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New Insight into the Relationship between TGF-β Superfamily and Noggin in hair cycle

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Abstract: *Members of TGF-β superfamily participate in controlling hair apoptosis, and the roles of those factors in the hair cycle have not been sufficiently clear. BMPs which belong to the TGF-β superfamily also play critical roles in governing hair growth. In the process of controlling hair growth through the interacting between BMPs and noggin, noggin not only acts as an inhibitor of BMP-2 and 4 but influents the wavy expressions of BMP-2 and 4. Furthermore, BMPs are similar with TGF-β1, 2, 3 in structures and biologic characters. We present the positions of TGF-β1, 2, 3, and among those factors TGF-β1, 2 have some consistency with the positions of noggin in the hair regeneration cycles. Furthermore, TGF-β1, 2 are known as apoptosis-inducing factors, they can cease the cell proliferation through downstream signaling factors. After checking the positions of TGF-β1, 2 and Noggin, we inferred that TGF-β1, 2 may induce hair enter into catagen phase by inhibiting cell division or noggin expression, the wavy expressions of TGF-β1, 2 probably specify the hair cycle.*

Keywords: *Bone morphogenetic protein, Bone morphogenetic protein receptor, Hair cycle, Noggin, Transforming growth factor beta*

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I. Introduction of TGF-β family

The introduction of the paper should explain the nature of the problem, previous work, purpose, and the contribution of the paper. The contents of each section may be provided to understand easily about the paper. (10)

Growth factors are involved in hair morphogenesis and cycle, among those growth factors, the transforming growth factor beta (TGF-β) family plays an important part in the hair biologic cycle. TGF-β superfamily is important in regulating differentiation, proliferation and apoptosis of many kinds of cells. Members of the TGF-β superfamily include: bone morphogenetic proteins (BMPs), growth and differentiation factors (GDFs), activins, inhibins, et al.[1] Furthermore, TGF-β superfamily is one of those superfamilies which have been most deeply studied.

TGF-β ligands bind to TGF-β receptors I, II and have two main downstream pathways (Smad and TAK1).[1] Molecules of TGF-β superfamily are involved in many developmental processes, those molecules are essential for hair, tooth and T-cells to maintain their normal functions.[2] Recently Maksim V. Plikus et al. published their research results; they specified the relationship between hair growth and its microenvironment. In study, they also expatiated the BMP superfamily administrated hair wavy growth,[3] and circular appearances of BMP-2, BMP-4 were the main factors of hair repetitive growth.

II. Role of TGF-1, 2, 3 in hair morphogenesis and cycle

We focus on functions of TGF-β1, 2, 3 in hair morphogenesis and cycle firstly. Hair bud morphogenesis is guided by a reciprocal exchange of signals between epithelium and mesenchyme.[5]

TGF-β2-deficient mice delay hair follicle development and have less hair follicles than normal mice, the reduction of hair follicle number has no relationship with the hair apoptosis process induced by TGF-β2. In vitro TGF-β2 is isolated from the basal layer of the epidermis and regulated by phosphorylated SMAD-2 which is the downstream effector of TGF-β2 signaling. Employing mutant mouse models and culturing keratinocytes, Fuchs, E. et al found that TGF-β2 signaling is necessary to transiently induce the transcription factor Snail and activate the Ras-mitogen-activated protein kinase (MAPK) pathway in the bud.[5] This may be the explanation that less developed hair follicles appear in the embryonic period in TGF-β2-deficient mice. However, for another two factors, TGF-β1 has slight influence on hair formation through inhibiting keratinocyte growth, and TGF-β3 has no effect on hair formation.[6]

TGF-β1 plays an important role in the hair cycle. In 18 days old TGF-β1-/- mouse, hair follicles are in early catagen, but in the same age of TGF-β1+/+ mouse, hair follicles are in telegen phase. There are more fast-

proliferation cells besides hair follicles of TGF-β1 -/- mouse than TGF-β1 +/+ mouse. These evidences prove that TGF-β1 inhibits hair growth,[7] and the mechanism of TGF-β1 in influencing hair development is unclear. In vitro culture, TGF-β1 derives from dermal papilla cells and has responsibility for inhibiting epithelial cell growth.[8] This means TGF-β1 could cease hair growth and may decide the time of hair cycle stages.

