纤毛疾病Joubert综合征与神经发育

朱 健 韩莹莹 徐 洪*

(南昌大学生命科学研究院, 生命科学学院, 南昌 330031)

摘要 Joubert综合征(Joubert syndrome)是一类常染色体隐性遗传神经发育障碍疾病, 主要症状表现为共济失调、肌张力低、呼吸和眼动异常、认知障碍以及发育迟缓等, 此外, 还不同程度地间杂其他多器官病变。Joubert综合征的典型影像学特征为“臼齿征”(molar tooth sign), 由小脑蚓部发育不良或缺如, 小脑上脚和皮质脊髓束交叉减少或缺失等所致。目前, 已发现20多种Joubert综合征致病基因, 有趣的是, 它们所编码的蛋白质大都与细胞纤毛(cilium)的结构和功能密切相关。纤毛广泛参与机体的发育和多种细胞功能, 其结构和功能异常所致疾病统称为纤毛疾病(ciliopathies)。Joubert综合征是一种典型的纤毛疾病, 然而, 对于这些纤毛病变基因如何导致神经发育障碍尚知之甚少。该文讨论了Joubert综合征与纤毛的相关性, 并重点阐述了Joubert综合征致病基因在神经发育中的作用及机制。

关键词 Joubert综合征; 致病基因; 纤毛; 纤毛疾病; 神经发育; Wnt和Shh信号通路

Ciliopathy Joubert Syndrome and Neural Development

Zhu Jian, Han Yingying, Xu Hong*

(*Institute of Life Science and School of Life Science, Nanchang University, Nanchang 330031, China*)

Abstract Joubert syndrome is a kind of autosomal recessive genetic neural development disorder, which is characterized by ataxia, hypotonia, irregular respiratory pattern, abnormal eye movement, developmental delay and cognitive defects. These main clinical signs are variably complicated by multiorgan defects. The typical imaging feature of Joubert syndrome is “molar tooth sign”, a complex malformation of the cerebellar vermis and brainstem with abnormalities of axonal decussation affecting the corticospinal tract and superior cerebellar peduncles. However, the underlying mechanism of the neural circuit defects in Joubert syndrome is still obscure. Up to date, more than 20 genes have been found to be mutated in Joubert syndrome patients. Interestingly, the proteins encoded by these genes are closely related to the primary cilium or its apparatus, making Joubert syndrome belong to a group of diseases called ciliopathies. In this review, we focus on discussing the relationship between Joubert syndrome and cilium and summarizing the potential roles of causative genes of Joubert syndrome in neural development.

Keywords Joubert syndrome; causative genes; cilium; ciliopathies; neural development; Wnt and Shh signalling pathway

细胞纤毛(cilium)是一种突出于细胞表面的细胞器, 几乎存在于人类所有细胞中, 从单细胞生物到高等生物细胞中都普遍存在。近十余年, 纤毛备受人们关注, 其结构和功能也被人们广泛认识。纤毛参与多种细胞功能并介导多种重要信号通路, 对机体发育起着至关重要的作用。纤毛结构

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*通讯作者。Tel: 0791-83827082, E-mail: xuhong@ncu.edu.cn

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*Corresponding author. Tel: +86-791-83827082, E-mail: xuhong@ncu.edu.cn

