小鼠毛囊发育分子遗传学机制研究进展

王正森 陈艺璇 林陈胜*

(福建师范大学生命科学学院, 福建省发育与神经生物学重点实验室, 福州 350117)

摘要 毛囊作为皮肤的附属器官, 具有不断进行组织再生的特点, 是研究干细胞的一种理想模型。毛囊发育机制十分复杂, 其形态发生与持续终生的再生循环过程涉及表皮(上皮)和真皮(间充质)之间的相互作用。现已有相关的小鼠遗传模型被用于研究毛囊发育及再生的分子机制。该综述介绍最新的小鼠遗传学研究, 主要涉及在毛囊发育过程中分别来自表皮和真皮中关键信号分子的敲除或过表达, 以描绘一个控制毛囊发育和周期性循环的信号网络, 为深入立体地理解毛囊发育机制和临床毛发疾病发病机制提供理论依据。

关键词 毛囊; 表皮; 真皮; 分子机制; 转基因模型

Advances on Molecular Genetic Mechanisms of Mice Hair Follicle Development

WANG Zhengsen, CHEN Yixuan, LIN Chensheng*

(*Fujian Key Laboratory of Developmental and Neurobiology, College of Life Science, Fujian Normal University, Fuzhou 350117, China*)

Abstract HF (hair follicle) is an appendage of the skin. The HF is regarded as an excellent model for studying stem cell activity because it continuously proceeds through rounds of tissue regeneration. The mechanism of HF development is very complex. HF morphogenesis involves a temporal series of reciprocal interactions between the epithelium (epidermis) and its underlying mesenchyme (dermis). Transgenic mice have been used for studying the molecular mechanism of HF development and regeneration. This paper summarizes the over-expression or knock-out of key signal molecules from the epidermis and dermis during HF development in mice and prints the latest signal network that regulated HF development and cycling. It may provide a theoretical basis for an in-depth understanding of HF development mechanism and hair diseases.

Keywords hair follicle; epidermis; dermis; molecular mechanism; transgenic model

一头乌黑浓密的头发是很多爱美人士的追求, 是青春和健康的外在体现。众所周知, 脱发一直是一个世界性难题, 其虽然不会影响患者的生存质量, 但会严重影响患者的生活质量。同时, 毛囊在个体的整个生命过程中不断循环生长, 是研究器官再生的理想模型之一。毛囊发育是一个上皮和间充质互作的过程。其发育的第一个信号来自间充质细胞, 该信号到达上皮后引起上皮增厚[1]。随后, 上皮也产生信号诱导下方的间充质细胞聚集。在毛囊周期性循环的过程中, 同样需要上皮和间充质之间的信号调控。目前对毛囊发育已有较为深入的理解[2-5], 同时已有相当多的小鼠遗传模型被用于研究毛囊发育

收稿日期: 2019-10-14 接受日期: 2020-01-30

福建省科技厅面上项目基金(批准号: 2019J01281)资助的课题

*通讯作者。Tel: 18050796256, E-mail: linchensheng@fjnu.edu.cn

Received: October 14, 2019 Accepted: January 30, 2020

This work was supported by the Natural Science Foundation of Fujian Province (Grant No.2019J01281)

*Corresponding author. Tel: +86-18050796256, E-mail: linchensheng@fjnu.edu.cn

URL: http://www.cjcb.org/arts.asp?id=5260

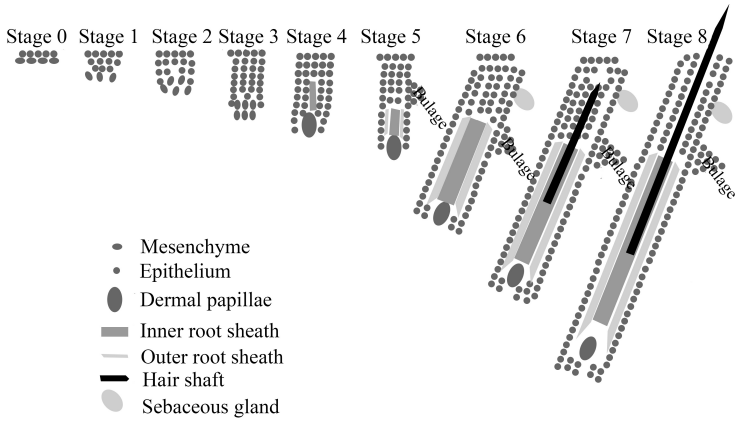

图1 毛囊形态发生与发育

Fig.1 Hair follicle morphogenesis and development

及再生的分子机制。在这里, 我们将对最新的小鼠遗传学研究进行综述, 主要涉及在毛囊发育和周期性循环过程中分别来自表皮和真皮中关键信号分子的敲除或过表达, 从而更加深入理解控制毛囊发育和周期性循环的信号网络。

1 毛囊的形态发生和周期循环

毛囊由表皮(上皮)和真皮(间充质)两个部分组成, 其形态发生、生长和再生需要二者的相互作用和诱导。小鼠具有多种不同类型的毛囊, 本文主要介绍小鼠背部第一批毛囊的发育模式(图1)。毛囊的形态发生一般分为八个阶段[6]。第一阶段, 来自间充质的信号诱导上皮增厚, 形成被称为毛基板的结构。第二阶段, 增厚的上皮不断向下生长, 形成体积更大的像帽子一样的结构覆盖着间充质。第三阶段, 毛囊已经成为一个由多层角质层细胞组成的细长上皮细胞柱, 而下方的间充质经过增殖和凝集形成真皮凝聚体。第四阶段, 毛囊真皮凝聚体继续向下生长, 发育形成真皮乳头(dermal papilla, DP), 上皮细胞进一步发育形成内根鞘(inner root sheath, IRS)结构(含Henle层)。第五阶段, IRS向外扩增, 形成外根鞘(outer root sheath, ORS)和隆凸(bulge, Bu)。第六阶段, 毛囊不断向下生长, 并且与表皮层形成40°角。此时, 临近的皮脂腺(sebaceous gland, SG)也开始形成。第七阶段, 毛干(hair shaft, HS)的顶端离开IRS, 进入与SG漏斗区水平的毛管, 与阶段六相比, DP几乎完全被毛球包围。第八阶段, 毛囊生长达到最大长度, 到达皮下肌肉层。最后毛干生长出皮肤表面, 毛囊成熟。