In early anagen TGF-β1 is expressed only in the bulge region of the out root sheath (ORS), which bellows the sebaceous gland.[7] TGF-β1-/- mice lack the downstream targets of TGF-β1 and have fewer label-retaining cells than normal mice,[9] most of those label-retaining cells are stem cells. At this growth phase, the stem cells are activated in the bulge area and then reinforce the dermal papilla cells, which give birth to the new hair. Those discoveries show tight relationship between stem cells and TGF-β1.

High expressions of TGF-β1 lie in out root sheath at full anagen phase and categen phase, the expression part of TGF-β1 extends to up part of hair follicle.[7] In late anagen stage, TGF-β1 expression increases, the immunostaining results show that expression locations of TGF-β1 are seen both in the ORS and epithelial strand during late anagen and catagen stages. But in those two growth phases, TGF-β1 is rarely detected in the inner root sheath.[7] In vitro culture, TGF-β1 has the function of blocking cell division and hair growth.

TGF-β2 aggregates when hair follicles are undergoing the growth phase between anagen and catagen. In this aggregating process, strong TGF-β2 deposition is demonstrated in the lower part of the boundary area between the dermal papilla and the germinative matrix cells. In vitro, when hair follicles are occupying catagen-like morphological changes, TGF-β2 deposits in the bulb area.[2]

During anagen to catagen phase, TGF-β2 appears in the outermost cell layer of the outer root sheath, and in this transient phase, strong TGF-β2 immunoreactivity appears in the lower bulb matrix cells which are adjacent to the dermal papilla.[4] TGF-β2 could induce catagen phase of murine and human hair follicles through inhibiting cell proliferation or inducing apoptosis of hair matrix keratinocytes.[5] In addition, TGF-β2 and TGF-β2 type II receptor resident in the regressing epithelial strands[4] and TGF-β2 deposits in the boundary area in early catagen, so TGF-β2 may decide the regression of hair at the catagen phase (Fig 1). After catagen phase, hair follicles come into the telogen phase. Molecular mediators of TGF-β superfamily are shown in table 1, locations of TGF-1, 2 are demonstrated in Fig. 1.

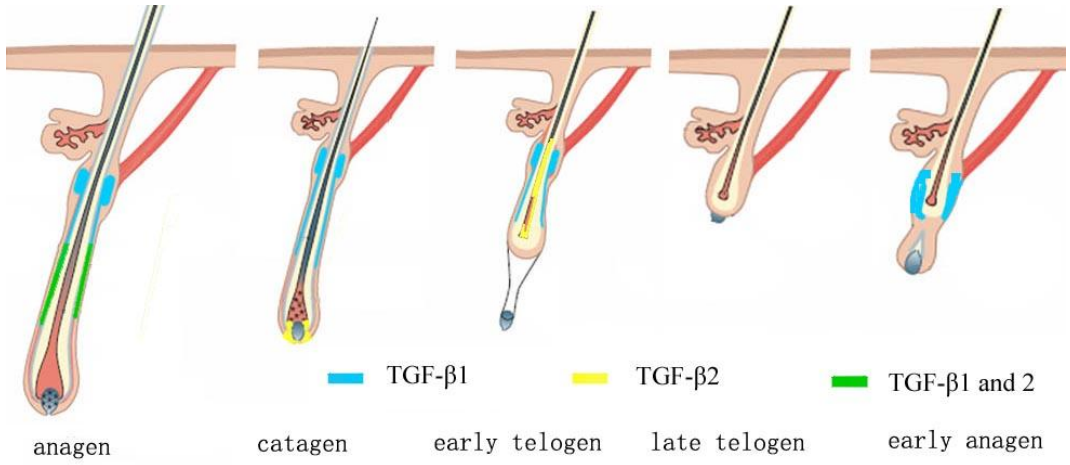

Fig.1 The location of TGF-β1, 2[1, 9, 31]

Table 1. Molecular mediators of TGF-β superfamily[1, 3, 9, 30-32]

