair cycle, which then help with building the hair shaft itself along with the structures around it that hold it up. Once the follicle is as big as it gets, this growing activity lessens in both the $Lgr5^+$ spots and other epithelial areas, pushing things towards the breakdown phase, as shown in reference [9]. Beyond just starting the regrowth process, it should be noted that $Lgr5^+$ HFSCs also help keep the follicle healthy long-term because their offspring become different types of cells, while matrix cells act as more final specialized cells rather than being the stem cells themselves [7].

2.3. Discovery and significance of Lgr5

Lgr5 was originally found as an indicator for hair follicle stem cells by Jakes with their team back in 2008, which is to say this finding really changed and moved forward the existing understanding about how hair follicle stem cells act and their dynamics [10]. The discovery also carries important significance when it comes to studies tracking cell lineages and research into regeneration processes. To put it simply, Lgr5 proves useful in these lineage-tracing investigations for identifying and monitoring the destiny of specific stem cell groups plus what becomes of their offspring over time in living organisms, usually through the use of genetically modified mouse models [6]. Furthermore, the knowledge we have gained from exploring Lgr5 provides the foundation for developing treatment strategies, for instance plans aimed at epidermal regeneration and also dealing with hair loss problems [11].

3. Wnt signaling in hair follicle regeneration

3.1. Overview of Wnt/β-catenin pathway

The Wnt/β-catenin pathway is important for keeping stem cell properties. It manages this by controlling how cells multiply and change. The main way it works involves making sure the key molecule β-catenin stays stable and moves into the cell nucleus, where it then turns on certain Wnt-related genes using factors called TCF/LEF that control genes. On the outside of cells, you have receptors named RZD and LRP5/6, which sit on the membrane by themselves when there are no Wnt signals around. Inside the cell, there's a group called the "destruction complex" that grabs β-catenin and changes it through phosphorylation by CK1 and GSK3β. To put it simply, this leads to β-catenin breaking down more, and also the co-repressor Groucho (or TLE) sticks to the TCF/LEF factors, which stops the genes that respond to Wnt from working. But when Wnt signals are present, that destruction complex gets tied up with RZD at the membrane and can't break down β-catenin anymore. This lets β-catenin build up and move into the nucleus, where it teams up with TCF/LEF to switch on other genes downstream. So, the movement of β-catenin between different parts of the cell, that is to say, from the cytoplasm to the nucleus, is a really important step for turning on the Wnt/β-catenin signal [12]. Altogether, these carefully controlled processes are vital for keeping stem cells steady and making sure tissues grow and fix themselves the right way (like you can see in Figure 1).

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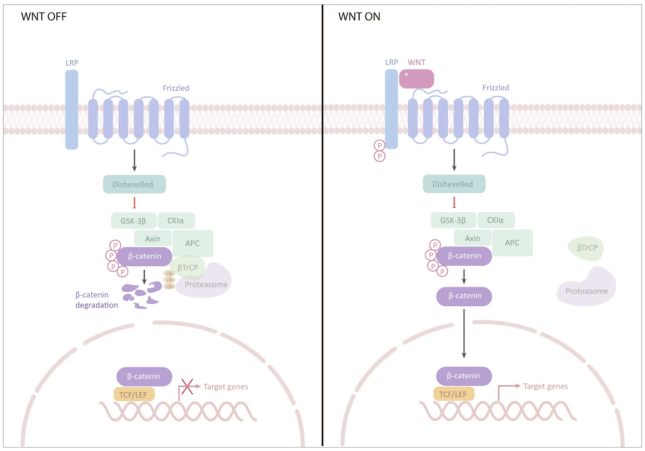

Figure 1. The Wnt/β-catenin pathway. Left: when the Wnt is absent. Right: when the Wnt is present