在哺乳动物的整个生命周期中, 成熟的毛囊会经历不断持续的动态变化: 增殖阶段(生长期)、凋亡阶段(退化期)和停息阶段(静止期), 被称为毛囊周期性循环。毛囊周期性循环需要一种被称为隆凸的干细胞库, 它位于ORS内部。在出生后, 毛囊会继续生长产生毛发。此生长期将一直持续到出生后14天(P14)。随后, 毛囊进入退化期。在退化期, 毛囊下方的2/3区域会退化, 直到毛囊底部的DP停留在隆凸的下方。此后, 毛囊发育进入静止期, 隆凸与DP保持接触的状态。随着静止期的结束, 毛囊进入了新一轮的生长期, 隆凸干细胞再次被激活, 分化形成ORS和能够促进毛囊再生的基质细胞, 基质细胞增殖向上分化产生毛干和IRS。第一个循环的静止期十分短暂, 只持续几天, 但之后的静止期可以持续3~4周以上。

毛囊的形态发生和周期性循环的过程是表皮和真皮信号在时间和空间上紧密的相互作用相互调节的过程。例如, 真皮凝聚体的形成需要来自表皮的毛基板的刺激才能形成。但是成熟的DP也可以诱导表皮形成新的毛囊。在这个相互诱导的过程中许多信号分子, 如Wnt、BMP(bone morphogenetic protein)以及Shh参与其中。研究表明, 在毛发发育的起始阶段, 表皮中广泛表达Wnt配体会激活真皮中Wnt信号, 并且表皮的Wnt信号对毛囊真皮凝聚体的形成是必需的。表皮中持续激活Wnt信号会导致真皮层成纤维细胞的过度增殖, 随后改变整个表皮命运从而导致异位毛囊的形成。在早期毛囊发育过程中, BMP4在真皮凝聚体中表达, 随后其表达范围从DP扩展到表皮的ORS中。表皮细胞中Shh信号的缺失会导致真皮中Shh信号的异常提高[3]。这些都说明, 在毛囊发育中, 表皮和真皮之间的相互作用对毛囊发育至关重要, 但关于二者之间相互作用的分子机制还不是很清楚。

2 来自表皮细胞的信号

在整个毛囊发育的过程中, Wnt、TGF-β和Shh等多个信号通路构成复杂的信号网络, 共同调控毛囊表皮细胞的命运。任何一个与之相关的信号分子的异常都有可能导致毛囊发育障碍(表1)。

2.1 Wnt信号

Wnt信号是最早被证实跟毛囊发育相关的信号。Wnt7b作为Wnt家族的一员, 已经被证明在表皮层细胞中缺失会造成毛囊生长期变短并过早进入退化期, 从而导致毛发变短[7]。表皮细胞中的β-catenin信号对毛基板的形成有着重要作用, 表皮中β-catenin信号失活会降低毛基板下方的间充质*Bmp4*的表达, 抑制毛囊的形态发生。若在毛囊形态发生完成后将其敲除, 会导致小鼠脱发[8]。然而, 在表皮中过表达β-catenin, 将激活Lef1/Tcf(lymphoid enhancer binding factor 1/T-cell factor)复合物, 最终诱导出现新的毛囊[9]。在毛囊隆凸干细胞中敲除*Ctnnb1*, 则会抑制毛囊的生长。同样在毛囊隆凸干细胞中敲除*Wntless*, 会出现毛发减少, 表皮增厚, 毛囊停留在静止期[10]; 在表皮细胞敲除*Wntless*, 将异常激活TGF-β/JNK(c-Jun N-terminal kinase), 使得毛囊过早地进入退化期[11]。Apc(adenomatous polyposis coli)作为Wnt信号的一员, 可以调控β-catenin的活性。研究发现, 在表皮细胞中*Apc*的缺失会导致毛囊发育延迟并且毛发变短[12]。Pygo2(pygopus 2)在Wnt/β-catenin信号传导过程中起着重要的作用, 其表达会激活β-catenin的活性, 导致毛囊干细胞不能被有效地激活, 进而影响毛囊再生[13]。在表皮细胞中异位过表达Wnt信号抑制剂*Dkk1*则会导致毛基板无法形成[14]。在毛囊表皮细胞中*Edar*(ectodysplasin-A receptor)是β-catenin的靶基因[15], *Eda*(ectodysplasin-A)在表皮细胞的过表达会导致新的毛囊发生[16-17], 而且*Edar*的持续激活可增加约40%毛基板的数量[18]。全身性敲除*Lef1*会导致毛囊发育停止在E17(胚胎17天), 出生后不能长出毛发[19]; 表皮中*Lef1*的过表达会导致部分小鼠的毛发变得稀疏[20]。Fz6(frizzled 6)是Wnt信号传导的重要参与者, 有报道称, 其在表皮层的缺失会使毛囊平面细胞极性出现混乱从而导致毛发的方向出现随机性[21]。