Factors	Location in hair cycle	Function
TGF-β1	In inner root sheath, out root sheath, of in mature follicle	Plays a role in inducing catagen; blocking anagen in vivo
TGF-β2	All expressed in developing follicle, aggregates at dermal papilla at catagen to telogen phase	Controls cell apoptosis, induces catagen
TGF-β3	Hair cortex and the hair cuticle in the keratogenous zone (KZ) of the upper hair bulb. upper hair bulb	Promotes epithelial cell adhesion
TGF-β-RI	In Out root sheath at late anagen/catagen	Signal receptor of TGF-β isoforms; plays a role in catagen development
TGF-β-RII	Same as TGF-β-RI	Specifies the differentiation inner root sheath.
BMP2	Anagen bulb; subcutaneous layer	Suppresses proliferative activity and supports differentiation
BMP4	Lower follicle mesenchyne	Suppresses hair growth

Noggin	Follicular mesenchyne; dermal papilla	Suppresses activity of BMP4 and induces hair growth

III. Interactions of BMP-2, 4 and Noggin in hair morphogenesis

Stem cells play an essential role in cellular specialization and pattern formation during embryogenesis and in tissue regeneration in adults.[6] At early embryonic stage, the stem cells are specified into daughter cells such as hair follicle stem cells, dermis and epidermis.[7]

Bmp signaling specify ectodermal cells to differentiate into epidermis, it begins in the neuroepithelium of embryonic period. Once the embryonic skin stem cell (SC) progenitor cells have been confirmed, the next crossroads for signaling appears to be at the juncture of hair placode formation. Placode formation is dependent on Noggin, in the presence of excess BMPs, or the absence of the BMP-inhibitor noggin or the follicle density is reduced.[8, 9] Conditional absence of the BMPR1A gene also results in the accumulation of large masses of undifferentiated, Lef1-expressing, placode-like cells, further emphasizing a role for Bmp inhibition in the early stages of HF morphogenesis.[8]

The appearance of the BMPR1A gene is also investigated as a positive role for Bmp signaling, especially in the differentiation of matrix cells into inner root sheath (IRS) and hair shaft lineages. Several markers of matrix cell differentiation are strongly reduced or absent following the BMPR1A-null mouse.[8] Using the BMPR1A-absence mutant mouse, Munehiro Yuhki1 et al. found the differentiation of inner root sheath, but not outer root sheath is severely impaired. The number of HFs (hair follicles) was reduced in the dermis and subcutaneous tissue, and cycling epithelial cells were reduced in mutant mice HFs. BMPR1A is essential for inner root sheath differentiation.[10]

Nuclear β-catenin is also influenced in the matrix cells of BMPR1A-deficient mouse, which means that BMP signaling lies upstream of β-catenin signaling during matrix cell differentiation. From those evidences, Bmp signaling is required for SC activation, furthermore BMP signaling is required for the differentiation of activating SCs in adopting one or more of its six different lineages which compose the mature HF.[12]

IV. BMP-2, 4 control hair wavy growth

The other factors of TGF-β surperfamily have also been deeply investigated recently, especially Bmp-2, 4. Those two growth factors and noggin protein which is an inhibitor of Bmp-2, 4 are seen as dominators of hair follicle stem cells. Functions of BMP-2, 4 and Noggin are critical for hair regeneration and cycle, which attract researchers' interests as hair regeneration is a perfect model of investigating organ regeneration.[11]

In embryonic stage BMP-2 gene expression locates in the thickened ectodermal placode. Gene of BMP-4 expression locates in the mesenchymal and aggregates under the ectodermal placode.[12] BMP-4 induces the expression of Lef1 through regulating some regulatory factors.[13] Noggin not only interacts with BMP-4 but triggers HF morphogenesis in the hair placode. Furthermore, in hair placode development, BMP-4 locates as downstream factor of β-catenin signaling which is necessary in deciding the fate of hair follicle stem cells.[10] On the whole, those studies suggest that BMP-4's downregulation may be a cue of starting HF development. Not only in the embryonic stage but in the secondary (Nontylotrich) hair follicles, Modulation of BMP signaling by noggin is required.[14]

In anagen, BMP-2 appears in the cortical cells of the lower hair shaft. And around the club ends of follicle fibres in catagen and telogen. BMP-4 expresses in follicles in all of hair cycle phases. In anagen hair follicles, BMP-4 just appears in the dermal papilla (DP), in catagen and telogen BMP-4 expresses not only in DP but in lower hair shaft whilst. Further more BMP-4 aggregates in the mesenchymal cells beneath the regressed follicle.[12] Fig.2.

