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综 述

细胞原纤毛与人类疾病

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摘 要：细胞原纤毛定位于绝大多数哺乳动物细胞表面，属于非常保守的细胞器，调节细胞增殖、分化、迁移、极性、信号级联等生命活动来调控细胞生命进程和维持细胞稳态。原纤毛结构蛋白或附属蛋白编码基因突变所导致的疾病统称为“纤毛类疾病”，发生在胚胎期、婴儿期甚至成人期。纤毛类疾病不仅累及单一器官，也涉及多器官多系统，表现出多变表型和重叠表型。本文主要综述原纤毛相关基因突变对骨骼、牙齿、皮肤、肝胆、肾脏、大脑、视网膜、心脏等器官的影响，揭示其致病机制，并对当前一些纤毛类疾病新型治疗方法进行探讨。

关键词：细胞原纤毛；纤毛类疾病；器官；治疗
中图分类号：R3；R33；R394

Cellular primary cilia and human diseases

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Abstract: Cellular primary cilium, located on the surface of virtually all mammalian cells, is a strictly conserved organelle which regulates cell biological process and maintains cell homeostasis by modulating cell proliferation, differentiation, migration, polarity, signal cascades and other life activities. Some diseases caused by mutations in genes encoding structural proteins or accessory proteins of primary cilia are collectively termed as “ciliopathies”, which can occur in embryo, infancy and even adulthood. Ciliopathies not only involve a single organ, but also involve multiple organs and multiple systems, showing variable symptoms and overlapping symptoms. This review mainly summarizes the effects of ciliopathy-associated gene mutations on bone, tooth, skin, liver and bile duct, kidney, brain, retina, heart and other organs, uncovers their molecular mechanisms and provides some novel insights into therapy of ciliopathies.

Key words: cellular primary cilium; ciliopathy; organ; therapy

1 介绍

原纤毛属于一种动态超微结构[1]，类似“天线”从细胞膜伸出，是进化过程中十分保守的信息集散枢纽型细胞器[2]，它参与细胞增殖[3]、分化[4]、信号转导[5, 6]、自噬[7]、迁移[8]、极性[9]等生命进程，其功能多样与狭窄“细胞室”含高密度膜受体的结构特点吻合。原纤毛结构包括基体、过渡区、内部轴丝骨架、纤毛膜和原纤毛尖端[10]，直径约 350 nm，长度约 1~10 μm[11]。纤毛的保守核心结构——轴丝，由 9 个外部 α-β 微管蛋白二聚体排列成环围

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绕内部 2 个或 0 个单微管，分别形成动纤毛或原纤毛，即“9+2”型或“9+0”型纤毛[12]。动纤毛有动力蛋白 ATP 酶，可以分解 ATP 使相邻微管滑动产生摆动或旋转[13]，耳鼻喉腔、肺、脑室和生殖道等特定组织有动纤毛[14]。原纤毛缺乏动力蛋白臂，无法自主运动但能被动地随周围液流摆动[15]，存在于几乎所有真核细胞表面，是 G_0/G_1 期细胞或终末分化细胞上由细胞膜包裹的孤立非活动突起，通过协调各种信号分子和受体的运输、定位参与 Hedgehog、Wnt、PDGFR-α、Notch、mTOR 等信号转导过程[16–21]。原纤毛内负责运输的蛋白质被称为纤毛内转运蛋白 (intraflagellar transport protein, IFT)，三种多亚基蛋白复合物——IFTA、IFTB 和 BBSome，协同微管马达驱动蛋白 2 (kinesin-2) 和胞质动力蛋白 2 (dynein-2，也称 dynein-1b) 在原纤毛内运输来自高尔基体的各种蛋白质分子[22]。IFTB 复合物负责原纤毛基底部到顶端的顺行运输，而从顶端到基底部的逆行运输依靠 IFTA 复合物，BBSome 则起着稳定 IFT 复合物和衔接输送蛋白的作用[23, 24]；在原纤毛基底部，kinesin-2 直接与 IFTB 结合，以微管轴丝为轨道输送 IFTA、非活性 dynein-2 和各种蛋白分子；一旦到达尖端，IFT 复合物构像发生改变，IFTA 复合物连接活性 dynein-2 介导逆行运输[25, 26] (图 1)。原纤毛随细胞周期动态变化，其组装、解聚、保持稳定是通过乙酰化、去酪氨酸化、谷氨酰化或糖基化微管蛋白等翻译后修饰来调控[27]。原纤毛组装发生在细胞周期 G_0/G_1 期或终末分化细胞，当细胞进入新的细胞周期后原纤毛解聚[28, 29]。但是，原纤毛持续存在阻滞细胞进入 S 期或 M 期，抑制细胞增殖[30]。Aurora-A 调控组蛋白去乙酰化酶 6 (histone deacetylase

