Notch Signaling in Hair Follicle Development

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Abstract

Notch pathway has been known as a major signal transduction route regulating stem cell homeostasis and development in multicellular organisms including hair follicles. Many studies have represented that Notch activity is critical to determine cell fate decision during hair follicle development. Also, growing results have revealed the pivotal role of Notch signaling pathway in controlling of hair follicle stem cell fates, regulation of hair cycles and resuscitation of injured hair organs. Furthermore, in hair bulb, Notch signaling pathway regulates hair follicle stem cell differentiation. The purpose of this review is to summarize considerable recent evidences in our understanding of Notch signaling and their regulating factors in hair follicle development to maintain their hair follicle homeostasis.

Keywords: Notch, Hair follicle, Stem cell, Growth, Development

Introduction

Hair basically serves to protective functions against injury, infection, dehydration, and thermoregulation of skin. Hair shaft is the part of the hair beyond the surface of the skin, and is generated from the hair follicle which is a complex miniorgan of the skin. Hair follicle constitutes the pilosebaceous unit together with its associated structures, including the sebaceous gland, the apocrine gland and the arrector pili muscle (Schlake, 2007; Schneider *et al.*, 2009). Hair follicle is composed of several concentric cylinders of epithelial cells (Powell & Rogers, 1990). Hair shaft consists of three layers of cells, the medulla, cortex, and hair shaft cuticle cells. Those cells are surrounded by an inner root sheet (IRS) which is composed of cuticle cells, Huxley's and Henley's layers (Schneider *et al.*, 2009). The companion layer is located between the IRS and outer root sheet (ORS) and can separates the IRS from ORS, which is contiguous with the basal layer of

the epidermis. They are produced by the mitotic active cells in the matrix of the hair bulb (Blanpain & Fuchs, 2006; Coulombe *et al.*, 1989). The mitotically active cells called dermal papilla cells in the matrix are in lower region of hair bulb (Blanpain & Fuchs, 2006). The upper region of hair bulb is called as the precortex where cells differentiate precursors of IRS and hair shaft (Schneider *et al.*, 2009). The precortex region also contains melanocyte to synthesize and transport melanin granules towards the keratinocytes of the forming hair (Limat *et al.*, 1999). In the uppermost part of its permanent portion, the hair follicle is surrounded by the sebaceous gland. The complex of sebaceous glands and hair follicle generates the mature pilosebaceous unit (Paus *et al.*, 1999). Just under the sebaceous gland, the ORS presents known as the bulge where the hair follicle stem cells are presented (Ohshima, 2007). The hair follicle undergoes cycles of growth (anagen), apoptosis-mediated regression (catagen) and relative quiescence (telogen). In each cycle, a new hair shaft is formed, and the

old hair is eventually shed, mostly in an actively regulated process termed exogen. Generation of the new hair shaft depends on the activation of hair-specific epithelial stem cells called hair follicle stem cells (Schneider *et al.*, 2009). Although the hair follicle is highly sensitive to growth factors (Booth & Potten, 2000), cytokines (Danilenko *et al.*, 1996, Hoffmann *et al.*, 1996), neuropeptides (Holub *et al.*, 2012), and hormones (Fischer *et al.*, 2007, van Beek *et al.*, 2008), the intracellular signaling pathways that play a functional role in hair follicle homeostasis are major interesting field in cellular and molecular biology. There have been many reports about various cellular signaling pathways controlling the hair cycle to maintain hair follicle homeostasis in their microenvironment called niche (Lee & Tumber, 2012; Rishikaysh *et al.*, 2014). The key event for hair follicle regeneration is the molecular communication between hair follicle stem cells in their niche and regulation of signaling pathway during hair cycle in hair bulb. Many studies have been established that the temporal differences of signaling pathway in hair follicle development (Lin *et al.*, 2004; Lin *et al.*, 2009; Plikus *et al.*, 2008). Notch signaling pathway is generally accepted to have a key role in cell asymmetric division and fate determination during stem cell development and tissue homeostasis. In this review, we focus on the recent evidences of regulatory activity of Notch signaling on hair follicle differentiation process, which is referred to cell fate decision.