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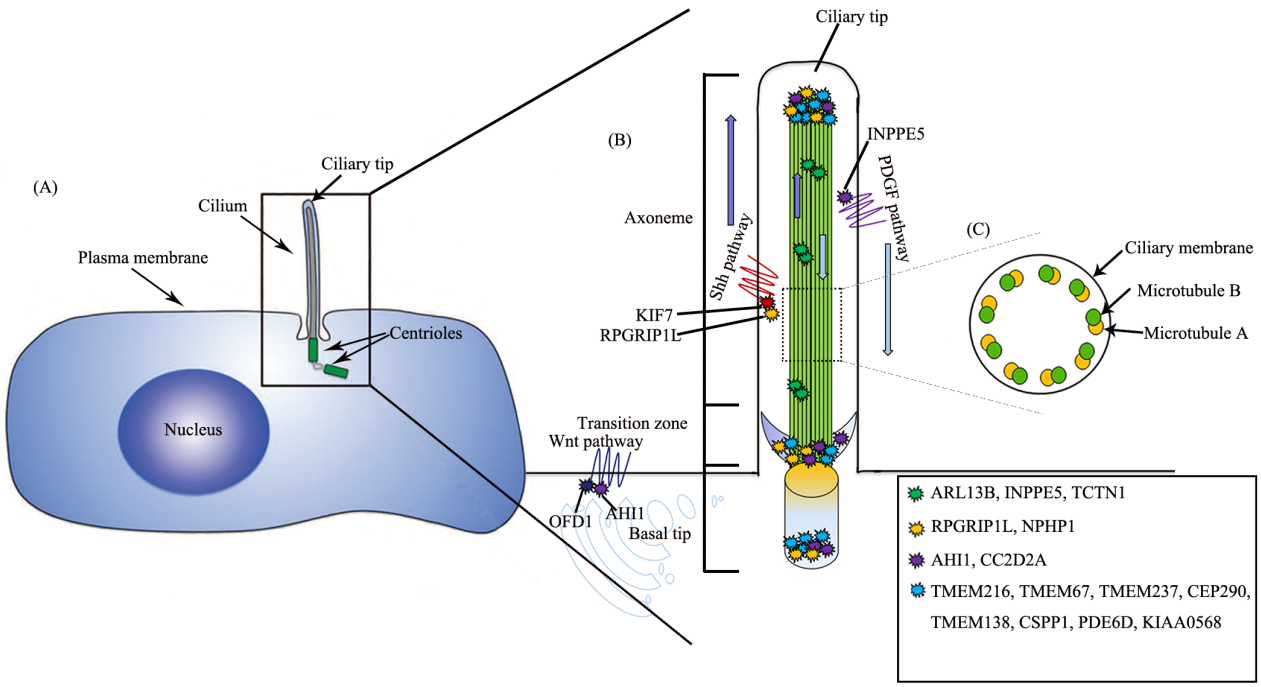
和功能的紊乱会导致一系列疾病, 统称为纤毛疾病(ciliopathies)。Joubert综合征是一种典型的纤毛疾病, 具有脑畸形、共济失调、智力障碍等神经发育缺陷。目前发现, Joubert综合征致病基因大部分都与纤毛紧密相关, 有关它们的研究报道也层出不穷。在此, 本文将介绍Joubert综合征的神经病理学特征, 讨论Joubert综合征致病基因与细胞纤毛的关系, 并重点阐述Joubert综合征致病基因在神经发育中的作用及其分子和细胞机制。

1　纤毛和纤毛疾病

纤毛突出于细胞表面, 形似天线, 是基于微管的一种亚细胞结构, 由特化的中心体(centrosome)组装而来(图1A)[1]。纤毛结构大致可以分为5个部分: 基体(basal body)、过渡区(transition zone)、轴丝(axoneme)、纤毛膜(ciliary membrane)、纤毛尖端(ciliary tip)[2](图1B)。根据纤毛是否具有运动性, 纤毛可分为运动纤毛和非运动纤毛。运动纤毛存在于呼吸道上皮、脑室壁等, 协助液体流动; 非运动纤毛也被称为初级纤毛(primary cilium), 存在于体内几乎所有其他细胞, 每个细胞仅有一根纤毛[3](图1A), 用于感受气味、光线、液体流动以及多种生长因子等胞外信号。本综述讨论的主要是初级纤毛, 其轴丝主要由9对双联微管构成(图1C)[3]。

初级纤毛被人们喻为"细胞天线", 能够感受外界信号并传递到胞内, 调节细胞极性、增殖分化并维持组织稳态等, 参与机体发育及维持器官的正常生理功能。纤毛结构和功能的紊乱会导致一系列纤毛疾病[4]。很多纤毛疾病具有致死性, 其表型在胚胎期就可见; 有些婴儿初期就出现器官畸形、功能缺陷等病征[3]。常见纤毛疾病有Meckel综合征(Meckel syndrome, MKS)、巴比二氏综合征(Bardet-Biedl syndrome)、Joubert综合征等。不同纤毛疾病可出现在同一家族中, 且它们之间存在共同的临床表征。同时, 同一基因的突变也能导致不同纤毛疾病的发生[5-6]。