2.2 TGF-β超家族信号

TGF-β超家族包含TGF-β和BMP两条信号通路。Smad4是BMP和TGF-β信号下游的共同的传导分子, 表皮细胞中*Smad4*的缺失会使小鼠毛囊周期循环发生异常, 导致小鼠在出生后20天左右出现脱毛现象[22]。Noggin作为BMP信号的抑制剂, 其在表皮中的过表达会缩短静止期的时间[23]。*Bmpr1a*作为BMP信号I型受体, 其在表皮细胞中被特异敲除后, 会影响IRS和HS的分化, 同时导致基质细胞的异常增殖和分化, 最终导致小鼠毛发稀疏, 甚至出现全身无毛[24-25]。Acvr1b也被称为*Alk4*, 属于TGF-β超家族中的一员, 表皮细胞中*Acvr1b*的失活会导致小鼠在出生后5天表现出不同程度的无毛症状, 并且随着年龄的增大而加剧脱毛[26]。

2.3 Shh信号

Shh信号通路同样参与毛囊发育。表皮细胞中*Shh*的过表达不会影响毛囊早期发育过程中毛基板的正常形成[27], 但在伤口愈合过程中可有效诱导毛囊的再生[28]。Shh信号通路受体——Smo在表皮细胞中的失活会导致真皮层的Shh信号水平增加, 导致小鼠毛囊无法发育, 全身无毛, 同时会形成许多新的囊泡结构[29]。Ptch1作为Shh信号通路的另一种受体, 其在表皮细胞中的表达缺失会导致脱发和毛囊过度角质化[30]。Gli1参与Shh信号的转录激活, 在表皮细胞中的*Gli1*过表达会导致小鼠出生后毛发的缺失[31]。

2.4 其他相关信号通路及信号分子

无论是胚胎时期或者出生后, 在表皮细胞中*Notch1*的失活都会导致小鼠几乎完全脱发并形成囊肿[32]。Jagged1是Notch信号配体, 在表皮细胞中敲除*Jagged1*则导致毛发稀疏和毛发缩短[33]。RBP-J(recombination signal binding protein for immunoglobulin kappa J region)作为Notch四种受体共同的核内转录因子, 在表皮细胞中的表达缺失会导致毛囊的IRS和毛干的分化异常, 最终毛囊变成囊状结构[34]。

FGF(fibroblast growth factor)是机体器官发育的一类重要生长因子, 其同样在毛囊发育过程中发挥必不可少的作用。研究表明, 在表皮细胞中过表达*Fgf7*(*KGF*)将抑制毛囊的形成, 同时提高真皮层成纤维细胞的增殖速度[35]。在表皮细胞中过表达*Fgf9*会提高创伤后的毛囊再生数量[36]。敲除表皮细胞中的*Fgf18*将导致毛囊的静止期缩短[37]。

NF-κB信号通路同样在毛囊发育中发挥重要作用。在表皮细胞中过表达IκBα(NF-κB抑制因子), 将抑制NF-κB的活性, 进而延迟毛囊从静止期到生长期的转变[38]。

在表皮细胞的敲除*PDPN*(podoplanin, 一种跨膜

糖蛋白)可提高生长期毛囊的生长[39]。

MAPK信号通路主要把信号从细胞表面传递到细胞核内, 对毛囊周期性循环具有重要的作用。Gab1是细胞支架蛋白, 其在表皮细胞中的敲除可引起MAPK信号降低, 导致毛囊无法进入退化期, 从而造成毛囊干细胞库无法形成。Shp2是Gab1下游蛋白,

表1 调节毛囊发育的关键信号通路和转录因子(表皮部分)

Table 1 Key signaling pathways and transcription factors involved in the regulation of hair follicle development (epidermis)

突变类型 Mutation type	主要表型 Phenotype	参考文献 Reference
Activation		
K14-Ctnnb1	*De novo* hair follicle induction	[9]
K14-Eda	*De novo* hair follicle induction	[16]
K14-Edar	Increase hair follicle density	[18]
K14-Shh	Wound-induced hair follcile neogenesis	[28]
K14rtTA-Fgf9	Wound-induced hair follcile neogenesis	[36]
K5-Cre;PDPN$^{f/f}$	Enhanced anagen growth	[39]
K14-Cre;Msx2$^{f/f}$	Increased hair follicle neogenesis upon wounding	[43]
K14-Cre;Wnt7b$^{f/f}$	Reduction of anagen length and premature catagen onset	[7]
K14-Cre;Fz6$^{f/-}$	Alter hair follicle orientation	[21]
Inhibition		
K14-Cre;Ctnnb1$^{f/f}$	Lack of placode formation, loss hair	[8]
Axin2-CreERT2;Ctnnb1$^{f/f}$	Aberrant hair follicle growth	[10]
K14-Cre;Apc$^{f/f}$	Aberrant hair follicle growth, short	[12]
K14-Lef1	Decrease hair follicle density	[20]
K14-Cre;Pygo2$^{f/-}$	Delay hair follcile neogenesis	[13]
Axin2-CreERT2;Wntless$^{f/f}$	Arrest hair follicle in telogen	[10]
K14-Cre;Wntless$^{f/f}$	Hair follicle prematurely regressed	[11]
K14-Dkk1	Lack of placode formation	[14]
Emx1-Cre;Bmpr1a$^{f/f}$	Impaired IRS differentiation, reduced number of hair follicle	[25]
K14-Cre Bmpr1a$^{f/f}$ *or K14-CreERT2;Bmpr1a*$^{f/f}$	Loss hair	[24]
K5-Cre;Smad4$^{f/f}$	Loss hair	[22]
K14-Cre;Acvr1b$^{f/f}$	Loss hair	[26]
K14-Noggin	Reduction of telogen length	[23]
K14-Cre;Smo$^{f/f}$	Complete hair loss	[29]
K14-Cre;Ptch1$^{f/f}$	Loss hair, epidermal hyperplasia	[30]
K14-Gli1	Postnatal hair loss	[31]
K14-Cre;Notch1$^{f/f}$ or *K5-CreERT;Notch1*$^{f/f}$	Almost complete hair loss, spontaneous skin tumors	[32]
K14-Cre;RBP-J$^{f/f}$	Impaired matrix cell differentiation to IRS and hair shaft	[34]
K5-Jagged1$^{f/f}$	Hairs were sparse and short	[33]
K14-KGF	Lack of hair follicle formation	[35]
K5-Cre;Fgf18$^{f/f}$	Reduction of telogen length	[37]
K5rtTA;tetO-Cre;IκBαΔN	Delay telogen-anagen transition	[38]
Krox20-cre;Shp2$^{f/-}$*;Krox20-cre;Gab1*$^{f/-}$	Hair follicle cannot enter catagen	[40]
K14-Cre;Crif1$^{f/f}$	Aberrant hair follicle morphogenesis	[41]
K14-Cre;Sox9$^{f/f}$	Abnormal hair follicle stem cell and complete hair loss	[42]
K14-Cre;TFAM$^{f/f}$	Impaired hair follicle development	[44]
K14-Cre;Lhx2$^{f/f}$	Accelerate the hair follicle cycle and baldness	[45]
K14-Cre;NFATc1$^{f/f}$	Reduction of telogen length	[46]
K14-Cre;Tbx1$^{f/f}$	Increment of telogen length	[47]
K14-Cre;Dlx3$^{f/f}$	Complete hair loss	[48]