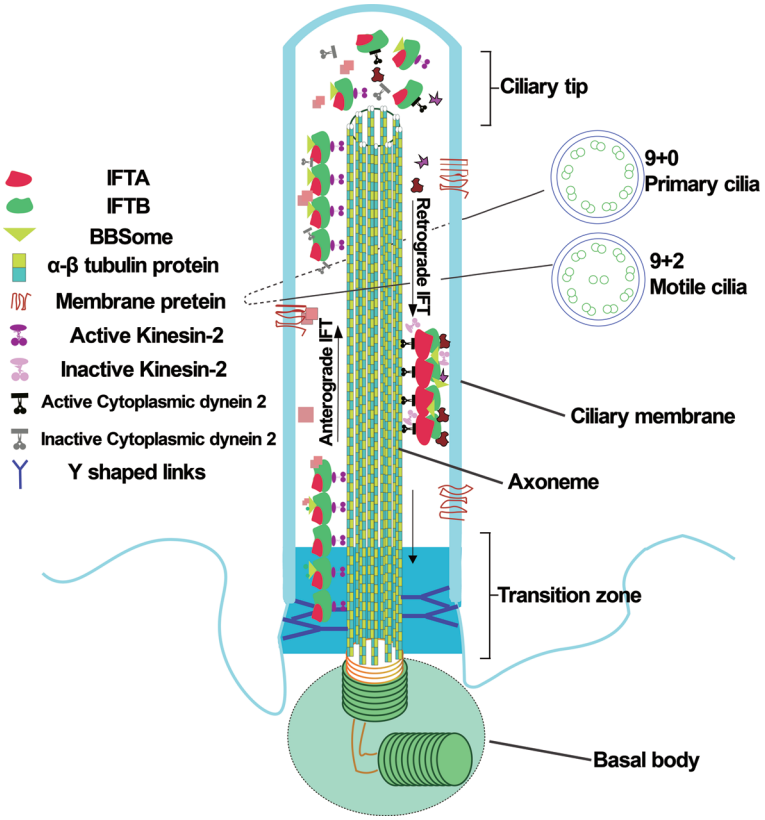

图 1. 原纤毛结构及纤毛内运输机制

Fig. 1. The structure of primary cilium and intraflagellar transport mechanism. In the basal body, IFTA, IFTB, kinesin-2, dynein-2 and BBSome are assembled into the intraflagellar transport protein (IFT) complexes. Subsequently, the substances that need to be transported (such as α-β tubulin dimer, membrane protein) are loaded onto the IFT complexes and transported across the transition zone into the primary cilia. In the primary cilia, the anterograde IFT complexes depending on kinesin-2 and IFTB can transport substrates from the cilia bottom to the cilia top along the microtubule tracks. At the top, the anterograde IFT complexes change configurations to release the transport materials and reassemble into new retrograde IFT complexes, which mainly rely on IFTA and cytoplasmic dynein-2 to transport cargos back to bottom.

6, HDAC6) 活性控制原纤毛组装[31, 32]，血清等营养物质的匮乏促进肝癌细胞、胚胎干细胞原纤毛的生长[1, 33]。原纤毛结构蛋白和相关附属蛋白是原纤毛保持完整和行使功能所必需的，这些蛋白的基因突变导致原纤毛降解或功能障碍[34]。涉及原纤毛结构蛋白或附属蛋白编码基因突变所导致的疾病统称为“纤毛类疾病”。目前报道的“纤毛类疾病”有 35 种，呈显著增加趋势，已经确定 187 个致病相关基因，筛选出 241 个候选基因[35]。原纤毛缺陷所造成的“纤毛类疾病”是复杂的多系统疾病，累及肾脏、大脑、眼睛、心脏等器官，尽管对该类疾病的致病机制研究有所进展，但治疗还仅仅局限在控制患者症状，无法有效根治。

2 原纤毛相关纤毛类疾病

2.1 骨原纤毛相关纤毛类疾病

在骨细胞、成骨细胞、间充质干细胞、软骨细胞的细胞膜上均观察到原纤毛[36, 37]，一些骨疾病表现出原纤毛形态异常 (图 2)，推测原纤毛及其附属蛋白在骨发育和稳态维持方面具有重要作用。短肋多指综合征 (short rid-polydactyly syndromes, SRPs) 的特征是狭窄胸腔、短肋骨、短管状骨及三叉形髋臼，*IFTA*、*DYNC2H1*、*IFT80*、*WDR35*、*WDR19*、*NEK1*、*WDR34*、*IFT140*、*IFT172*、*WDR60*、*TTC21B* 等多种基因突变 (表 1) 会造成 SRPs[38]。*DYNC2LI1* 编码的动力蛋白轻中链调节软骨生长板原纤毛长度、原纤毛内转运和 Hedgehog 信号，敲除该基因使原纤毛异常，损害逆行运输和 Hedgehog 信号[39]，*TCTEX1D2* 编码的动力蛋白轻链和 *WDR60*、*WDR34* 编码蛋白结合并共同定位在微管组织中心 (microtubule organizing center, MTOC)，调节原纤毛生长，这些基因突变和 SRPs 发生相关联[40]。缩窄性胸廓窘迫综合征 (Jeune asphyxiating thoracic dystrophy, JATD) 是一种成骨和软骨发育不良所导致的胸腔、肋骨和四肢发育异常[41]，和 SRPs 有部分重叠表型。*WDR60* 和 *IFT80* 均编码原纤毛内转运蛋白，敲除 *WDR60* 使动力蛋白 2 组装减少[42, 43]，*IFT80* 突变损害原纤毛 /Hedgehog 信号，这两种基因突变会同时引起