3.2. Wnt/β-catenin signaling

Wnt signaling plays a really important role in controlling how hair follicles (HF) develop and go through their cycles. Hair follicle development has basically three main stages, which are induction, organogenesis, and cytodifferentiation. Wnt signaling represents the earliest and most essential signal for getting hair follicle induction started. The primary Wnts involved include Wnt3, 4, 6, which are responsible for kicking off the formation of hair follicles. Secondary Wnt molecules, for instance Wnt2, 7b, 10a, and 10b, participate in the further development of the hair follicle; whereas Wnt5a handles the secondary dermal signals needed for hair follicle proliferation that happen downstream of Shh. The secretion of Wnt is induced by Wntless (Wls), that is to say, a protein expressed in the hair follicle primordia and the hair follicle region itself. In order to create hair follicle primordia, the dermal β-catenin signaling pathway stimulates the aggregation of dermal fibroblasts and also causes epithelial thickening. This process then sends signals back to the dermis to strengthen the forces holding things together. The Wnt/β-catenin and EDA/EDAR/NF-κB pathways interact at the same time within epithelial cells. By carefully controlling the boundaries and the overall patterning of these structures, this interaction makes sure the plate-like structures form correctly and effectively gets the hair follicle development process going. This specific interaction finds a balance between signals that stop things like Dkk4 and signals that help plate formation happen, such as Wnt10b. After the hair follicle induction phase is complete, the Wnt signaling remains active all the way through the organogenesis and cytodifferentiation stages, continuing to influence the hair follicle.

In organ development, even though it's not the only factor involved, Wnt signaling continues to work upstream of the Shh pathway to maintain the epithelial proliferation, growing downward, and also interacts with the inhibition of BMP signals through Noggin. Moving to the next stage where cells become specific types, Wnt signaling helps the particular lineage and final differentiation of hair follicle cells, especially the ones that build the hair shaft itself. This happens by working with certain molecules like BMPRIA, Lef1, and β-catenin, to put it simply. That is to say, Wnt signaling also shows important crosstalk or interaction with the Notch pathway, which helps ensure the precise control of what kind of cell a cell becomes, making sure the decisions about cell fate are correct. Furthermore, in the cycling and regeneration process of the hair follicle, Wnt signaling also has a central part to play, because the reactivation of Wnt, by working together with BMP

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antagonism to turn on stem cells, is needed for the change from the resting phase to the growth phase, which is essential for hair follicle regeneration [13].

4. Wnt dysregulation, hair loss, and therapeutic strategies

4.1. Reduced Wnt signaling and stem-cell inactivation

Insufficient Wnt signaling can lead to several negative outcomes for stem cell function and the hair growth cycle, particularly impacting hair follicles. The main consequences include failure to start the growth phase, reduced activity in certain stem cells, and thinning and miniaturization of hair. That is to say, during the hair cycle, the Wnt signaling pathway is important for the transition from the resting phase to the active growth phase. Consequently, inadequate Wnt activity prevents hair follicles from entering the growth phase normally. Moreover, since Lgr5 serves as a marker for specific stem cells in the hair follicle bulge, decreased Wnt signaling inhibits the activation and proliferation of these important cells, which are essential for hair regeneration. Over time, hair becomes incapable of regenerating properly, leading to significant hair loss and persistent miniaturization of follicles.

4.2. Excessive or uncontrolled Wnt activation

While moderate Wnt activation is crucial for normal hair follicle development, that is to say, excessive or uncontrolled activation can pose health risks. For instance, abnormal growth of epithelial tissue may occur. This is one potential cause for the development of various cancers, including certain skin and gland tumors associated with hair follicles. Additionally, instead of healthy cycling hair follicles, the unchecked cell growth may result in malformed or non-functioning follicles [14]. To put it simply, abnormal hair patterning is another possible outcome, as the balanced interaction between Wnt activators and inhibitors like DKK1 ensures normal spacing and patterning of hair follicles in skin. Disruption of this balance might lead to unusual hair growth patterns or hair forming in areas that are typically hairless [15].

4.3. Clinical research and emerging treatments

4.3.1. Wnt-targeted therapies

Given the Wnt/β-catenin pathway's significant role in several important hair growth stages, it is seen as a possible treatment focus. Though most current studies are still at early testing phases. In actual patient research, treatment drugs often make the growth phase last longer by turning on this pathway and might help hair follicles renew themselves.

Treatment methods using peptides, which are small protein pieces, have come up as a way to handle diseases. For instance, PTC-DBM is a peptide made to get in the way of how CXXC5 and Dvl connect by targeting where they bind together. When this connection gets disrupted, it stops interference with the downstream Wnt/β-catenin signals, which means the pathway works better. Even with these positives, using peptide treatments in real patients is still held back by issues like staying stable in the body and getting delivered properly inside living systems.