A: 初级纤毛示意图, 初级纤毛突起于细胞膜, 形状似一根"天线"。B: 纤毛结构主要由纤毛基体、过渡区、轴丝、纤毛膜、纤毛尖端5个部分构成。Joubert综合征致病基因编码的蛋白质形成复合体大多集中在纤毛的基体和过渡区, 能够调节纤毛的发生、纤毛内分子的转运, 与纤毛介导的Shh(Sonic hedgehog)、Wnt、PDGF(platelet-derived growth factor)等信号转导密切相关。C: 初级纤毛轴丝横切面图, 由9对双联微管构成, 每对双联微管由微管A、B构成。

A: schematic representation of cilium, cilium akin to antennae projecting from the cell membrane. B: the causative genes of Joubert syndrome encode proteins which can form large complexes. Most complexes are enriched in the basal body or the transition zone of the cilium. These complexes are important for ciliogenesis, molecule trafficking in the cilium, and are implicated in signalling pathways mediated by the cilium, such as Shh, Wnt and PDGF pathways. C: the cross section of the structure of primary cilium.

图1　初级纤毛及其结构示意图(根据参考文献[1,15]修改)

Fig.1　Schematic representation of primary cilium and ciliary structure (modified from references [1,15])

2 Joubert综合征

Joubert综合征是一种罕见发育缺陷疾病, 患者从新生儿期就出现神经病理学上的症状, 包括共济失调、肌张力低、眼动异常、呼吸紊乱和整体发育迟滞等[7-8]。除神经发育缺陷外, 部分Joubert患者也同时存在其他器官病变, 如视网膜病变、肝硬化和多囊肾等[8-11]。患者一般由于呼吸暂停、肾衰竭、肝纤维化或其他原因导致寿命缩短[11]。目前, 磁共振成像(magnetic resonance imaging, MRI)为Joubert综合征首选的神经影像学检测方法, 能够清楚显示后颅脑等相关脑发育畸形。Joubert综合征主要诊断标志为具有独特的小脑和脑干发育畸形, 影像学上呈“臼齿征”(molar tooth sign)。“臼齿征”是由小脑蚓部发育不良或缺如, 小脑上脚和皮质脊髓束交叉减少或缺失等所致, 即小脑蚓部发育不良, 上脚增厚延长, 横断面脚间窝增深, 类似臼齿[12-13]。

3 Joubert综合征是一种典型的纤毛疾病

目前已明确报道的Joubert综合征致病基因有23种, 有趣的是, 这些基因所编码的蛋白质大都分布于纤毛或其基体上(表1和图1B), 与纤毛的结构和功能密切相关[14]。这些蛋白质的复杂多样和差异分布赋予它们自身多样的功能。例如, 限制细胞质膜蛋白等运输到纤毛的速率, 维持纤毛膜与过渡区之间的联系等。Joubert综合征致病基因与其他纤毛疾病基因类似, 它们突变或缺陷都会导致相应的复合体发