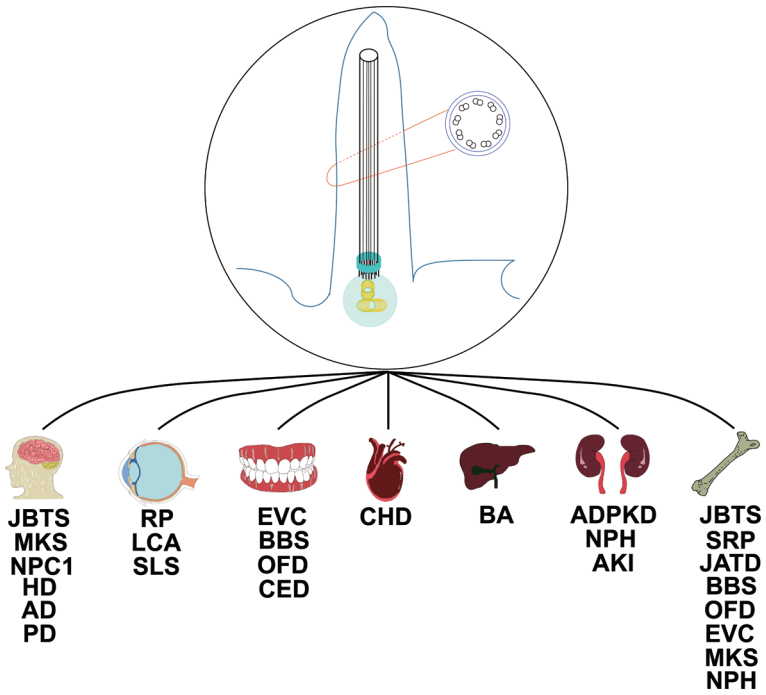

图 2. 纤毛类疾病和相关器官

Fig. 2. Ciliopathies and related organs. JBTS: Joubert syndrome; MKS: Meckel-Gruber syndrome; NPC1: Niemann-Pick disease type C1; HD: Huntington’s disease; AD: Alzheimer’s disease; PD: Parkinson’s disease; RP: retinitis pigmentosa; LCA: Leber’s congenital amaurosis; SLS: Senior-Loken syndrome; EVC: Ellis-van Creveld syndrome; BBS: Bardet-Biedl syndrome; OFD: oral-facial-digital syndrome; CED: cranioectodermal dysplasia; CHD: congenital heart disease; BA: biliary atresia; ADPKD: autosomal dominant polycystic kidney disease; NPH: nephronophthisis; AKI: acute kidney injury; SRP: short rid-polydactyly syndrome; JATD: Jeune asphyxiating thoracic dystrophy.

JATD、SRPs。原纤毛缺陷抑制 Hedgehog 信号，阻碍成骨细胞分化和矿化，Smoothened 蛋白激动剂能补救成骨分化缺陷 [44]。我们在诱导软骨细胞分化实验中发现，沉默 *IFT80* 下调 Hedgehog 信号，却上调 Wnt 信号，破坏 II 型胶原蛋白合成和硫酸蛋白聚糖沉积，这也说明原纤毛能平衡 Hedgehog 信号和 Wnt 信号来调节软骨发育 [45]。糖尿病患者骨机械强度降低和骨折风险增加 [46]，与糖尿病异常生理环境导致的原纤毛受损有关 [47, 48]，淫羊藿苷通过原纤毛 /Hedgehog 信号增强成骨细胞增殖和分化 [49]，有望被用来治疗糖尿病性骨质疏松症。因此，骨作为一个高度动态的器官，通过原纤毛及其附属蛋白感知和响应细胞内外信号变化来维持骨发育和稳态，提示原纤毛未来有望作为骨疾病治疗靶点。

2.2 牙齿原纤毛相关纤毛类疾病

牙齿发育需要成牙本质细胞、成釉质细胞和牙髓细胞通过多条信号通路共同调控，原纤毛作为细胞信号枢纽对牙齿早期发育和晚期发育起关键作用 [50]。牙生成涉及上皮 - 间质转换 (epithelial-mesenchymal transition, EMT)，原纤毛被证实参与这一过程 [51]。通过对小鼠牙胚、牙周韧带和口腔组织原纤毛标志 —— 腺苷酸环化酶 3、γ- 微管蛋白进行双染色免疫荧光实验，发现原纤毛在不同发育阶段频繁改变长度和分布来响应 FGF、BMP、Shh 等信号分子，维持牙胚和口腔组织正常发育 [52]。牙髓细胞和成牙本质细胞上都存在原纤毛 [53]，在牙髓干细胞 (dental pulp stem cell, DPSC)，*IFT80* 突变会损害原纤毛发生、FGF/FGFR1 和 Hedgehog/BMP2 信号，导致牙髓干细胞分化缺陷 [54]。在牙齿发育的不同阶段，Wnt 信号和 Hedgehog 信号表现出协同或拮抗作用 [55, 56]，在牙上皮细胞和间充质细胞中检测到的 Wnt 信号分子 [57] 是后期成釉细胞和成牙细胞分化所必需的 [58, 59]。原纤毛整合并严格调控这两种信号。*KIF3a* 编码的驱动蛋白 2 亚基参与调节原纤毛长度 [60]，在牙源性间充质细胞中，敲除 *KIF3a* 抑制 Hedgehog 信号而过早激活 Wnt 信号，导致牙釉质器官体积显著增大，但却很少产生牙釉质 [61]，而 Wnt 信号核转录因子 β-catenin 缺失突变造成牙齿发育异常，包括畸形牙蕾、异位牙 [62]。流体静压力能激活 Wnt 信号来协助矿化，PIEZO1 作为成牙本质细胞膜上阳离子通道，能检测流体静压力并转化成 Ca^{2+} 信号来调节 Wnt 信号和原纤毛发生，敲除该基因抑制原纤毛表达和成牙本质细胞分化 [63, 64]。Shh 信号在脊椎动物牙齿发育中高度保守，从小鼠胚胎发育第 11 天到发育晚期，Shh 信号先后在牙齿上皮细胞、釉质结和成釉细胞中表达 [65]。上皮增厚是牙齿形成的信号，缺失 Shh 信号会抑制上皮增厚，而 Shh 信号过度活跃则导致牙齿上皮过度内陷和畸形牙蕾 [66]。埃利 - 伟氏综合征 (Ellis-van Creveld syndrome, EVC) 患者出现明显牙齿发育不良和畸形牙，*EVC* 和 *EVC2* 编码的原纤毛蛋白能以复合物形式直接作用于 Smo 来调节 Hedgehog 信号，其突变导致 Hedgehog 信号破坏 [65, 67]。由于原纤毛协调 Hedgehog、Wnt、FGF/AKT [68] 等信号通路与牙发育息息相关，其缺失可能会导致各种牙齿发育缺陷。除 EVC 综合征外，Bardet-Biedl 综合征 (Bardet-Biedl syndrome, BBS)、口面指综合征 (oral-facial-digital syndrome, OFD)、颅外胚层发育不良 (cranioectodermal dysplasia, CED) 等纤毛类疾病中均可见到异常牙表型 (图 2)，表明原纤毛可能在牙发生早期和晚期都起关键调节作用。