The role of Notch signaling pathway in hair follicle development

1. Basic insights of Notch signaling

Notch signaling is highly conserved through evolution and is crucial for cell death, proliferation, differentiation, and development (Artavanis-Tsakonas *et al.*, 1999; Sato *et al.*, 2012). Notch, a cell-surface receptor, is a family name of transmembrane proteins sharing special structural characteristics including an extracellular domain consisting of multiple epidermal growth factor (EGF)-like repeats, and Notch intracellular domain (NICD) (Rana & Haltiwanger, 2011). The canonical Notch signaling pathway is depicted in Figure 1. Notch signaling is initiated by interactions between physically neighboring cells through binding of Notch receptors (Notch1–4) to their cognate Notch ligands (Jagged1–2 and

Figure 1. Schematic view of Notch signaling.

Signal transduction from Notch receptor is activated by interaction with its ligands, such as Delta and Jagged. This binding results in a cascade cleavage triggered by the ADAM17 metalloprotease and Presenilin protease. These cleavage reactions result in the release of the NICD. Then, NICD translocates to the nucleus where NICD interacts with transcription factors, CSL and cofactor A. This interaction induces transactivation of downstream target genes including Hes and Hey. ADAM17, ADAM metalloproteinase domain 17; NICD, Notch intracellular domain; CSL, C-promoter binding factor 1 (CBF1), Suppressor of Hairless, Lag1; Hes, Hairy/enhancer of split; Hey, Hairy/enhancer-of-split related with YRPW motif.

Delta1–4) (Chillakuri *et al.*, 2012; Kopan & Ilagan, 2009). The Notch receptor is translated as a single protein (pre-Notch). The preproprotein is proteolytically processed in the trans-Golgi network to generate two polypeptide chains that heterodimerize to form the mature cell-surface receptor (Logeat *et al.*, 1998). A Furin-like convertase cleaves pre-Notch into the extracellular and intracellular domain (S1 cleavage). This results in a heterodimeric receptor with non-covalently associated domains that is transported to the plasma membrane. Notch ligand binding triggers two proteolytic cleavages (S2 and S3). The first, mediated by a disintegrin and metalloproteinase (ADAM) proteinase, occurs in the extracellular domain. S2 cleavage sequentially activates the gamma-secretase complex, which is responsible for the second proteolytic cleavage (S3), which located in the transmembrane domain (Brou *et al.*, 2000; Struhl & Greenwald, 2001). Then, NICD protein is endocytosed and translocated to the nucleus, where it forms a transcriptional complex with the immunoglobulin-like fold, plexins and transcription factors (IPT)-domain-containing C-promoter binding factor 1 (CBF1), Suppressor of Hairless and Lag1 (CSL) (Bray, 2006; Kopan & Ilagan, 2009). Docking of the ankyrin-repeat domain of Notch to the Rel-homology region

of the CSL protein generates a composite binding surface for the recruitment of Mastermind-like proteins (Maml). These interactions convert CSL from a transcriptional repressor to an activator by displacing co-repressors (CoR) and histone deacetylases and recruiting histone acetyltransferases. Maml, in turn, recruits additional co-activators (CoA), such as p300. To date, it has been established that combinatorial interactions between Notch transcription complexes and tissue-specific transcription factors enables the diversity of tissue-specific target genes; biological consequences of pathway activation can vary depending on multiple factors, such as cell type-dependent combination of signaling (Sato *et al.*, 2012). Primary Notch target genes include two families of bHLH transcriptional factors Hairy/enhancer of split (Hes) proteins (Hes1 and Hes5) and Hairy/enhancer-of-split related with YRPW motif (Hey) proteins (Hey1 and Hey2) (Grbavec & Stifani, 1996; Iso *et al.*, 2003). Notch signaling is regulated by other proteins including Numb, Itch, Nrarp, Mint, and Deltex (Krebs *et al.*, 2001; Kuroda *et al.*, 2003; Matsuno *et al.*, 1995; McGill & McGlade, 2003). Numb and Itch are negative regulators of Notch signaling by preventing nuclear localization and targeting the NICD for degradation through the E3 ligase Itch (McGill & McGlade, 2003).