表1 Joubert综合征致病基因

Table 1 The genes mutated in Joubert syndrome

类型 Type	基因 Gene	编码蛋白质 Protein	蛋白质在纤毛上的分布 The distribution of protein in the cilium	遗传方式 Inheritance
JBTS1	*INPP5E*	Inositol polyphosphate-5-phosphatase	Ciliary axoneme[18]	Autosomal recessive
JBTS2	*TMEM216*	Transmembrane protein 216	Ciliary membrane, basal body[19]	Autosomal recessive
JBTS3	*AHI1*	Jouberin	Basal body, transition zone[20]	Autosomal recessive
JBTS4	*NPHP1*	Nephrocystin 1	Basal body, transition zone[14]	
JBTS5	*CEP290*	Centrosomal protein 290 kDa	Basal body, transition zone[21]	Autosomal recessive
JBTS6	*TMEM67*	Transmembrane protein 67/Meckelin	Ciliary membrane, transition zone[22]	Autosomal recessive
JBTS7	*RPGRIP1L*	RPGRIP1L	Centrosome, tansition zone[23]	
JBTS8	*ARL13B*	ADP-ribosylation factor-like 13B	Ciliary membrane, the base and tip of the cilium[24]	
JBTS9	*CC2D2A*	Coiled-coil and C2 domain-containing protein 2A	Transition zone[25]	Autosomal recessive
JBTS10	*OFD1*	Oralfaciodigital syndrome 1	Centrosome, basal body[26]	X-linked recessive
JBTS11	*TTC21B*	Tetratricopeptide repeat protein 21B	Basal body, ciliary axoneme[27]	
JBTS12	*KIF7*	Kinesin-like protein 7	Basal body, the tip of the cilium[28]	
JBTS13	*TCTN1*	Tectonic-1	Axoneme, basal body, transition zone[5,29]	
JBTS14	*TMEM237*	Transmembrane protein 237	Ciliary transition zone[30]	Autosomal recessive
JBTS15	*CEP41*	Centrosomal protein 41 kDa	Basal body[31]	Autosomal recessive
JBTS16	*TMEM138*	Transmembrane protein 138		Autosomal recessive
JBTS17	*C5ORF42*	C5Orf42	Basal body, transition zone[28]	
JBTS18	*TCTN3*	Tectonic-3	Ciliary transitionzone[32]	
JBTS19	*ZNF423*	Zinc finger protein 423		Autosomal dominant
JBTS20	*TMEM231*	Transmembrane protein 231	Axoneme, basal body, transition zone[33]	Autosomal recessive
JBTS21	*CSPP1*	Centrosome and spindle pole associated protein 1	Ciliary basal body, transition zone, centrosome[17]	Autosomal recessive
JBTS22	*PDE6D*	Prenyl-binding protein	Transition zone[18]	
JBTS23	*KIAA0586*	KIAA0586 protein	Basal body, centrosome[34]	

Joubert综合征致病基因大部分都是常染色体隐性遗传, 且大多集中在纤毛的基体和过渡区。这些已被鉴定出来的Joubert综合征致病基因仅存在于62% Joubert综合征患者家族中, 意味着可能存在其他基因突变导致Joubert综合征的发生[9]。

Most Joubert syndrome causative genes are autosomal recessive, and mostly concentrated in the basal body and transition zone of the cilia. These causative genes that have been identified are only present in 62% of Joubert syndrome families, which suggests that other genes mutation may cause Joubert syndrome[9].

生故障, 进而使得纤毛的整体性遭到破坏, 导致纤毛形态改变或结构和功能的异常等[15]。由于纤毛在体内广泛分布、功能多样, 因此, Joubert综合征的症状现于多系统、多器官。

Joubert综合征致病基因突变影响纤毛的结构和功能。*ARL13B*(JBST8)突变后, 细胞纤毛长度明显变短, 仅有正常纤毛的一半长, 且纤毛双微管结构紊乱, 微管B不能闭合或不能与微管A正常连接[16]。*CSPP1*(JBST21)缺失后, 初级纤毛形成发生障碍, 纤毛数目减少, 长度变短, 相应的纤毛蛋白[如ARL13B、腺苷酸环化酶III(adenylate cyclase III, AC3)]在纤毛轴丝上的定位与运输也发生紊乱[17]。由此可见, Joubert综合征致病基因对纤毛的形成与维护有作用, 对纤毛功能的发挥也尤为重要。因此, Joubert综合征被认为是一种典型的纤毛疾病。

4　Joubert综合征致病基因在神经发育中的作用

虽然目前已发现多种Joubert综合征致病基因, 但这些基因的致病机理特别是导致神经发育异常的机制尚未完全阐明。多种纤毛疾病中都伴随小脑发育障碍, 而Joubert综合征是一种典型的纤毛疾病, 其临床影像学诊断特征为"臼齿征", 主要由小脑发育障碍所致。小脑中的神经元主要包括颗粒细胞和浦肯野细胞, 这两类神经元上都有纤毛分布。由于小脑中颗粒细胞数量庞大, 在小脑形态发育和功能发挥中有重要作用, 所以多数研究都集中在其增殖和分化。分析Joubert综合征病人样本发现, 颗粒细胞在小脑蚓部和半球的增殖都同样减弱[35], 然而病人中仅小脑蚓部而非半球选择性地受到影响, 因此, 小脑蚓部缺陷可能发生在更早期的发育过程中。这一推测在动物模型中似乎得到证实。在小鼠中敲除*RPGRIP1L*(JBTS7)基因, 在胚胎发育后期, 部分小脑脑区的颗粒细胞增殖减弱[36]。另外, 两个Joubert综合征致病基因, *AHI1*(JBTS3)和*CEP290*(centrosomal protein 290)的突变也导致胚胎发育期的颗粒细胞增殖减弱[37]。值得指出的是, 在这两个基因突变的颗粒细胞中, 纤毛结构仍然存在[37], 因此, 这些细胞的增殖障碍与纤毛结构完整性似乎无关, 而是由于纤毛所介导的信号通路遭到破坏。