2.3 皮肤原纤毛相关纤毛类疾病

皮肤作为一个高度极化的代谢组织，其稳态依赖于细胞增殖、分化和基底角质细胞脱落之间平衡。原纤毛参与角质细胞分化、毛发形成、表皮应激等生理过程 [19]，出现缺陷会打破皮肤稳态，可能导致进行性表皮隆起、腹侧脱发、基底细胞增生、角质细胞分化异常和真皮内异位表皮生长 [69]。*Kur* 编码的胞质蛋白富集在原纤毛基底部，参与动力蛋白外侧臂募集，它也将原纤毛随液流摆动和细胞极化连接起来，并通过与 *INVS*、*Dvl* 编码蛋白相互作用抑制经典 Wnt 信号 [70]，*Kur* 突变使原纤毛动力蛋白臂受损，导致原纤毛运动障碍 (primary ciliary dyskinesia, PCD)[71]。原纤毛生成是细胞自发过程，发生在细胞极化后，皮肤分化程序启动前，*Fuz* 作为细胞平面极化 (planar cell polarity, PCP) 信号效应基因参与原纤毛生成，其突变使原纤毛生成受阻，Hedgehog 信号下调致毛囊形成障碍和表皮角质化 [72]。在皮肤早期发育中，原纤毛激活 Notch 信号通路，平衡增殖和分化；发育晚期，原纤毛增强 Shh 信号促进毛囊形态发生，原纤毛缺陷造成表皮增生 [19]。原纤毛 / Hedgehog 信号负调控黑色素生成，原纤毛内部微管作为黑素体转运通道，其异常导致皮肤色素沉积 [73]。*Plk4* 控制中心粒复制 [74]，它的异常激活使中心粒过度复制，阻碍原纤毛生成，打破表皮前体细胞增殖与分化平衡，黑色素合成降低，导致皮肤斑秃、毛发颜色变浅 [75]。原纤毛对 Ras/MAPK 信

号有拮抗作用，Smoothened 蛋白抑制剂治疗基底细胞癌 (basal-cell carcinoma, BCC) 效果欠佳被证实与原纤毛减少相关，即癌细胞增殖已摆脱 Hedgehog 信号依赖，转而依靠高度活化的 Ras/MAPK 信号 [76]。总之，真皮细胞和表皮细胞中的原纤毛，通过调节细胞定向分裂、细胞分化和毛囊平面方向来控制细胞形态变化 [77]。

2.4 肝胆原纤毛相关纤毛类疾病

肝细胞没有原纤毛，肝胆纤毛类疾病更准确应称为“胆管纤毛类疾病”，因为胆管细胞是肝脏中唯一含有原纤毛的上皮细胞，胆管纤毛类疾病主要包括囊性或纤维化性肝病 [78]。原纤毛能对胆道渗透压、胆汁酸和管腔张力进行实时监测 [79, 80]，并将其转换为细胞内 Ca^{2+} 和 cAMP 信号 [81]，通过和胆道外泌体相互作用来保持细胞间通讯 [82, 83]，研究显示肝移植失败与胆管并发症引起的上皮细胞原纤毛消失相关 [84]。胆管闭锁症 (biliary atresia, BA) 作为一种侵袭性炎症纤维化胆道闭塞，组织学检测发现 BA 患者胆管细胞原纤毛结构存在显著缺陷 [85]，这与长期炎症环境 [85]，或是胆汁淤积产生细胞毒性有关 [86]。*TALPID3* 编码中心粒末端蛋白，参与基体锚定，其突变造成原纤毛缺失和 Hedgehog 信号传导障碍，使胆管细胞畸形增生并压迫肝脏导管板细胞，胆汁由于肝脏空间狭窄错误贮存在胆管细胞内和胆管外，造成胚胎期肝脏发育畸形 [87, 88]。乳腺癌、肾细胞癌、黑色素瘤和胰腺癌等多种癌症中观察到原纤毛减少 [89–91]，癌细胞增殖、转移和侵袭表型被证实与原纤毛相关 [33]，如胆管细胞型肝癌被证实高表达 HDAC6，损害原纤毛，导致癌细胞恶性转移 [92]。多囊肝病 (polycystic liver disease, PLD) 是一种以胆管扩张和肝囊肿为特征的常染色体显性或隐形遗传病，可以单独发生，也可以继发于多囊肾病 [93]，原纤毛相关基因 *PKD1*、*PKD2*、*PKHD1* (表 1) 突变导致多囊肾病并发 PLD。肝、肾囊肿也伴随 HDAC6 和 cAMP 异常高表达，HDAC6 抑制剂和生长抑素类似物联用补救原纤毛生长，同时减少 cAMP 表达，为多囊肝病提供了新的治疗途径 [94]。原纤毛作为一个化学、机械、渗透压信号感受器，在胆管细胞生理和病理生理及肝脏发育中发挥重要作用 (图 2)。