它和Gab1的结合共同调节MAPK信号, 在表皮细胞中的敲除*Shp2*可降低MAPK信号, 同样导致毛囊无法进入退化期[40]。

Crif1是一种线粒体蛋白, 可调节线粒体的氧化磷酸化多肽的合成。在表皮层中敲除*Crif1*可引起Wnt/β-catenin信号降低, 从而抑制毛囊的形态发生[41]。

2.5 转录因子

一些转录因子对毛囊的发育同样发挥重要作用。在表皮细胞中敲除*Sox9*会导致毛囊干细胞形成异常, 并且小鼠会完全脱毛[42]。*Msx2*对皮肤创伤后的毛发再生具有重要的促进作用[43]。*TFAM*(mitochondria transcription factor A)的缺失会影响Wnt/β-catenin信号传导, 从而破坏表皮的分化和毛囊的生长[44]。*Lhx2*的敲除会导致毛囊干细胞无法维持静止状态, 加快毛囊周期性循环, 并且随着时间推移, 该缺失小鼠会发生秃发[45]。*NFATc1*(nuclear factor of activated T cells 1)缺失的成年小鼠毛囊静止期缩短[46]。*Tbx1*敲除会导致毛囊静止期时间延长, 随着不断脱毛诱导再生后毛囊干细胞数量会大量下降[47]。*Dlx3*敲除的小鼠会导致毛干和IRS的形成失败, 从而导致脱毛[48]。

3 来自真皮细胞的信号

毛囊的真皮主要分为两个部分: DP和真皮鞘(dermal sheath, DS)。DP位于毛囊的底部, DS沿着毛囊表皮从隆起部位一直到DP底部。DS由三层不同方向的胶原纤维组成, 成纤维细胞大部分位于增厚的中间胶原层。DP和DS内的细胞都是间充质来源的成纤维细胞。通过追踪神经嵴干细胞的后代以及对DP细胞表达的神经元标志物和转录图谱的分析, 发现一部分的DP细胞是来自于神经嵴[49-51]。在毛囊周期中, DS被认为是DP的细胞库[52], 有假说认为, 干细胞位于DS中, 类似于真皮的外根鞘[53]。在经典的大鼠触须横切实验中, OLIVER等[54]发现, 在隆起以下部分切除毛囊, DP可以再生, 而在隆起部分切除则DP不能再生。但是也有一种理论认为, 在正常的毛囊周期性循环期间, DP和DS可能存在细胞双向的交流, 当毛囊在生长期中DP达到最大长度时, 其细胞数量大约是静止期的两倍, 这些增加的细胞来自DS募集, 在下一个静止期前, 这些募集的细胞会再一次回到DS中[52,55-56]。虽然真皮细胞对毛囊发育调节的分子机制研究还相对较少, 但近几年随着有效工具鼠的出现, 越来越多的分子机制已被阐明(表2)。

Blimp1(B-lymphocyte-induced maturation protein 1, 又被称为Padm1)是一种锌指蛋白转录因子, 在真皮层细胞中*Blimp1*(*Dermo1-Cre;Prdm1$^{f/f}$*)缺失将造成毛囊发育延迟和毛发生长期缩短, 并且导致毛囊基质细胞增殖受损[57]。Shh信号通路受体*Smo*(*Prx1-Cre;Smo$^{f/-}$*)在真皮细胞中的失活会导致DP前体真皮凝聚体形成失败, 毛囊发育停滞; 但是若在真皮细胞中过表达Noggin可以挽救*Smo*缺失所造成的发育缺陷[58]。在真皮细胞中初级纤毛蛋白*Kif3a*(*Prx1-Cre;Kif3a$^{f/-}$*)和*Ift8*(*Prx1-Cre;Ift88$^{f/-}$*)的缺失都将造成部分毛囊的发育停滞在第二阶段, 同时降低Shh信号, 小鼠出生后毛发稀疏[59]。在真皮细胞中敲除*β-catenin*降低Wnt信号, 将增加创伤后再生毛囊的数量[60]。在Pdgfrα阳性表达的真皮细胞中敲除*β-catenin*(*Pdgfrα-CreERT;Ctnnb1$^{f/f}$*)会降低真皮凝聚物和上皮细胞的增殖率[61]。Pygo2是一种转录因子, 它可以和*β-catenin*结合共同调控Wnt信号下游靶基因的表达, 在神经嵴来源的细胞中敲除*Pygo2*(*Wnt1-Cre;Pygo2$^{f/f}$*)会导致毛发密度降低, 毛发厚度变薄, 并且不同毛囊类型的相对比例改变[62]。