Joubert综合征中除了特征性的小脑发育缺陷以及运动平衡障碍外, 还存在智力障碍, 这可能与大脑发育缺陷有关。大脑皮层发育始于放射状胶质细胞的形成, 这些细胞既作为前体增殖细胞, 又同时作为细胞迁移的"脚手架", 协助新增殖细胞在脑室区和皮层表面之间定向迁移。*ARL13B*(ADP-ribosylation factor-like 13B)集中分布于纤毛上, 其突变导致放射状胶质细胞"脚手架"的基底−顶端极性反转[38]。正常放射状胶质细胞的胞体靠近脑室区, 而*ARL13B*突变导致这些细胞胞体异常分布于皮层表面; 相应地, 这些前体细胞增殖产生的子代细胞也异常分布于皮层表层。*ARL13B*突变所致的"脚手架"极性反转, 导致随后的皮层神经元的迁移和分层定位异常, 这一切与初级纤毛长度变短、动态过程发生紊乱(不能有效地伸缩、分支、重构)直接关联。*ARL13B*突变后, 脑室区初级纤毛动态过程发生紊乱导致相应的纤毛信号异常, 使得能够感受外部因子对放射状胶质细胞发育重要的关键信号受体IgfR1(type 1 Igf receptor)分布异常。*ARL13B*突变也影响大脑皮层中间神经元的迁移与定位。初级纤毛对中间神经元的迁移和定位具有重要的向导作用, 而这一作用主要是通过调控对中间神经元迁移至关重要的导向因子在初级纤毛上的分布来实现。*ARL13B*突变后, 初级纤毛功能发生缺陷, 导致相应的导向因子[如酪氨酸激酶受体B(tropomyosin receptor kinase B, TrkB)、ErbB4、5-Htr6等]在中间神经元初级纤毛上的分布发生改变, 使得中间神经元感应外部导向因子的能力发生障碍, 不能正确迁移、定位[39]。

Joubert综合征中存在神经轴突交叉障碍, 如胼胝体发育不良、皮质脊髓束交叉减少或缺失等。分析Joubert综合征病人样本, 发现在*CC2D2A*(coiled-coil and C2 domain-containing protein 2A)、*KIF7* (Kinesin-like protein 7)以及*C5ORF42*(JBTS17)突变的部分Joubert综合征患者中存在胼胝体发育不全[40-42]。在模式动物研究中, 也观察到相同病症。敲除*RPGRIP1L*(JBTS17), 小鼠胼胝体发育严重缺陷, 这与路标细胞(guidepost cells)在端脑背侧中央区的定位紊乱相关联。路标细胞对胼胝体轴突路径具有一定向导性, 对胼胝体轴突发生至关重要。在*RPGRIP1L*(JBTS7)突变鼠中, 路标细胞的定位异常源于端脑中央区早期图示发生缺陷以及皮质隔膜边界(cortico-septal boundary)形成异常, 而这一类缺陷主要由抑制性*Gli3*(Gli3R)的表达水平降低所致[43]。值得注意的是, *RPGRIP1L*位于纤毛过渡区, 对纤毛形成及功能的发挥都有重要作用, 纤

毛通过调控抑制性Gli3在体内的表达水平从而介导胼胝体的形态发生。同时, 在*INPP5E*(JBTS7)突变小鼠中, 丘脑皮层轴突束发生缺陷, 这与*Rfx*(regulatory factor X)突变鼠相似[44]。在*Rfx*突变鼠中, 神经轴突导向发生错误, 皮层丘脑轴突束不能正确迁移到端脑腹侧软膜表面, 丘脑皮层轴突束也不能离开端脑正常投射到杏仁核[44]; 这与端脑腹侧轴突导向因子Slit1、Netrin1分布发生异位有直接关联。值得指出的是, *INPP5E*(inositol polyphosphate-5-phosphatase)能够维持纤毛稳定性并调控纤毛信号, *Rfx*转录因子调控众多与纤毛发生及其功能相关的基因的表达。两者突变均导致轴突投射发生错误, 意味着纤毛通过建立正确的细胞环境对丘脑皮层/皮层丘脑轴突束路径的形成有重要作用。