Many dermal cells show the expressions of BMP-4 mRNA in early anagen hair follicles, BMP-4 transcripts are detected in the proximal hair matrix, dermal papilla, outer root sheath and inner root sheath of fully developed anagen hair follicle.[15]In telogen phase of the secondary hair follicle cycle phase, RT-PCR results show high steady-state level of BMP-4 exists in skin and BMP4 gene transcripts are found in the dermal papilla by in situ hybridization.[15, 16]

V. Roles of Noggin in hair cycle

Noggin should be referred no matter as the inhibitor of BMP or its functions in hair development. In E15.5-17.5 mice, expression of noggin which is the antagonist of BMP is seen in mesenchymal cells under the basal membrane of the epidermis. In adult mouse noggin is restricted to the dermal papilla and connective tissue sheath of the hair follicle.[17] Noggin functions in hair morphogenesis through inhibiting BMPs. (The expression of noggin displays in Fig. 3) Enhanced expression of BMP4 or targeted inactivation of noggin results in significantly blocking the hair follicle formation and inducing the hair follicle apoptosis. The highest noggin expression level is in the early anagen phase and the expression locations of noggin coincide with the positions of epithelial stem cells marker-K15. Variety of noggin expression may influent the expression level of

BMPs,[18] which relate to the expression of Lef1 and Wnt signaling, which specify hair follicle morphogenesis and cycle by exerting their functions on hair follicle stem cells.[8]

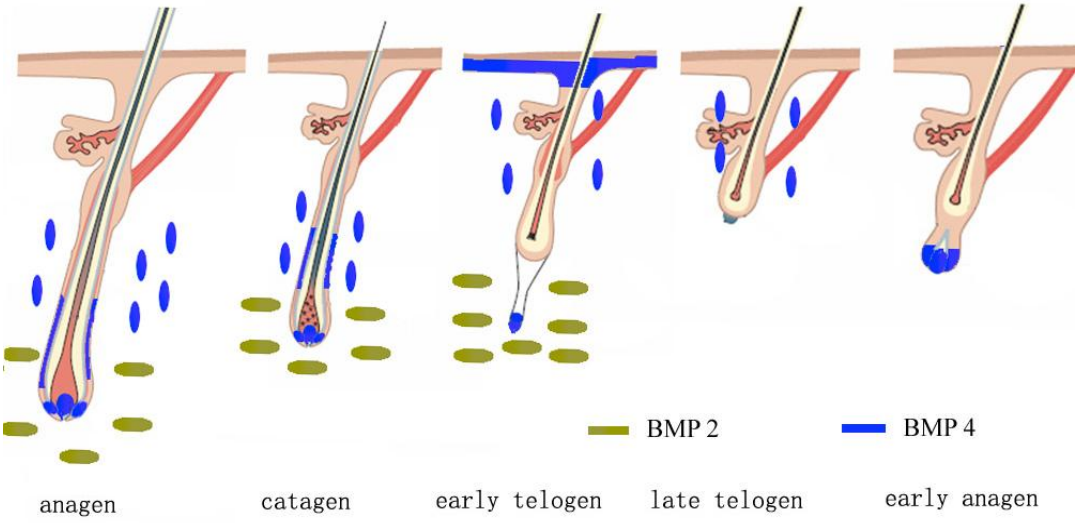

Fig.2 The location of BMP-2 and BMP-4

In early anagen there is highest noggin expression; this increased noggin expression influences the BMPs signaling in K15-positive epithelium stem cells.[18] Those stem cells are induced by the intensive noggin expression which inhibits BMPs in early anagen. Noggin's mRNA is seen in the dermal papilla and distal outer root sheath at the secondary hair germ and it also can be seen at all the anagen at the same position.[15] Those results strongly support the immunohistochemistry (IHC) results, for the locations of Noggin's mRNA expression are almost the same as the positions of Noggin. Noggin's expression in epithelium stem cells coincides with the activaton of Wnt/β-catenin signaling at the anagen phase of HF growth cycle. Noggin induces hair growth phase in postnatal skin, the noggin-treated mice show the hair grow out but the untreated group have no new hair.[15] Mis-expression of Noggin in transgenic mice induces premature onset of catagen in second hair follicles cycle.[19] Fig.3 shows the location of noggin in hair cycle.