Tbx18是新近被发现的可作为毛囊DP前体细胞的特异性标记物, *Tbx18-Cre*工具鼠也被广泛应用于研究毛囊真皮细胞在毛囊发育中的作用[63]。在DP前体细胞中敲除*Sox2*(*Tbx18-Cre;Sox2$^{f/f}$*), 虽然不影响毛囊形态发生, 但会降低Sostdc1表达, 增强BMP信号, 导致小鼠毛干长度缩短[64]。在DP前体细胞中特异敲除*β-catenin*的转基因小鼠(*Tbx18-Cre;Ctnnb1$^{f/f}$*), 其第一波的针毛毛囊发育失败, 并且所有类型毛囊的毛发变短且数量减少[65]。*Stat5*(signal transducers and activators of transcription 5)是一种转录因子, 在Sox18阳性的DP前体细胞中敲除*Stat5*(*Flash$^{/+}$;Sox18$^{tm1(GFP/cre/ERT2)/+}$;Stat5a/b$^{f/f}$*)会延迟小鼠毛囊进入生长期[66]。

Corin是在心脏中表达的跨膜蛋白酶, 在小鼠早期毛囊发育的DP中就有着特异性表达。但是, Corin-Cre的活性直到P3才能在DP中检测到, 其介导的*β-catenin*的缺失(*Corin-Cre;β-catenin$^{f/f}$*)会导致毛发变短和厚度变薄[67]。CD133是已知的造血干细胞标记物, 在小鼠3~4期毛囊中和早期生长期毛囊的DP中强烈表达。在CD133阳性的DP细胞中过表达*β-catenin*(*CD133-CreER^{T2};Rosa-rtTA;tetO-Ctnnb1*)会加速生长期毛囊的生长[68]。

表2 调节毛囊发育的关键信号通路和转录因子(真皮部分)

Table 2 Key signaling pathways and transcription factors involved in the regulation of hair follicle development (dermis)

突变类型 Mutation type	主要表型 Phenotype	参考文献 Reference
CD133-CreER^{T2};Rosa-rtTA;tetO-Ctnnb1	Increase hair growth in anagen	[68]
Dermo1-Cre;Prdm1$^{f/f}$	Delay hair follicle development and Reduction of anagen length	[57]
Prx1-cre;Smo$^{f/-}$	Arrest hair follicle development	[58]
Prx1-Cre;Kif3a$^{f/-}$ or Prx1-Cre;Ift88$^{f/-}$	Arrest hair follicle development	[59]
Pdgfrα-CreERT;Ctnnb1$^{f/f}$	Reduce proliferation of epidermal cells and dermal papillae aggregate	[61]
Wnt1-Cre;Pygo2$^{f/f}$	Reduces hair density and thickness	[62]
Tbx18-Cre;Sox2$^{f/f}$	Shorter hair shaft	[64]
Tbx18-Cre;β-catenin$^{f/f}$	Shorter hair shaft, decrease hair follicle density	[65]
Flash$^{f/+}$;Sox18$^{tm1(GFP/Cre/ERT2)/+}$;STAT5A/B$^{f/f}$	Delay hair follicle enter anagen	[66]
Corin-Cre;β-catenin$^{f/f}$	Shorter hair shaft	[67]

4 问题和展望

近年来, 随着研究技术的不断突破, 越来越多与毛囊干细胞和单细胞测序相关的研究被发表。例如, 研究发现, Foxc1的缺失会导致毛囊干细胞被过度的激活, 老龄小鼠出现毛发稀疏[69-70]。WANG等[71]通过单细胞测序发现, 来自表达TREM2的巨噬细胞能够通过分泌Oncostatin M激活JAK-STAT5, 进而抑制毛囊干细胞的激活。这些研究进一步加深了我们对毛囊发育机制的了解。

目前已有相关研究成果应用到临床毛发疾病的治疗和动物绒毛的生产。临床上主要应用于治疗雄激素脱发。例如, Samumed公司生产的SM04554药物, 可以通过提高Wnt信号活性从而达到治疗雄激素脱发的目的[72]。除此之外, Wnt/β-catenin激活剂香草酸甲酯对治疗女性雄激素脱发具有良好的效果[73]。对其他动物如作为绒毛产业主力军的绒山羊的毛囊发育研究发现, 其在发育过程中所需要的重要信号分子与小鼠相似, 包括PDGF信号[74]、Sox9[75]和Lef1[76]等。这些研究成果提供了丰富的实验数据, 为今后脱发的临床治疗的突破以及绒毛产业生产力的提升奠定了坚实的基础。

毛囊的形态发生和周期性循环受很多因素的影响, 包括外在环境以及内在的分子机制。但是目前关于调控毛囊发育内在的分子机制还未被充分理解和阐述。例如: (1)调控毛囊发育的信号分子之间是如何相互作用从而调控毛囊发育; (2)表皮和真皮细胞之间是如何相互作用诱导毛囊发生和发育; (3)体内的激素和微环境是如何参与毛囊发育的, 这些问题都有待进一步被阐明。随着技术的革新以及实验的推进, 越来越多在毛囊发育过程中起到关键性作用的信号分子被发现, 例如, Shh、Lef1、β-catenin和Bmp4等。经典重组实验证明, 只有有毛区的真皮与有毛区或者无毛区的表皮重组才能进一步发育为毛囊, 说明毛囊诱导能力位于真皮层细胞。此外, 发育成熟的毛囊DP仍然保留毛囊的诱导能力和发育成各种毛发类型的潜能。最近研究发现, 基底层的表皮细胞和巨噬细胞共同吞噬退化期毛囊表皮细胞凋亡所产生的碎片, 同时DP会调控表皮细胞凋亡速度[77]。这些研究都说明了表皮、真皮和周围环境存在着相互调控, 庞大复杂的毛囊发育信号网络也正一点一点地被揭开神秘的面纱。我们相信, 对毛囊发育调控机制更深入和全面的理解, 将为临床毛发疾病治疗和动物绒毛产业提供坚实的理论基础和新的研究思路。

参考文献 (References)

[1] HARDY M H. The secret life of the hair follicle [J]. Trends Genet, 1992, 8(2): 55-61.