Joubert综合征患者除主要表现为神经发育缺陷外, 一些病人还会出现眼组织缺损、多指趾畸形等症状, 也有些病人会出现视网膜营养不良、肝纤维化以及肾缺陷等症状。由此可见, Joubert综合征致病基因不仅对神经发育至关重要, 对其他组织器官的发育也发挥着必不可少的作用, 这也可能反映了纤毛的广泛分布及其功能的多样性。

5 Joubert综合征致病基因与Shh、Wnt信号通路

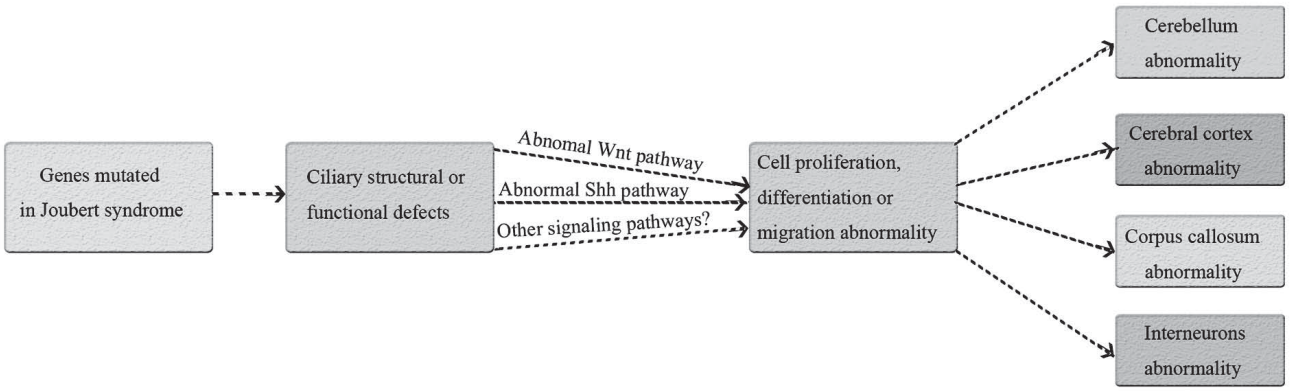
Joubert综合征基因突变影响纤毛介导的多种信号通路, 其中研究较多的是Shh和Wnt信号通路。Shh信号通路对胚胎发育以及神经环路的构建都有着重要且保守的作用, 能够调节神经元极化, 对轴突、树突的发育以及突触的形成也发挥着必不可少的作用[45]。在Joubert综合征病人样本中, *CEP290*(JBTS5)、*CC2D2A*(JBTS9)、*TMEM67*(transmembrane protein 67)突变后, 小脑颗粒前体细胞的增殖发生缺陷, 与Shh信号通路异常相关[35]。在小鼠中, Shh在胚胎后期和出生后的小脑中高度表达, 促进颗粒细胞的增殖[46]。但Joubert综合征致病基因具体是如何介导Shh信号通路来影响机体神经发育的, 目前还没有明确报道。

有研究表明, Shh信号通路的关键分子如Patched(Ptch1)、Smoothened(Smo)等都位于纤毛上[47]。部分Joubert综合征致病基因突变会引起纤毛结构和功能发生变化, 从而影响纤毛介导的Shh信号通路。例如, Joubert综合征致病基因*ARL13B*突变后, 纤毛结构和功能异常, Shh信号通路相关蛋白在纤毛上的分布发生紊乱, 小鼠出现一些与Shh信号通路相关的表型, 如多指趾畸形以及神经管闭合缺陷、后脑和颅脑畸形等发育异常[16]。同时, 体外用Shh配体激活*ARL13B*突变小鼠成纤维细胞Shh信号通路, 发现与正常水平相比, 该通路的信号分子Smo在纤毛上的富集明显增多, Ptch1表达并未明显减少, Gli1、Gli2以及Sufu在纤毛尖端的分布及表达均发生缺陷[24]。*ARL13B*参与神经管的发生, 可能是通过调节Shh信号通路分子Smo在细胞纤毛上的动态分布, 从而影响机体发育。此外, Joubert综合征致病基因*TCTN1*(JBTS13)、*KIF7*(JBTS12)均被认为是Shh信号通路的调节因子。*TCTN1*与Shh在神经管腹侧的表达图式密切相关, 敲除小鼠*TCTN1*, Shh信号通路分子Ptch1、Gli1、Gli3表达均发生紊乱[29]。KIF7被认为是一纤毛运动蛋白, 主要通过调节初级纤毛的微管动态从而进一步调控Shh信号通路[41,48]。