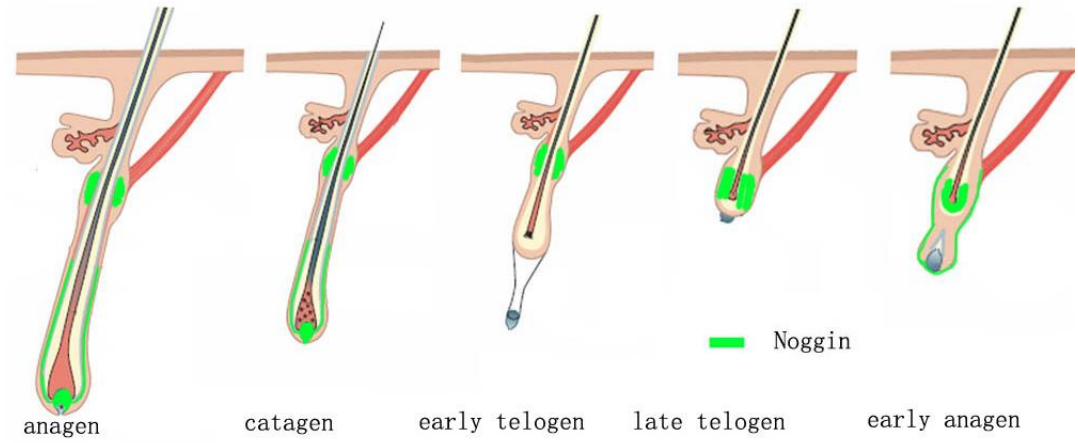

Fig. 3 The location of noggin in hair cycle.[3, 15, 17]

VI. Downstream signaling factors of TGF-β superfamily

Members of TGF-β signaling family exert their functions through type I and type II receptors, and those factors have been identified in vertebrates. Each member of the TGF-β superfamily binds to a characteristic combination of type I and type II receptors. [20]

During hair follicle development in embryonic period, initially TGF-β-RI appears in all basal epidermal layers. In later stage TGF-β-RI immunoreactivity is demonstrated strongly in epithelia cells, and sebocytes and interfollicular epidermal keratinocyte cells also display clear TGF-β-RI immnunoreactivity.[21] TGF-β-RII transcripts during skin development exclusively in the mesenchyme,[22] at early stage of hair follicle morphogenesis TGF-β-RII was restricted in epithelial cells. Within the first 3 weeks there is no TGF-β-

RII immunoreactivity in dermal papilla, fibroblasts or their precursor cells, only the epidermal region that subsequently formed a hair placode which generates a new hair follicle displays TGF-β-RII immunoreactivity. Later, after dermal papilla formation, TGF-β-RII appears in out root sheath and infundibulum.[21]

Postnatal mouse, TGF-β-RI emerges in sebaceous gland in all of hair cycle phases. Early anagen, TGF-β-RI can be detected in transit-amplifying cells and the part adjacent to dermal papilla. Later anagen, TGF-β-RI immnunoreactivity was in out root sheath and inner root sheath. At catagen phase, TGF-β-RI expression residents in the hair bulb disappears together with the out root sheath regression, the immunoreactive cell population just emerges proximally in epithelial strand. At telogen, TGF-β-RI expression is restricted to the sebaceous gland and the epidermis.[21, 23]

No TGF-β-RII is detected in skin in telogen and early anagen; subsequently it can be seen in inner root sheath and lightly expressed in out root sheath. At late anagen, TGF-β-RII reaches up to out root sheath border with epidermis, and absents in dermal papilla and hair bulb. During the regression phase, TGF-β-RII stays in hair bulb and inner root sheath, it doesn't scatter anywhere of skin after this stage.[21] (Fig. 4 is the locations of TGF-β-RI and II in hair cycle.) TGF-β superfamily members convey signals through type I and type II receptors and other downstream factors, termed Smads. After ligand binding, the activated receptor/ligand combines receptor- regulated Smad proteins (R-Smad), which bind to the common partner proteins (Co-Smad) and subsequently translocate to the nucleus to regulate the transcription of target genes.[2] And Smad6 and Smad-7 are inhibitory Smad proteins (I-Smad) which function in the cytoplasm as negative regulators of the intracellular signal transduction network.[24]