[2] LEE J, TUMBAR T. Hairy tale of signaling in hair follicle development and cycling [J]. Semin Cell Dev Biol, 2012, 23(8): 906-16.

[3] SENNETT R, RENDL M. Mesenchymal-epithelial interactions during hair follicle morphogenesis and cycling [J]. Semin Cell Dev Biol, 2012, 23(8): 917-27.

[4] SAXENA N, MOK K W, RENDL M. An updated classification of hair follicle morphogenesis [J]. Exp Dermatol, 2019, 28(4): 332-44.

[5] YANG C C, COTSARELIS G. Review of hair follicle dermal cells [J]. J Dermatol Sci, 2010, 57(1): 2-11.

[6] PAUS R, MULLER-ROVER S, VAN DER VEEN C, et al. A comprehensive guide for the recognition and classification of distinct stages of hair follicle morphogenesis [J]. J Invest Dermatol, 1999, 113(4): 523-32.

[7] KANDYBA E, KOBIELAK K. Wnt7b is an important intrinsic

regulator of hair follicle stem cell homeostasis and hair follicle cycling [J]. Stem Cells, 2014, 32(4): 886-901.

[8] HUELSKEN J, VOGEL R, ERDMANN B, et al. beta-Catenin controls hair follicle morphogenesis and stem cell differentiation in the skin [J]. Cell, 2001, 105(4): 533-45.

[9] GAT U, DASGUPTA R, DEGENSTEIN L, et al. *De Novo* hair follicle morphogenesis and hair tumors in mice expressing a truncated beta-catenin in skin [J]. Cell, 1998, 95(5): 605-14.

[10] LIM X, TAN S H, YU K L, et al. Axin2 marks quiescent hair follicle bulge stem cells that are maintained by autocrine Wnt/beta-catenin signaling [J]. Proc Natl Acad Sci USA, 2016, 113(11): E1498-505.

[11] HUANG S, ZHU X, TAO Y, et al. Involvement of epithelial Wntless in the regulation of postnatal hair follicle morphogenesis [J]. Arch Dermatol Res, 2015, 307(9): 835-9.

[12] KURAGUCHI M, WANG X P, BRONSON R T, et al. Adenomatous polyposis coli (APC) is required for normal development of skin and thymus [J]. PLoS Genet, 2006, 2(9): e146.

[13] SUN P, WATANABE K, FALLAHI M, et al. Pygo2 regulates beta-catenin-induced activation of hair follicle stem/progenitor cells and skin hyperplasia [J]. Proc Natl Acad Sci USA, 2014, 111(28): 10215-20.

[14] ANDL T, REDDY S T, GADDAPARA T, et al. WNT signals are required for the initiation of hair follicle development [J]. Dev Cell, 2002, 2(5): 643-53.

[15] ZHANG Y, TOMANN P, ANDL T, et al. Reciprocal requirements for EDA/EDAR/NF-kappaB and Wnt/beta-catenin signaling pathways in hair follicle induction [J]. Dev Cell, 2009, 17(1): 49-61.

[16] MUSTONEN T, PISPA J, MIKKOLA M L, et al. Stimulation of ectodermal organ development by Ectodysplasin-A1 [J]. Dev Biol, 2003, 259(1): 123-36.

[17] ZHANG M, BRANCACCIO A, WEINER L, et al. Ectodysplasin regulates pattern formation in the mammalian hair coat [J]. Genesis, 2003, 37(1): 30-7.

[18] MOU C, JACKSON B, SCHNEIDER P, et al. Generation of the primary hair follicle pattern [J]. Proc Natl Acad Sci USA, 2006, 103(24): 9075-80.

[19] VAN GENDEREN C, OKAMURA R M, FARINAS I, et al. Development of several organs that require inductive epithelial-mesenchymal interactions is impaired in LEF-1-deficient mice [J]. Genes Dev, 1994, 8(22): 2691-703.

[20] ZHOU P, BYRNE C, JACOBS J, et al. Lymphoid enhancer factor 1 directs hair follicle patterning and epithelial cell fate [J]. Genes Dev, 1995, 9(6): 700-13.

[21] CHANG H, SMALLWOOD P M, WILLIAMS J, et al. The spatiotemporal domains of Frizzled6 action in planar polarity control of hair follicle orientation [J]. Dev Biol, 2016, 409(1): 181-93.

[22] YANG L, WANG L, YANG X. Disruption of Smad4 in mouse epidermis leads to depletion of follicle stem cells [J]. Mol Biol Cell, 2009, 20(3): 882-90.

[23] PLIKUS M V, MAYER J A, DE LA CRUZ D, et al. Cyclic dermal BMP signalling regulates stem cell activation during hair regeneration [J]. Nature, 2008, 451(7176): 340-4.

[24] ANDL T, AHN K, KAIRO A, et al. Epithelial Bmpr1a regulates differentiation and proliferation in postnatal hair follicles and is essential for tooth development [J]. Development, 2004, 131(10): 2257-68.

[25] YUHKI M, YAMADA M, KAWANO M, et al. BMPR1A signaling is necessary for hair follicle cycling and hair shaft differentiation in mice [J]. Development, 2004, 131(8): 1825-33.

[26] QIU W, LI X, TANG H, et al. Conditional activin receptor type 1B (Acvr1b) knockout mice reveal hair loss abnormality [J]. J Invest Dermatol, 2011, 131(5): 1067-76.