2.5 肾脏原纤毛相关纤毛类疾病

在肾脏中，原纤毛从上皮细胞顶端伸入鲍曼氏囊间隙和管状内腔 [95, 96]，它的长度不仅与血流 [97]、超滤成分 [98] 等生理因素有关，而且受到细胞因子、ROS [99] 等病理生理因素影响。原纤毛激活趋化因子信号来招募炎症细胞，*LKB1* 编码的肝激酶 B1 是原纤毛上的代谢传感器，在肾脏形态调节和功能维持中扮演重要角色，并和 *NPHP1*、*ANKS3*、*PKD1*、*NEK7*、*STRAD* 等基因 (表 1) 编码蛋白组成复合物，抑制原纤毛 /CCL2/ 单核巨噬细胞信号 [100]，*LKB1* 突变引起趋化因子 CCL2 表达上调并招募单核巨噬细胞聚集在肾小管周围造成肾囊肿。*PKD1* 编码的多囊蛋白 1 作为 Ca^{2+} 通道，维持细胞内钙稳态并参与细胞间通讯，*PKD1* 突变导致常染色体显性多囊肾病 (autosomal dominant polycystic kidney disease, ADPKD)；*NPHP4* 编码一种定位在原纤毛上的蛋白质，对于肾发育和修复十分关键，*NPHP4* 突变导致肾消耗病 (nephronophthisis, NPH)，患者出现小肾，并伴有肾皮质、髓质交界处囊肿 [101]。ADPKD 和 NPH 发生炎症表型被认为和 CCL2 高表达相关 [102]，研究发现原纤毛促进囊肿发展，去除原纤毛能有效改善多囊肾病 [103]。虽然原纤毛正向促进囊肿的发生，抑制原纤毛生长可能是治疗 ADPKD 的方法，但是原纤毛缺陷又会导致其它疾病，如肝脏手术后肝缺血再灌注 (hepatic ischemia/reperfusion, HIR) 导致 ROS/氧化应激产物增加，损伤肾小管细胞和肾上皮细胞原纤毛，引起急性肾损伤 (acute kidney injury, AKI)[99]。Hedgehog 信号作为原纤毛周边信号的最佳代表，它在肾脏和尿道发育中起着关键作用 [104]，该通路基因突变导致肾发育不全、肾积水、输尿管积水和重复肾等表型 [105]。此外，Hippo 信号和其下游效应复合物 TAZ (transcriptional coactivator with PDZ-binding domain)/YAP (Yes-associated protein) 活性的平衡对肾发育和功能至关重要，*NPHP4*、*NPHP9* 编码蛋白共同负调控 Hippo 信号，TAZ/YAP 异常活跃可能会发生 ADPKD 等器官畸形增生疾病，而活性被抑制导致 NPH 等退行性疾病 [106]。总之，肾脏原纤毛不仅在肾脏结构和功能维持中起着重要作用，而且对肾脏损伤非常敏感，原纤毛长度和数量动态变化反映疾病发展过程，未来可能成为识别肾脏疾病的生化指标和潜在治疗靶点 (图 2)。

2.6 脑、神经原纤毛相关纤毛类疾病

原纤毛参与神经元迁移、脑发育和学习认知 [107]，它对中枢神经系统 (central nervous system, CNS) 发育至关重要。许多纤毛类疾病 (图 2)，如 Joubert 综合征 (Joubert syndrome, JBTS)、OFD 患者通常表现出中枢神经系统畸形、智力障碍和共济失调 [107, 108]，