部分Joubert综合征基因与Wnt信号通路密切相关。经典Wnt通路和非经典通路都广泛参与神经发育。其中, 经典Wnt通路的关键分子GSK3(glycogen synthase kinase 3)、APC1(anaphase-promoting complex 1)和β-catenin, 是常见的神经环路调节因子[49]。GSK3除介导Wnt信号通路外, 还介导神经生长因子等的信号转导。AHI1能够介导β-catenin进入细胞核, 从而调控Wnt信号通路[50]。AHI1缺失后, 小鼠小脑中线处Wnt活性明显降低, 细胞增殖减弱, 用氯化锂激活Wnt信号通路能够部分挽救这一缺陷[37]。敲除*TMEM67*基因能使经典Wnt信号通路受干扰, 纤毛异常, Wnt刺激后, 细胞核内β-catenin积累明显减少[22]。由上可知, Joubert综合征神经发育障碍与Shh、Wnt信号通路紊乱密切相关(图2)。此外, 还可能存在其他纤毛介导的信号通路与Joubert综合征神经发育障碍相关联, 如PDGF、Notch等信号通路, 这些信号通路对胚胎发育、神经发生等都有关键作用[51-52], 但是否与Joubert综合征致病机理相关联, 还有待于进一步研究。

6 结语与展望

纤毛疾病Joubert综合征典型的神经发育缺陷为小脑、脑干发育不良, 并伴有共济失调, 智力发育迟滞等病症, 这与其他纤毛疾病存在共同的临床表征。部分Joubert综合征致病基因的突变也能导致不



Joubert综合征致病基因与纤毛密切相关, 其突变会导致纤毛结构或功能发生缺陷, 从而影响纤毛介导的信号通路, 如Shh和Wnt通路等。重要的信号通路异常, 导致细胞增殖、分化或迁移发生紊乱, 机体出现一系列神经发育障碍病征, 如小脑、大脑皮层、胼胝体等发育异常。

Joubert syndrome causative genes are closely related with cilia, its mutations can lead to ciliary structural or functional defects, which affects the cilia mediated signaling pathways, such as Shh and Wnt pathways. Cell proliferation, differentiation, or migration happens disorder if important signaling pathway abnormality, it will appear a series of neural developmental disorders symptoms.

图2　Joubert综合征致病基因在神经发育中的作用

Fig.2　The roles of causative genes of Joubert syndrome in neural development

同纤毛疾病的发生。因此, 进一步探讨Joubert综合征致病机理显得很有必要。尽管近年来有关纤毛、Joubert综合征以及它们之间的相关性的研究都有了较大进展, 但在研究Joubert综合征神经发育缺陷的致病机理方面, 仍有许多问题尚待解决。(1)Joubert综合征中典型的小脑发育缺陷的细胞分子机制是什么？Joubert综合征呈现的认知障碍是否与其直接相关？深入透彻地研究Joubert综合征小脑发育异常机理, 将有助于我们探讨该病以及其他小脑发育障碍相关疾病的致病机制, 为临床治疗方案提供更好的实验和理论基础。(2)Joubert综合征中皮质脊髓束和小脑上脚等神经束不能正确形成交叉, 是否直接与轴突导向发生障碍相关？这些区域的路标细胞分布是否存在异常？这一过程中纤毛又是如何发挥作用？ (3)Shh和Wnt像其他轴突导向因子一样, 在轴突导向中扮演着重要角色。Joubert综合征致病基因是否可能通过调节Shh、Wnt信号通路从而参与轴突导向？解决这一系列问题将有助于我们进一步理解Joubert综合征以及其他纤毛疾病的致病机理, 从而为更好地提供临床诊断、遗传咨询以及治疗方案等奠定实验和理论基础。

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