

Wnt Signaling in Hair Follicle Development

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Abstract

Hair follicle (HF) is a miniature organ composed of epithelial and mesenchymal (dermal) compartments, and has a pivotal role in hair development and growth. In embryonic, the formation of HF is mainly regulated by mesenchymal-epithelial interactions within the dermal papilla (DP) niche, and this interaction is also responsible for the postnatal hair growth cycle and regeneration. DP cells are the main components of the mesenchymal compartments in hair bulb, and have an instructive role by generating several signals to regulate the behavior of neighbor epithelial cells in hair cycle. Among the many signaling pathways implicated in HF development and growth, Wnt/ β -catenin signaling in DP cells plays critical roles in the reciprocal instructive communication between DP and epithelial cells. It is clear that Wnt/ β -catenin signaling pathway is important for HF morphogenesis and regeneration. The goal of this review is to summarize our current knowledge of Wnt signaling pathway in HF development and cycling.

Keywords: Hair follicle, Dermal papilla cell, Wnt/ β -catenin signaling, Growth, Development

Introduction

HF is a mini-organ formed with mesenchymal-epithelial interaction (Schmidt-Ullrich & Paus, 2005). HF development and cycle are depended on signaling between its epidermal and dermal components. Especially, dermal organizing center, DP, is both chemical and physical niche for epithelial stem cells. DP plays an important role in HF induction and cycling by controlling self-renewal and differentiation of epithelial stem cell (Zhang *et al.*, 2009). During HF development, secreted unknown Wnt ligands are considered to induce epidermal stem cells to switch to a hair induction fate (Chen *et al.*, 2012). Indeed, canonical Wnt signaling in the DP is essential for HF formation (Alonso & Fuchs, 2003).

Molecular insights into hair development: a focus on Wnt signaling

1. Basic insights of Wnt signaling pathway

Wnt is a short-range secreted signaling molecule that regulates the development of multiple organ systems. Wnt ligands bind to their receptors, Frizzled (FZD) and low density lipoprotein receptor related protein (LRP) family, that activate a canonical signaling pathway that induces stabilization of β -catenin protein. Stabilized β -catenin is translocated into the nucleus, in which β -catenin interacts with T cell factor/lymphoid enhancer binding factor (TCF/LEF) transcription factor to target gene for activation (Bejsovec, 2000; Wodarz & Nusse, 1998). Research revealed that bone morphogenetic protein 4 (*BMP4*) and sonic hedgehog (*SHH*) are target genes of β -catenin, and have pivotal roles in hair development and regeneration (Huelsenken *et al.*, 2001) indicating that Wnt/ β -catenin signaling is closely connected with hair biology.

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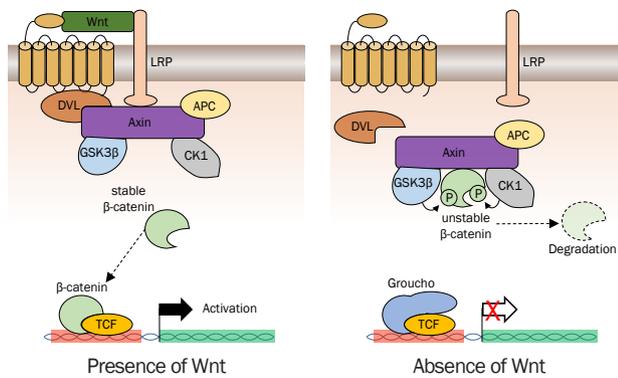


Figure 1. Schematic view of Wnt/ β -catenin signaling.

In presence of Wnt, DVL protein binds Axin, inactivates GSK3 β and β -catenin is not phosphorylated. The stable β -catenin is translocated into the nucleus, in which it interacts with TCF/LEF1 transcription factor, activating Wnt target genes. In absence of Wnt, β -catenin is phosphorylated by GSK3 β and CK1, ubiquitinated and degraded. DVL, Dishevelled; LRP, low density lipoprotein receptor related protein; APC, adenomatous polyposis coli; GSK3 β , glycogen synthase kinase 3 beta; CK1, casein kinase 1; TCF, T cell factor; LEF1, lymphoid enhancer binding factor 1.

2. Wnt signaling in hair cycle

Various Wnt ligands are associated with hair cycling. During telogen, Wnt-responding stem cells in the bulge produce Wnt1, Wnt4, and Wnt7b. During telogen to anagen transition, Wnt6, Wnt10a and Wnt10b are strongly expressed in DP. Whereas, during anagen, other Wnts including Wnt5a and Wnt5b are mainly expressed in peripheral layers of DP. Furthermore, hair stem cells produce autocrine Wnts that specify the positional identity of cells residing within the HF (Hsu *et al.*, 2011). Therefore, Wnt regulates not only anagen initiation in DP, but also maintenance of HF stem cells during telogen.