[27] ORO A E, HIGGINS K M, HU Z, et al. Basal cell carcinomas in mice overexpressing sonic hedgehog [J]. Science, 1997, 276(5313): 817-21.

[28] LIM C H, SUN Q, RATTI K, et al. Hedgehog stimulates hair follicle neogenesis by creating inductive dermis during murine skin wound healing [J]. Nature Commun, 2018, 9(1): 1-13.

[29] GRITLI-LINDE A, HALLBERG K, HARFE B D, et al. Abnormal hair development and apparent follicular transformation to mammary gland in the absence of hedgehog signaling [J]. Dev Cell, 2007, 12(1): 99-112.

[30] VILLANI R M, ADOLPHE C, PALMER J, et al. Patched1 inhibits epidermal progenitor cell expansion and basal cell carcinoma formation by limiting Igfbp2 activity [J]. Cancer Prev Res (Phila), 2010, 3(10): 1222-34.

[31] ORO A E, HIGGINS K. Hair cycle regulation of Hedgehog signal reception [J]. Dev Biol, 2003, 255(2): 238-48.

[32] VAUCLAIR S, NICOLAS M, BARRANDON Y, et al. Notch1 is essential for postnatal hair follicle development and homeostasis [J]. Dev Biol, 2005, 284(1): 184-93.

[33] ESTRACH S, AMBLER C A, LO CELSO C, et al. Jagged 1 is a beta-catenin target gene required for ectopic hair follicle formation in adult epidermis [J]. Development, 2006, 133(22): 4427-38.

[34] BLANPAIN C, LOWRY W E, PASOLLI H A, et al. Canonical notch signaling functions as a commitment switch in the epidermal lineage [J]. Genes Dev, 2006, 20(21): 3022-35.

[35] GUO L, YU Q C, FUCHS E. Targeting expression of keratinocyte growth factor to keratinocytes elicits striking changes in epithelial differentiation in transgenic mice [J]. EMBO J, 1993, 12(3): 973-86.

[36] GAY D, KWON O, ZHANG Z, et al. Fgf9 from dermal gammadelta T cells induces hair follicle neogenesis after wounding [J]. Nat Med, 2013, 19(7): 916-23.

[37] KIMURA-UEKI M, ODA Y, OKI J, et al. Hair cycle resting phase is regulated by cyclic epithelial FGF18 signaling [J]. J Invest Dermatol, 2012, 132(5): 1338-45.

[38] KRIEGER K, MILLAR S E, MIKUDA N, et al. NF-kappaB Participates in mouse hair cycle control and plays distinct roles in the various pelage hair follicle types [J]. J Invest Dermatol, 2018, 138(2): 256-64.

[39] YOON S-Y, DIETERICH L C, TACCONI C, et al. An important role of podoplanin in hair follicle growth [J]. PLoS One, 2019, 14(7): e0219938.

[40] AKILLI OZTURK O, PAKULA H, CHMIELOWIEC J, et al. Gab1 and Mapk Signaling are essential in the hair cycle and hair follicle stem cell quiescence [J]. Cell Rep, 2015, 13(3): 561-72.

[41] SHIN J M, CHOI D K, SOHN K C, et al. Targeted deletion of Crif1 in mouse epidermis impairs skin homeostasis and hair morphogenesis [J]. Sci Rep, 2017, 7: 44828.

[42] NOWAK J A, POLAK L, PASOLLI H A, et al. Hair follicle stem cells are specified and function in early skin morphogenesis [J]. Cell Stem Cell, 2008, 3(1): 33-43.

[43] HUGHES M W, JIANG T X, PLIKUS M V, et al. Msx2 supports epidermal competency during wound-induced hair follicle neogenesis [J]. J Invest Dermatol, 2018, 138(9): 2041-50.

[44] HAMANAKA R B, GLASAUER A, HOOVER P, et al. Mitochondrial reactive oxygen species promote epidermal differentiation and hair follicle development [J]. Sci Signal, 2013, 6(261): ra8.

[45] FOLGUERAS A R, GUO X, PASOLLI H A, et al. Architectural niche organization by LHX2 is linked to hair follicle stem cell function [J]. Cell Stem Cell, 2013, 13(3): 314-27.

[46] HORSLEY V, ALIPRANTIS A O, POLAK L, et al. NFATc1 balances quiescence and proliferation of skin stem cells [J]. Cell, 2008, 132(2): 299-310.

[47] CHEN T, HELLER E, BERONJA S, et al. An RNA interference screen uncovers a new molecule in stem cell self-renewal and long-term regeneration [J]. Nature, 2012, 485(7396): 104-8.

[48] HWANG J, MEHRANI T, MILLAR S E, et al. Dlx3 is a crucial regulator of hair follicle differentiation and cycling [J]. Development, 2008, 135(18): 3149-59.

[49] FERNANDES K J, MCKENZIE I A, MILL P, et al. A dermal niche for multipotent adult skin-derived precursor cells [J]. Nat Cell Biol, 2004, 6(11): 1082-93.

[50] DRISKELL R R, GIANGRECO A, JENSEN K B, et al. Sox2-positive dermal papilla cells specify hair follicle type in mammalian epidermis [J]. Development, 2009, 136(16): 2815-23.

[51] RENDL M, LEWIS L, FUCHS E. Molecular dissection of mesenchymal-epithelial interactions in the hair follicle [J]. PLoS Biol, 2005, 3(11): e331.

[52] TOBIN D J, GUNIN A, MAGERL M, et al. Plasticity and cytokinetic dynamics of the hair follicle mesenchyme: implications for hair growth control [J]. J Invest Dermatol, 2003, 120(6): 895-904.