2. Notch signaling pathway in hair follicle development

Many studies have been carried out on the effects of Notch signaling on stem cell maintenance and cell fate decision in various origins. The effects of Notch signaling in hair follicles has been studied using immunohistochemical analysis and transgenic mouse model carrying either loss or gain of function mutations (Aubin-Houzelstein, 2012; Lee & Tumber, 2012; Rishikaysh *et al.*, 2014). Notch is expressed throughout embryogenesis and postnatal period (Favier *et al.*, 2000; Powell *et al.*, 1998). During embryogenesis, Notch1 expressions are detected in the hair placode inner cells and Notch ligand Jagged1 and 2 expressions are also founded in the same locations as Notch1 transcripts in hair follicles (Favier *et al.*, 2000; Powell *et al.*, 1998). Another Notch ligand, Delta1, is expressed in the dermal papilla and bulb region of embryonic hair follicles during embryogenesis period (Estrach *et al.*, 2008). Vauclair *et al.* (2005) performed functional comparisons between embryonic and postnatal period. They revealed that inactivation of Notch1 does not perturb the formation and patterning of hair follicle placodes

in early embryonic period. However, tissue-specific ablation of Notch1 gene shows a phenotype of hair loss and shortened anagen and premature entry into catagen in late stages of hair follicle development during embryogenesis (Vauclair *et al.*, 2005). These data suggest that Notch1 signaling has a key role in postnatal hair follicle development and homeostasis. Although Notch signaling do not function during hair germ cell induction or cell fate acquisition within the embryonic hair follicle, previous studies reveal that Notch signaling is required to complete terminal differentiation in IRS cells (Cai *et al.*, 2009; Pan *et al.*, 2004). Notch1 is mainly expressed and activated in mitotically active IRS and cortex precursors. In the absence of Notch signaling, a hair shaft still forms and contains properly positioned cells expressing markers for each fate (Pan *et al.*, 2004). This follicular architecture by unstable adherent to each other lead to the transformation of aberrant hair follicles into epidermal cysts during the first anagen by overproliferating ORS cells (Pan *et al.*, 2004). One noteworthy feature is that Notch signaling has a functional role in differentiation process of various progenitor cells rather than in stem cell maintenance of hair follicle germ cells. In this review, recently studied various factors which modulate the Notch signaling pathway during hair follicle differentiation are focused.

1) Musashi family

The Musashi (Msi) is highly conserved through evolution and is a family name of RNA-binding proteins (Okano *et al.*, 2002; Okano *et al.*, 2005). Two members of the group, such as Msi1 and Msi2, have been identified to date (Sakakibara *et al.*, 1996; Sakakibara *et al.*, 2001). A revealed function of Msi1 is a translational repression of specifically bound mRNAs by directly binding of 3'-untranslated region of targets mRNA (Horisawa *et al.*, 2009). Several researches have revealed that Msi1 plays pivotal roles in maintaining the stem cell status (stemness) of neural stem/progenitor cells in adults and in the development of central nervous system through translational regulation of its target mRNAs (Horisawa *et al.*, 2010; Okano *et al.*, 2005). Furthermore, Msi1 and 2 were expressed in the epidermis and hair follicles at early developmental stages until adulthood in mice (Sugiyama-Nakagiri *et al.*, 2006). Of note, Msi1 and 2 were both expressed in the bulge region of hair follicle in the transition from telogen to anagen phase. During anagen phase, Msi1 and 2 were also expressed in matrix

cells. These results suggest Msi-positive cells may represent progenitor cells, or hair follicle stem cells.