On the other hand, the ways that negative controllers work are different. Small-molecule drugs can kickstart the Wnt/β-catenin pathway by copying Wnt signals or making β-catenin stay put from outside. For example, stopping GSK3β inside the complex that breaks down β-catenin makes β-catenin much more stable. This helps it move into the cell's center more easily and turn on genes that

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help hair grow, which is important for making hair thicker. Recent patient trials suggest these therapies could improve how thick hair is and better hair density, but how safe they are long-term isn't fully clear and whether they really work well is still talked about. Future work will need to make treatments more specific and targeted, with new tiny particle technologies possibly opening doors for such advances.

Additionally, other supportive treatment methods, such as low-level light therapy, can improve how cells work, leading to more energy production and signaling through certain molecules. These cell responses are known to activate important signaling pathways and thereby support hair follicle regrowth. Similarly, micro-needling, which is a form of physical stimulation, has recently become popular for how it might influence those same signaling pathways. Put simply, combining these extra approaches with drug treatments could create combined effects that improve hair regrowth results [16].

4.3.2. Stem-cell and regenerative approaches

There are several methods based on cell biology and regenerative medicine to encourage hair regeneration. These include, for example, expanding Lgr5+ cells for transplantation purposes, and using techniques that change genes to bring back the natural hair cycle.

Ex vivo expansion of Lgr5+ cells for transplantation, that is to say, involves growing these cells under special conditions that keep their signaling active and maintain their basic properties and ability to regenerate. The long-term growth of individual Lgr5+ cells becomes possible through three-dimensional culturing methods, making transplantable structures. After putting in these structures, the cells might join with the existing hair follicle environment, thus helping create intermediate cells and eventually supporting functional hair follicle regeneration. However, keeping the long-term identity of these cells and their treatment effectiveness might be challenging [17].

Another useful approach involves gene-modulating techniques to fix the natural hair cycle. This mainly focuses on controlling important signaling pathways using methods like reprogramming cells, gene-based treatments, and giving certain growth factors and microRNAs [16].

5. Conclusion

In a nutshell, regeneration of hair follicles depends on the exquisite interactions between stem cells, the niche which exists in its surroundings and tightly controlled signaling pathways. Lgr5 + follicle cells of the hair with Wnt/β-catenin signaling pathway are key regulators of such a regenerative response. Lgr5 HFSCs represent a highly sensitive stem cell reservoir, during the transition between the telogen and the anagen differentiation phase, they differentiate quickly into transit-amplifying progenitor cells that regenerate the hair shaft and follicles of the associated structures. By this action, follicle integrity and long-term functionality are preserved. Furthermore, Lgr5 has been identified as a defining stem cell marker and this has significantly enhanced lineage-tracing methods as well as enhanced existing knowledge on the functioning of hair follicle stem cells.

The Wnt/β-catenin signaling is a primary controller of hair follicle growth, cyclical regeneration, and stem cell fate determination. WNT signaling co-interacts with pathways such as Shh, BMP, Notch, and EDA/EDAR/NF-kB to regulate cell growth, normal follicle formation and to direct lineage differentiation. Nonetheless, this pathway should be well-regulated. Lack of enough and excess Wnt activity may cause an issue. WNT Loss results in the mainly inactive state of the stem cells, inhibition of proper transition to anagen phase, smaller follicles, and progressive alopecy.

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Moreover, unregulated Wnt signaling may cause improper cell proliferation, follicular integrity and predisposition to tumorigenesis.

It is based on these mechanistic developments that modern therapeutic approaches are more and more targeted at controlling Wnt/β-catenin signaling as well as using the repairing properties of Lgr5 + hair follicle stem cells. In spite of the positive outcomes that have been achieved with the application of approaches to Wnt-directed pharmacological apparatus, physical stimulation therapy, and the intervention focused on the stem cell or gene regulation, there are still a number of challenges, such as the lack of specificity of pathways, the difficulties of its targeted delivery, and the long-term safety prospect, as well as the maintenance of stem cell identity. As a result, the appropriate control of Wnt signaling in future research should focus on specific and context-dependent reduction in aims at achieving a higher level of regenerative efficiency and lower in the context of outlying adverse effects to effectively create safe and effective hair loss and follicle-related therapy.

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