表 1. 纤毛类疾病相关基因功能及定位

Table 1. Function and localization of ciliopathies-related genes

Human disease	Inheritance	Gene	Ciliary position and function	Affected organ
Joubert syndrome	AR, XR	*ARL13B, TALPID3, TMEM216, AHI1, NPHP1, CEP290, MKS3, RPGRIP1L, CC2D2A, OFD1*	Locating on centrosome or primary cilium, participating in cilium biosynthesis and stabilization, vesicle transport, *etc*	Brain, eye, kidney, liver, bone [112, 166, 167]
Short ridpolydactyly syndrome	AR	*DYNC2H1, TCTEX1D2, IFT80, WDR35, WDR19, NEK1, WDR34, IFT140, IFT172, WDR60, TTC21B*	Locating on the primary cilium and encoding intraflagellar transport protein	Mainly bone defect, also affecting the heart and kidney [168]
Jeune asphyxiating thoracic dystrophy	AR	*DYNC2H1, IFT140, IFT80, WDR34, WDR60, IFT172, CSPP1, CEP120, TTC21B, WDR19*	Encoding intraflagellar transport protein, centrosomal protein [169]	Mainly bone dysplasia, also affecting the liver, kidney function [166, 170]
Bardet-Biedl syndrome	AR	*BBS1-14* [171]	Locating on the basal body and axoneme, participating in intraflagellar transport	Bone, tooth, kidney, liver, heart, eye [172]
Oral-facial- digital syndrome	XD	*OFD1, C2CD3, TMEM107*	Locating on the transition zone [173] and centrosome, participating in cilium biosynthesis [174, 175]	Brain, bone, tooth, heart, eye
Ellis-van Creveld syndrome	AR	*EVC, EVC2*	Locating on ciliary membrane, participating in conducting Hedgehog [176]	Mainly bone dysplasia, also affecting the tooth and heart
Primary ciliary dyskinesia	AR	*DNAI1, DNAI2, DNAH5, DNAHI1, TXNDC3, RSPH9, RSPH4A, KTU, LRRC50*	The subunit of cytoplasmic dynamin [177]	Ear, reproductive system, skin, heart
Polycystic kidney disease	AR, AD	*PKD1, PKD2, PKHD1*	Locating on the primary cilium or basal body, regulating Ca^{2+} flux [178]	Kidney, liver
Nephronophthisis	AR	*NPHP1-9, MRE11, ZNF423, CEP164*	Locating on the primary cilium or centrosome	Affecting kidney, eye, liver, brain, bone, heart [179, 180]
Meckel-Gruber syndrome	AR	*TCTN1-3, MKS1, TMEM216, MKS3, CEP290, CC2D2A, B9D1*	Locating on the basal body or centrosome [181]	Brain, eye, kidney, bone, heart, liver
Niemann-Pick type C disease	AR	*NPC1, NPC2, TMEM135*	NPC1, NPC2 locating on the membrane of endosome or lysosome [182], TMEM135 locating on the membrane of peroxisome and mitochondrion [117], regulating the length and morphology of the primary cilium	Brain

续表1

Human disease	Inheritance	Gene	Ciliary position and function	Affected organ
Retinitis pigmentosa	AR, XR	*PRPF5*, *RPGR*	Locating on the outer segment of primary cilium of rod-shaped photoreceptor, splicing pre-mRNA [137]	Eye
Leber's congenital amaurosis	AR	*CEP290*, *NPHP5*, *LCA3*, *LCA5*, *LCA6*, *LCA15*, *MAK*	Locating on the primary cilium or centrosome [183]	Eye
Senior-Loken syndrome	AR	*NPHP1*, *NPHP4*, *CEP290*	Locating on the primary cilium or centrosome [141]	Eye, kidney
Congenital heart disease	AD	*AVC1*, *KIF7*, *DNAI1*, *DNAH5*	Locating on the primary cilium [149]	Heart
Huntington's disease	AD	*HTT*, *HAP1*	Locating on the primary cilium or centrosome [118]	Brain
Alzheimer's disease	AD	*ARL13B*, *SSTR3*, *AnkG*, *HT6R*	Locating on the primary cilium [124]	Brain
Parkinson's disease	AD, AR	*LRRK2*	Locating in the cytoplasm and phosphorylating Rab [128]	Brain

AD: autosomal dominant inheritance; AR: autosomal recessive inheritance; XD: X-linked dominant inheritance; XR: X-linked recessive inheritance.

Meckel 综合征 (Meckel-Gruber syndrome, MKS) 是一种出生早期致死疾病，和 JBTS 和 BBS 有部分重叠表型，并伴有枕部脑膨出、囊性肾和多指 (趾) 畸形 [109]。JBTS 是一种小脑畸形综合征，患者出现小脑蚓部发育不全、肌张力减退、共济失调，也并发眼病、肾病、多指 (趾) 畸形等多种混合表型 [110, 111]，主要变现为常染色体隐形遗传，但有一种 X 性染色体连锁隐性遗传 JBTS 与 *OFD1* 编码基因的第 21 个外显子发生移码突变相关 [112]。*RPGRIP1L* (*JBTS7*)、*CC2D2A* (*JBTS9*)、*ARL13B* (*JBTS8*)、*CSPP1* (*JBTS21*)、*CEP104* (*JBTS25*) 等超过 35 个基因突变 (表 1) 与 JBTS 相关，这些基因大多数定位在原纤毛跨膜区 [113, 114]。*ARL13B* 编码一种小 GTP 酶，调节原纤毛形态结构和 Hedgehog 信号，神经元中 *ARL13B* 突变导致细胞形态畸变和细胞间识别受损是 JBTS 病因之一 [115, 116]。C1 型 Niemann-Pick 病 (Niemann-Pick disease type C1, NPC1) 是一种罕见遗传病，其特征是内吞型胆固醇和其他脂质在胞内体或溶酶体中错误累积，可能与跨膜蛋白编码基因 *TMEM135* 突变导致原纤毛生成障碍有关 [117]。亨廷顿舞蹈病 (Huntington's disease, HD) 是一种神经退行性遗传病，其病因是亨廷顿基因 (*HTT*) 出现 CAG 扩增，HTT 蛋白多聚谷氨酰胺化 (polyQ-HTT) 而错误折叠并积累，破坏原纤毛内微管运输和基因转录 [118, 119]；自噬发生依赖于原纤毛 /Shh 信号通路 [120]，HD 患者自噬功能异常，polyQ-HTT 不能被有效清除导致神经元异常凋亡 [121, 122]。*HTR6* 编码的 5- 羟色胺受体定位在神经元原纤毛，调控原纤毛形态和长度，影响神经元生长、分化和迁移 [123]。阿尔茨海默病 (Alzheimer's disease, AD) 模型小鼠 *HTR6* 上调，诱导海马区神经元原纤毛过度生长，导致附属蛋白 ARL13b、SSTR3、AnkG 分布紊乱甚至解离，5- 羟色胺受体拮抗剂恢复原纤毛形态并改善 AD 小鼠认知 [124]。Shh 信号维持神经元存活和生理功能 [125]，帕金森病 (Parkinson's disease, PD) 是一种神经系统病变，患者出现震颤、运动障碍和认知障碍 [126]，*LRRK2* 是家族性和偶发性 PD 最重要的相关基因之一 [127]，它编码一种富含亮氨酸的蛋白激酶，发生突变能磷酸化 Rab10 去招募 RILPL1 从而损害原纤毛 /Shh 信号 [128]，胆碱能神经元由于缺少 Shh 信号发生退行性病变导致 PD。大脑主要由神经元和神经胶质细胞组成，原纤毛在大脑发育中起关键作用，参与小脑发育过程中前体细胞池扩大、海马神经干细胞和前体细胞形成，调节海马神经元树突细化