[53] ITO M, LIU Y, YANG Z, et al. Stem cells in the hair follicle bulge contribute to wound repair but not to homeostasis of the epidermis [J]. Nat Med, 2005, 11(12): 1351-4.

[54] OLIVER R F. Whisker growth after removal of the dermal papilla and lengths of follicle in the hooded rat [J]. J Embryol Exp Morphol, 1966, 15(3): 331-47.

[55] JAHODA C A. Cell movement in the hair follicle dermis-more than a two-way street [J]? J Invest Dermatol, 2003, 121(6): ix-xi.

[56] RAHMANI W, ABBASI S, HAGNER A, et al. Hair follicle dermal stem cells regenerate the dermal sheath, repopulate the dermal papilla, and modulate hair type [J]. Dev Cell, 2014, 31(5): 543-58.

[57] TELERMAN S B, ROGNONI E, SEQUEIRA I, et al. Dermal Blimp1 acts downstream of epidermal TGFbeta and Wnt/beta-Catenin to regulate hair follicle formation and growth [J]. J Invest Dermatol, 2017, 137(11): 2270-81.

[58] WOO W M, ZHEN H H, ORO A E. Shh maintains dermal papilla identity and hair morphogenesis via a Noggin-Shh regulatory loop [J]. Genes Dev, 2012, 26(11): 1235-46.

[59] LEHMAN J M, LAAG E, MICHAUD E J, et al. An essential role for dermal primary cilia in hair follicle morphogenesis [J]. J Invest Dermatol, 2009, 129(2): 438-48.

[60] ROGNONI E, GOMEZ C, PISCO A O, et al. Inhibition of β-catenin signalling in dermal fibroblasts enhances hair follicle regeneration during wound healing [J]. Development, 2016, 143(14): 2522-35.

[61] GUPTA K, LEVINSOHN J, LINDERMAN G, et al. Single-cell analysis reveals a hair follicle dermal niche molecular differentiation trajectory that begins prior to morphogenesis [J]. Dev Cell, 2019, 48(1): 17-31,e6.

[62] NARYTNYK A, GILLINDER K, VERDON B, et al. Neural crest stem cell-specific deletion of the Pygopus2 gene modulates hair follicle development [J]. Stem Cell Rev, 2014, 10(1): 60-8.

[63] GRISANTI L, CLAVEL C, CAI X, et al. Tbx18 targets dermal condensates for labeling, isolation, and gene ablation during embryonic hair follicle formation [J]. J Invest Dermatol, 2013, 133(2): 344-53.

[64] CLAVEL C, GRISANTI L, ZEMLA R, et al. Sox2 in the dermal papilla niche controls hair growth by fine-tuning BMP signaling in differentiating hair shaft progenitors [J]. Dev Cell, 2012, 23(5): 981-94.

[65] TSAI S Y, SENNETT R, REZZA A, et al. Wnt/beta-catenin signaling in dermal condensates is required for hair follicle formation [J]. Dev Biol, 2014, 385(2): 179-88.

[66] LEGRAND J M D, ROY E, ELLIS J J, et al. STAT5 activation in the dermal papilla is important for hair follicle growth phase induction [J]. J Invest Dermatol, 2016, 136(9): 1781-91.

[67] ENSHELL-SEIJFFERS D, LINDON C, KASHIWAGI M, et al. beta-catenin activity in the dermal papilla regulates morphogenesis and regeneration of hair [J]. Dev Cell, 2010, 18(4): 633-42.

[68] MIKI T, WONG W, ZHOU E, et al. Biological impact of xeno-free chemically defined cryopreservation medium on amniotic epithelial cells [J]. Stem Cell Res Ther, 2016, 7: 8.

[69] LAY K, KUME T, FUCHS E. FOXC1 maintains the hair follicle stem cell niche and governs stem cell quiescence to preserve long-term tissue-regenerating potential [J]. Proc Natl Acad Sci USA, 2016, 113(11): E1506-15.

[70] WANG L, SIEGENTHALER J A, DOWELL R D, et al. Foxc1 reinforces quiescence in self-renewing hair follicle stem cells [J]. Science, 2016, 351(6273): 613-7.

[71] WANG E C E, DAI Z, FERRANTE A W, et al. A Subset of $TREM2^{+}$ dermal macrophages secretes oncostatin m to maintain hair follicle stem cell quiescence and inhibit hair growth [J]. Cell Stem Cell, 2019, 24(4): 654-69,e6.

[72] YAZICI Y, SMITH S, SWEARINGEN C, et al. Safety and efficacy of a topical treatment (SM04554) for androgenetic alopecia (AGA): results from a phase 1 trial [J]. J Am Acad Dermatol, 2016, 74(5): AB138.

[73] TOSTI A, ZAIAC M N, CANAZZA A, et al. Topical application of the Wnt/β-catenin activator methyl vanillate increases hair count and hair mass index in women with androgenetic alopecia [J]. J Cosmet Dermatol, 2016, 15(4): 469-74.

[74] PAZZAGLIA I, MERCATI F, ANTONINI M, et al. PDGFA in cashmere goat: a motivation for the hair follicle stem cells to activate [J]. Animals, 2019, 9(2): 38.

[75] HE N, DONG Z, TAI D, et al. The role of Sox9 in maintaining the characteristics and pluripotency of Arbas Cashmere goat hair follicle stem cells [J]. Cytotechnology, 2018, 70(4): 1155-65.

[76] HAO F, YAN W, GUO X, et al. Regulatory role of LEF-1 in the proliferation of Arbas White Cashmere goat dermal papilla cells [J]. Canadian journal of animal science, 2018, 98(4): 667-74.

[77] MESA K R, ROMPOLAS P, ZITO G, et al. Niche-induced cell death and epithelial phagocytosis regulate hair follicle stem cell pool [J]. Nature, 2015, 522(7554): 94-7.