Recent reports have been noted about the functional crosstalking mechanism between Msi family and Notch signaling in hair follicles (Imai *et al.*, 2001). Imai and colleagues have reported that Msi protein augments the Notch signal through the translational repression of its target, Numb (Imai *et al.*, 2001). Numb functions as a Notch downstream repressor, thereby contributing to the self-renewal of neural and epithelial stem cells. Therefore, further studies will be of interest to examine whether Msi signaling is able to affect the Notch activity for hair follicle stem cell maintenance. Recently, Ma and colleagues were reported that forced Msi2 expression retards anagen entry and consequently, delay hair growth using transgenic and conditional knockout mouse model (Ma *et al.*, 2017). They also showed that Msi2 maintains quiescent state of hair follicle stem cells in the process of telogen-to-anagen transition (Ma *et al.*, 2017). Although they present the Msi2-Hh signaling pathway using bioinformatics analysis, they may not be able to rule out the possibility of Msi and Notch signaling crosstalk (Ma *et al.*, 2017).

2) Reactive oxygen species

Mitochondria are essential organelles for aerobic respiration to provide the adenosine triphosphate energy by oxidative phosphorylation. The mitochondrial oxidative phosphorylation plays a role in the cellular redox regulation and reactive oxygen species (ROS) generation (Handy & Loscalzo, 2012). Evidences suggest that stem cells reside in niches characterized by hypoxia and low ROS, both of which are critical for maintaining the potential for self-renewal and stemness (Eliasson & Jönsson, 2010; Ezashi *et al.*, 2005; Fehrer *et al.*, 2007; Mohyeldin *et al.*, 2010). In the last decade, several studies have revealed that mitochondrial metabolism is a functional regulator of keratinocyte and hair follicle differentiation (Hamanaka & Chandel, 2013; Hamanaka *et al.*, 2013; Lemasters *et al.*, 2017; Tang *et al.*, 2016). Hamanaka and his colleagues have reported that mitochondrial ROS promote epidermal differentiation and hair follicle development (Hamanaka *et al.*, 2013). They used Krt14-specific Tfam-deleted conditional knockout mouse (TFAM/KRT14-Cre⁺ mouse) which was characterized by impaired mitochondrial functions in epidermis and showed that mice lacking Tfam also exhibited the transcriptional suppression of Notch downstream signaling. Although they

did not provide a defined mechanism for the activation route of Notch signaling by ROS, a study suggesting the possible mechanism has been reported. Recently, Kavian and his colleagues have reported that ROS could activate Notch pathway in fibroblast model (Kavian *et al.*, 2010). They showed that intradermal ROS can induce the expression of ADAM17 which cleaves the ectodomain of Notch receptor for first step activation of Notch (Kavian *et al.*, 2010). ROS-induced ADAM17 could be a possible factor for activation of Notch signaling in hair follicles. Further researches will be needed on clarify the activation mechanism of Notch signaling by ROS.

3) Tspear

It has been known that hair follicle morphogenesis and differentiation is dependent on Wnt, Shh, Bmp and Notch signaling pathway interplaying between epithelial and mesenchymal cells. Notch signaling participates in hair follicle morphogenesis in several ways for cell fate decision: lateral inhibition, boundary formation and lineage decision (Bray, 1998). Although, it has been known that Notch has not an essential role in the initial step of embryonic hair follicle development, it plays a key role in cell differentiation in hair follicles during late hair follicle differentiation (Lin *et al.*, 2011; Vauclair *et al.*, 2005). Cell fate is dependent on asymmetrical inheritance of Notch regulators and regulating differentiation and promoting boundary formation by altering adhesive properties of keratinocytes (Bray, 2006). Recently, Peled and his colleagues were reported that mutation in Tspear affects hair follicle morphogenesis in conditional knockdown mouse model (Peled *et al.*, 2016). They further demonstrated that Tspear downregulation lead to transcriptional suppression of Notch1 and its downstream genes in cultured keratinocyte. Although they did not show the detailed mechanism of action of Tspear during tooth and hair follicle morphogenesis, this observation support the possibility that Tspear regulates Notch signaling, a key biological pathway previously shown to affect the development of many ectodermal tissues. Further studies on the molecular mechanism of Tspear regulating Notch signaling remain to be fully delineated.