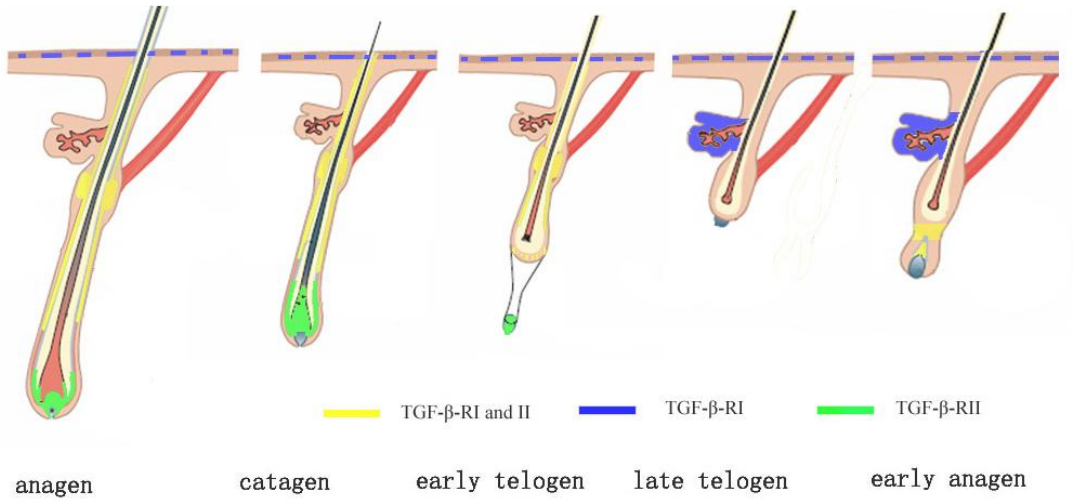

Fig. 4 The location of TGF-β-RI and II in hair cycle.[21, 24, 33]

Receptor-regulated Smad proteins (R-Smad) include Smad-1, 2, 3, 5, 8, Smad-2 and -3 are regulated by TGF-β and activin, whereas Smad-1, -5, and -8 are primarily activated by BMPs.[25]

So far Smad-2, 4 and 7 are the mostly concerned Smads by published research of hair biology.

In the wild-type mouse, however, there is very low level of endogenous Smad-2 expression in the epidermis.[26] Yang Chai, et al. developed transgenic mice that overexpress Smad-2 in epidermis under the control of keratin 14 promoter. Overexpression Smad-2 enhanced the expression of Smad-4, which discovers the interaction of Smad-2 and Smad-4 in conducting or controlling TGF-β signaling during skin development.[26] Owing to the failure of germ layer and streak formation, Smad-2 mouse dies before hair follicle germ appearance.[25, 27] Overexpression of Smad-2 elevates the endogenous TGF-β1 level while heterozygous loss of Smad-2 reduced TGF-β1 expression, when Smad-2 transgene expression in epidermis, its effects on keratinocyte proliferation and differentiation.[28]Conditional Smad-4 knockout mice develop epidermal hyperplasia, progressive hair loss beginning at the first catagen phase on P16, and spontaneous skin tumor formation later in life. Whether the elimination of Smad-4 causes the consequence of hair follicle degeneration and affects epidermal differentiation is unknown.[29]

VII. Conclusion

The appearance of noggin coincided with the wavy emergence of TGF-β. In anagen phase, the noggin resident in the same parts of hair follicles with TGF-β1, but just noggin appears in the dermal papilla, which produces new cells to complement the hair. In TGF-β1 -/- mouse, hair has a longer anagen phase than normal mouse. And culture in vitro, TGF-β1 inhibits the hair growth, makes the hair come in to catagen phase in advance. BMPs and TGF-βs share 30% amino acid homology and some downstream signaling pathways, for

example Smad-dependent pathways.[2] Roles of TGF-β1 in hair cycle may be explained as follow, TGF-β1 inhibits the extension of out root sheath and then controls the hair growth, and this process may be achieved through suppressing noggin.

For TGF-β2, in the early anagen phase, the high immunohistochemistry staining shows TGF-β2 concentrates at the dermal papilla. TGF-β2 control cell apoptosis, TGF-β2 may stop the dermal papilla growth by blocking the noggin expression. The late telogen can also be called competent telogen. In this phase, the hair is going to regenerate. And at this phase there is no expression of TGF-β1 or 2, at this phase noggin was activated and stimulus the hair follicle stem cells to give birth the new hair.

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