3. Wnt signaling in HF development

Wnt signaling is one of the fundamental mechanisms that regulate embryonic development and tissue homeostasis (MacDonald *et al.*, 2009; Merrill, 2012). As shown in Figure 1, in the absence of Wnt, the cytoplasmic β -catenin protein is constantly degraded by the action of the Axin complex. Axin complexes include the scaffolding protein Axin, the tumor suppressor adenomatous polyposis coli (APC), casein kinase 1 (CK1), and glycogen synthase kinase 3 (GSK3). CK1 and GSK3 phosphorylate the amino terminal region of β -catenin sequentially result in conformational change. The conformational change of β -catenin helps regulate its binding to beta-transducin repeat containing E3 ubiquitin protein ligase

(BTRC), subsequent β -catenin ubiquitination and proteasomal degradation. This cytoplasmic degradation of β -catenin prevents the nuclear translocation, and target genes are repressed by the histone deacetylase (HDAC)/DNA-bound TCF/LEF complex. The canonical Wnt signaling transduction initiated by Wnt ligand that binds to a seven-pass transmembrane FZD receptor and its co-receptor, LRP6 or its close relative LRP5. The formation of a likely Wnt-FZD-LRP6 complex together with the recruitment of the scaffolding protein Dishevelled (DVL) results in LRP6 phosphorylation and activation and the recruitment of the Axin complex to the receptors. These events lead to inhibition of Axin-mediated β -catenin phosphorylation and thereby to the stabilization of β -catenin, which accumulates and localizes to the nucleus to engage TCF/LEF transcription factors and activates Wnt target gene expression.

It is widely accepted that the canonical Wnt signaling is required for HF morphogenesis and differentiation (Lim & Nusse, 2013). Activation of canonical Wnt signaling and subsequent stabilization and nuclear localization of β -catenin are critical for onset of anagen phase. Wnt/ β -catenin, temporally and spatially regulates the growth of stem cells and progeny cells during hair cycle. Proliferation in the matrix also depends on Wnt signaling (Lim & Nusse, 2013). Recently, using live imaging analysis of mouse model harboring the high sensitive Wnt reporter, the distinct activation is visualized in some HF stem cells in bulge region at telogen-to-anagen transition phase (Deschene *et al.*, 2014). Furthermore, Wnt10b and Wnt16 expression are dominantly localized to new hair growth foci (Deschene *et al.*, 2014). Interestingly, Wnt10b ligand-mediated β -catenin activation is also involved in development of types of progenitor cells including melanocyte stem cells and follicular outer root sheath (ORS) cells (Ye *et al.*, 2013).

Recent works focus attention on the role of Wnt/ β -catenin signaling in the DP for HF induction and growth. Zhou L and his colleagues were reported that Wnt/ β -catenin signaling accelerates the spontaneous growth of CD133+ DP cells and matrix keratinocyte following HF differentiation (Zhou *et al.*, 2016a). In following study, they further demonstrated that Wnt ligands produced by CD133+ DP cells play an important role in postnatal hair growth by maintaining the growth onset of DP cells and mediating the signaling cross-talk in hair bulge region (Zhou *et al.*, 2016b). However, it is unclear how the signals act upon HF stem cells and progenitor cells in bulge region control cell type-specific development to organize growth during the hair cycle.

Recent studies on Wnt signaling in DP cells are very important in this respect. It has been reported that HF quiescence is maintained dependent on BMP signaling (Plikus *et al.*, 2008). Temporally activations of BMP2/4, Noggin, a BMP antagonist, and Wnt signals elaborately regulate the development of HF bulge stem cell activation and growth during hair cycle (Plikus *et al.*, 2008). It could be inferred that BMP signaling is overcome by activating Wnt signals, proliferation begins first in the hair germ possibly due the proximity of these cells to the DP which is the likely source of these signals (Rompolas & Greco, 2014).

Conclusion

It has been cleared that Wnt/ β -catenin signaling pathway is important for reciprocal interaction and communication between dermal/mesenchymal and epidermal components in hair bulb at the bottom of the HF. Further studies are needed to elucidate the mechanism of cross-talking between Wnt/ β -catenin signal and other signaling pathways that may act upon maintenance of the HF homeostasis.