和突触整合，参与神经上皮早期极化和放射状胶质形成[129]。

2.7 视网膜原纤毛相关纤毛类疾病

视网膜光感受器障碍导致遗传性视网膜病(inherited retinal diseases, IRDs)，涉及200多个致病基因(表1)[130]。杆状和锥状光感受器外节段是特殊的“光感受器感觉纤毛”(photoreceptor sensory cilium, PSC)[131, 132]，它们和原纤毛结构相似，也包括基体、过渡区和纤毛轴[133]。色素性视网膜病变(retinitis pigmentosa, RP)是最常见的IRDs，由于视网膜视锥细胞、视杆细胞进行性退化，患者首先出现夜盲症，视野逐渐收缩，并最终丧失视力[134]。对光感受器特异性受体转录本剪接程序的精确调控，包括涉及原纤毛形成的剪接程序，在视网膜发育中至关重要，大约15% RP是由pre-mRNA处理因子(pre-mRNA processing factors, *PRPFs*)突变引起[135, 136]，视网膜色素细胞*PRPF31*丢失突变使原纤毛呈现球状并变短，导致光感受器形态紊乱和进行性退化[137]。利伯尔先天性黑蒙(Leber’s congenital amaurosis, LCA)是一种儿童期视力丧失疾病，分子机制是中心体蛋白290编码基因*CEP290*发生剪接缺陷引起PSC病变[138, 139]。Senior-Loken综合征(Senior-Loken syndrome, SLS)是一种罕见常染色体隐性遗传病，患者出现NPH并伴随视网膜变性[140]，肾囊素-5编码基因*NPHP5*突变造成光传导所需PSC不能生成，通过免疫共沉淀发现肾囊素-5、视网膜色素变性GTPase调节因子和钙调蛋白共定位于PSC，为SLS的肾脏、眼睛表型提供分子证据[141]。综上所述，PSC发育和功能正常对脊椎动物眼睛健康至关重要，多种基因发生突变导致视网膜原纤毛形态和功能改变通常是复杂多器官综合征的部分症状(图2)，这些研究让我们对原纤毛在视网膜发育和功能中的重要性有更深认识。

2.8 心脏原纤毛相关纤毛类疾病

原纤毛参与左右体轴、心脏循环方向和第二生心区(second heart field, SHF)的确立[142, 143]，通过Hedgehog信号调控心脏发育[144, 145]。PCD引起心血管发育畸形与动力蛋白臂编码基因*DNAI1*和*DNAH5*突变相关[146, 147](表1)。原纤毛结构基因*MKS1*和*IFT172*在SHF高表达，激活Hedgehog信号造成房室间隔缺损(atrioventricular septal defects, AVSDs)[148]；心源性*AVC1* (*IFT172*亚等位基因)发生突变与原纤毛缩短和Hedgehog信号受损相关，导致先天性心脏病(congenital heart disease, CHD)[149](图2)。英国一项针对389名PCD患者的回顾性队列研究发现，PCD患者中CHD患病率至少比普通人群高3倍，建议诊断为PCD患者进行心脏和腹部超声检查[150]。原纤毛顶端蛋白CEP104增强微管稳定性，参与Hedgehog信号传导过程中Smoothened蛋白在原纤毛累积，调节心脏发育[151, 152]。心脏发育还与原纤毛相关基因的染色质重塑相关，*RNF20*编码蛋白催化染色质组蛋白寡聚泛素化，调节原纤毛转录因子Rfx3水平，影响心脏发育，*RNF20*缺失突变导致心脏循环异常等CHD表型[153, 154]。心脏发育需要原纤毛和动纤毛，它们在左右体轴引导的心房不对称、心脏循环方向与流出道分隔等心脏发育过程中起重要作用[155, 156]。未来，对原纤毛在协调心血管系统生长发育中所起作用的详尽研究将为治疗心脏疾病提供一些新观点。