4) Leptin

Leptin, a signaling cytokine released by adipocyte, well known as one of the endogenous regulators of body weight and energy metabolism (Farooqi & O'Rahilly, 2009; Friedman,

1999-2000). Moreover, it has been reported that leptin can affect cancer progression using the leptin-Notch axis in breast and pancreatic cancers (Battle *et al.*, 2014; Harbuzariu *et al.*, 2017). Recently, leptin has been studied the functional role in skin (Goren *et al.*, 2003; Tadokoro *et al.*, 2015). Leptin and its receptors are expressed by both fibroblasts and keratinocytes and regulate the keratinocyte proliferation for wound repair and skin regeneration. Notably, Sumikawa and his colleagues have been reported that molecular function of leptin in hair cycling (Sumikawa *et al.*, 2014). They demonstrated that leptin was detected in dermal papilla cells in catagen, telogen and early anagen by immunohistochemistry. Moreover, real-time polymerase chain reaction analysis revealed that leptin expressions in dermal papilla cells were upregulated at hypoxic condition during the hair cycle (Sumikawa *et al.*, 2014). Also, Stat3 activation was observed in keratinocytes after the treatment of leptin *in vitro* (Sumikawa *et al.*, 2014). However, the molecular role of leptin in the bulge region where dermal papilla cells are located has not been studied extensively including hair follicle differentiation. Further studies on the molecular function of leptin and the relevance of the leptin-Notch axis are needed to be examined.

Conclusion

Hair follicle is a very complex miniorgan. Many studies have been found that Notch signaling affects the development process from stem cell self-renewal through progenitor cell differentiation. Furthermore, recent accumulation of stem cell studies of various origins has identified many factors that may influence the Notch signaling in hair follicles during hair follicle development. In this review, we summarize current reports about the various factors that may modulate the signaling of Notch on hair follicle development. These factors have already been reported in cell models of various cell origins and may be suspected of cell-specific activity in the hair follicle development process. In addition, it has already been reported that direct binding of beta-catenin to NICD is possible and that various mutual regulatory mechanisms exist in the cells. In future studies, it is necessary to confirm the possibility of cross-talking of two signaling mechanisms. The information gained from Notch signaling pathway involved in hair follicle development will elucidate in the hair follicle abnormalities

arising from their dysregulation. Furthermore, knowledges from depth research on Notch signaling on hair follicle can be applied to stem cell-based therapeutics.

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국문초록

모낭 발달에 있어서의 Notch 신호전달체계의 역할

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Notch 신호전달체계는 줄기세포의 항상성 조절뿐만 아니라 모낭을 포함한 다세포 조직의 발달 조절에도 주요한 역할을 담당한다. 다양한 연구논문을 통해 Notch 활성화는 모낭 발달과정에 있어 세포의 운명을 결정하는데 매우 중대한 역할을 수행한다고 밝혀졌다. 또한, 모낭 줄기세포의 운명 조절과 모발 주기 조절 그리고 손상된 두피의 재건에도 중심적인 역할을 담당한다고 보고되고 있다. 게다가 모구에 있어 Notch 신호전달체계는 모낭줄기세포의 분화 조절까지 그 기능이 보고되고 있다. 본 총설은 모낭의 발달 및 모낭의 항상성 유지에 관여하는 Notch 신호전달체계 및 관련 조절 단백질들에 대한 최신 지견을 요약하고자 한다.

핵심어: Notch, 모낭, 줄기세포, 성장, 발달

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中文摘要

Notch 信号在毛囊发育中的作用

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Notch信号通路被认为是不仅调节干细胞稳态, 而且调节包括毛囊在内的多细胞组织发育的重要信号转导途径。许多研究表明, 在毛囊发育过程中, Notch活性在细胞命运决定方面起着关键作用。还有越来越多的研究结果表明, Notch信号通路在控制毛囊干细胞命运、调控毛发周期和损伤毛发器官再生方面起着关键性的作用。此外, 在毛球中, Notch信号通路调节毛囊干细胞分化方面发挥了重要作用。本文综述了近年来参与毛囊发育和维持毛囊稳态的Notch信号通路以及相关调控蛋白的最新研究进展。

关键词: Notch, 毛囊, 干细胞, 生长, 发育