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References

- Alonso L, Fuchs E. Stem cells in the skin: waste not, Wnt not. *Genes & Development*, 17: 1189-1200, 2003.
- Bejsovec A. Wnt signaling: an embarrassment of receptors. *Current Biology*, 10: R919-922, 2000.
- Chen D, Jarrell A, Guo C, Lang R, Atit R. Dermal β -catenin activity in response to epidermal Wnt ligands is required for fibroblast proliferation and hair follicle initiation. *Development*, 139: 1522-1533, 2012.
- Deschene ER, Myung P, Rompolas P, Zito G, Sun TY, Taketo MM, Saotome I, Greco V. β -Catenin activation regulates tissue growth non-cell autonomously in the hair stem cell niche. *Science*, 343: 1353-1356, 2014.
- Hsu YC, Pasolli HA, Fuchs E. Dynamics between stem cells, niche, and progeny in the hair follicle. *Cell*, 144: 92-105, 2011.
- Huelsken J, Vogel R, Erdmann B, Cotsarelis G, Birchmeier W. β -Catenin controls hair follicle morphogenesis and stem cell differentiation in the skin. *Cell*, 105: 533-545, 2001.
- Lim X, Nusse R. Wnt signaling in skin development, homeostasis, and disease. *Cold Spring Harbor Perspectives in Biology*, 5: a008029, 2013.
- MacDonald BT, Tamai K, He X. Wnt/ β -catenin signaling: components, mechanisms, and diseases. *Developmental Cell*, 17: 9-26, 2009.
- Merrill BJ. Wnt pathway regulation of embryonic stem cell self-renewal. *Cold Spring Harbor Perspectives in Biology*, 4: a007971, 2012.
- Plikus MV, Mayer JA, de la Cruz D, Baker RE, Maini PK, Maxson R, Chuong CM. Cyclic dermal BMP signalling regulates stem cell activation during hair regeneration. *Nature*, 451: 340-344, 2008.
- Rompolas P, Greco V. Stem cell dynamics in the hair follicle niche. *Seminars in Cell & Developmental Biology*, 25-26: 34-42, 2014.
- Schmidt-Ullrich R, Paus R. Molecular principles of hair follicle induction and morphogenesis. *BioEssays*, 27: 247-261, 2005.
- Wodarz A, Nusse R. Mechanisms of Wnt signaling in development. *Annual Review of Cell and Developmental Biology*, 14: 59-88, 1998.
- Ye J, Yang T, Guo H, Tang Y, Deng F, Li Y, Xing Y, Yang L, Yang K. Wnt10b promotes differentiation of mouse hair follicle melanocytes. *International Journal of Medical Sciences*, 10: 691-698, 2013.
- Zhang Y, Tomann P, Andl T, Gallant NM, Huelsken J, Jerchow B, Birchmeier W, Paus R, Piccolo S, Mikkola ML, *et al.* Reciprocal requirements for EDA/EDAR/NF- κ B and Wnt/ β -catenin signaling pathways in hair follicle induction. *Developmental Cell*, 17: 49-61, 2009.
- Zhou L, Xu M, Yang Y, Yang K, Wickett RR, Andl T, Millar SE, Zhang Y. Activation of β -catenin signaling in CD133-positive dermal papilla cells drives postnatal hair growth. *PLoS ONE*, 11: e0160425, 2016a.
- Zhou L, Yang K, Xu M, Andl T, Millar SE, Boyce S, Zhang Y. Activating β -catenin signaling in CD133-positive dermal papilla cells increases hair inductivity. *The FEBS Journal*, 283: 2823-2835, 2016b.

국문초록

모낭 발달에 있어서의 Wnt 신호전달의 역할

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모낭은 상피와 간엽 부분으로 구성된 작은 조직기관으로서, 모발의 발달과 성장에 매우 중요한 역할을 담당하고 있다. 배아초기단계에서 나타나는 모낭의 형성은 주로 모낭 니치(niche) 안에서의 상피-간엽 상호작용을 통해 조절되며, 이러한 상호작용은 또한 출생 이후의 모발 성장 주기와 재생에도 관여한다. 진피 모유두 세포는 모구(hair bulb)의 간엽부분에 존재하는 주요한 구성세포로, 다양한 신호물질을 발생시켜 인접한 상피세포에 전달하여 해당 세포의 행동을 조절한다. 현재까지 많은 신호전달체계가 모낭의 발달과 성장에 관여됨이 보고되고 있으며, 가장 대표적으로 진피 모유두 세포 내 Wnt/ β -catenin 기반 신호가 모낭세포와 상피세포간의 상호작용에 중요하다고 보고되고 있다. 이러한 Wnt/ β -catenin 신호전달체계는 모낭 형성 및 재생에 중요하게 관여된다. 본 총설은 모낭 형성 및 주기에 있어 Wnt 신호전달체계에 대하여 현재까지 밝혀진 연구결과를 요약하고자 한다.

핵심어: 모낭, 진피 모유두 세포, Wnt/ β -catenin 신호전달, 성장, 발달

본 논문을 위해 조언해주신 건국대학교 안성관 교수님과 배승희 교수님께 감사의 말씀을 드립니다.

中文摘要

Wnt信号通路对毛囊发育的影响

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毛囊是由上皮及真皮间充质组成的微型器官, 在头发发展和生长中起关键作用。在胚胎初期, 毛囊的形成主要由真皮乳头细胞生态位内的上皮-间充质相互作用调节, 并且这种相互作用也涉及生长后的毛发生长周期和再生。真皮乳头细胞是毛球 (hair bulb) 内的间充质组成成分, 并且通过产生多种信号来调节周围相邻的上皮细胞的行为。至今, 有许多信号通路涉及毛囊的发展和生长的报道中, 真皮乳头细胞内Wnt/ β -catenin信号通路对毛囊细胞和上皮细胞之间的相互作用起关键作用。这种Wnt/ β -catenin信号通路对毛囊的形成和再生是重要的。本文综述了Wnt信号通路在毛囊形成和周期中的研究。

关键词: 毛囊, 真皮乳头细胞, Wnt/ β -catenin信号通路, 生长, 发展