2.9 内脏转位相关纤毛类疾病

原纤毛在器官正常偏侧化发育中扮演重要角色，PCD造成两类有重叠表型的偏侧化疾病，即器官发育位置随机化和胸腹部器官异常排列[157](图2)。原肠胚形成过程中，在中线附近形成一个三角凹形结构称为胚胎结(embryonic node)，组成该结构的细胞上有胚胎结纤毛(node cilia)[158]。作为一种特殊的原纤毛，胚胎结纤毛缺乏中心微管对，微管仍按照“9 + 0”模式排列，但有动力蛋白臂，能旋转运动[159]。它顺时针旋转产生的左向液流被周围细胞原纤毛检测到，决定后续胚胎左右不对称发育[160]。作为临时胚胎组织者，胚胎结是促进早期胚胎左右不对称发育的起始位置，而左右模式正确形成需要精确信号传导和物质运输[161]。靶向破坏原纤毛内蛋白编码基因*KIF3b*造成小鼠胚胎结纤毛缺失，左右不对称随机化，敲除*KIF3a*基因也出现类似情况[156, 158]。Bardet-Biedl综合征(Bardet-Biedl syndrome, BBS)患者内脏异位，*BBS-7*和*BBS-8*基因突变造成原纤毛结构和功能缺陷，BBS蛋白在原纤毛组装和运输功能上具有重要作用[162]。完整原纤毛对肾脏发育十分重要，*INVS* (*NPHP2*)基因突变模型鼠肾囊肿表型与人类常染色体隐性多囊肾病(autosomal recessive polycystic kidney disease, ARPKD)、NPH都出现左右不对称缺陷[163]。PCP信号可能在节点纤毛旋转轴向后倾斜中起关键作用，该通路中的核心蛋白编码基因*Dvl*、*Vangl*、*Prickle*突变会导致节点纤毛定位错误及后续的左右模式缺陷[158, 164, 165]。

3 总结与展望

原纤毛为细胞信号交流中心，调节信号级联、维持细胞对内外环境信号反应和组织正常发育。随着科技手段提升，运用激光共聚焦显微镜、电子显微镜解析原纤毛结构，我们对原纤毛有更加立体直观的认识；通过亲和纯化 - 质谱 (affinity purification-mass spectrometry, AP-MS) 技术，识别 1 319 种原纤毛相关蛋白，加深了我们对原纤毛组成成分的理解 [184]。目前，研究者逐渐揭示某些纤毛类疾病的遗传方式和发病机制，即人类纤毛类疾病是 35 种 [35] 具有重叠表型的临床疾病，由纤毛、基体锚定结构以及附属蛋白基因突变造成。

原纤毛调节细胞增殖、分化，与肿瘤细胞增殖和分化以及侵袭和转移密切相关，我们研究组也一直致力于原纤毛调控骨发育和肿瘤发生与发展方面的研究。*IFT20* 和 *IFT80* 均编码原纤毛内转运蛋白 IFTB 复合物组成成分，参与调控细胞增殖与分化。我们研究发现 *IFT20* 在卵巢癌高表达，在乳腺癌、小肠癌、胃癌中量表达，在肺癌、胰腺癌、骨癌低表达，前列腺癌中不表达 [185]；而 *IFT80* 在肺癌、胃癌高表达，在乳腺癌、小肠癌中量表达，在骨癌、卵巢癌低表达，在前列腺癌、胰腺癌中不表达 [186]，证明原纤毛能直接或间接参与肿瘤的发生及发展。对肺癌细胞的研究发现靶向干扰 *IFT20* 减少肺癌细胞原纤毛表达，促进癌细胞增殖 [187]。细胞外基质降解是肿瘤转移和侵袭过程中不可或缺的环节，研究胃癌临床标本后发现 *IFT80* 高表达，直接上调基质金属蛋白酶 9 (matrix metalloprotein 9, MMP9) 表达，增强胃癌细胞的增殖和侵袭 [188]。我们发现胃癌患者在癌细胞骨转移前就发生骨丢失，并在胃癌裸鼠模型上得到证实。通过胃癌细胞 HGC-27 与成骨细胞共培养体系发现，癌细胞促进成骨细胞原纤毛生长并激活 Wnt/β-catenin 信号通路抑制成骨分化，特异性拮抗剂 DKK1 逆转原纤毛生长引起的骨丢失 [189]。说明原纤毛出现缺陷或过表达都会影响细胞增殖和分化，原纤毛有望成为癌症的诊断和治疗靶点。

原纤毛维持骨、牙齿、皮肤、肾脏、心脏、脑、肝胆以及视网膜等器官发育和功能，治疗纤毛类疾病的方法正在积极探索。基因层面的靶向疗法，为纤毛类疾病治疗提供更加精准的策略，如寡核苷酸疗法、基因替代疗法和基因编辑。反义寡聚核苷酸 (antisense oligonucleotide, AO) 高度特异性结合目的 mRNA 位点并使其降解，特异性剪接 pre-mRNA，甚至介导外显子跳读，使突变蛋白正确表达 [190]；AO 可以靶向突变序列，纠正异常剪接过程并恢复蛋白正常功能，成功纠正 LCA 患者 *CEP290* 剪接突变 [191]；导入野生型基因到病灶处替代疗法具有一定可行性，通过慢病毒介导完整 *DNAI1* cDNA 恢复纤毛摆动 [192]，挑选有效的靶向特异性传递载体是技术难点；CRISPR/Cas9 基因编辑能纠正突变基因，修复 *RPGR* 移码突变 [193]。纤毛类疾病可在单一器官发生病变，也累及多系统，表型多变且重叠，治疗存在极大难度，单一治疗法对某器官纤毛类疾病有效但却不一定能治疗其他器官纤毛类疾病。因此，今后对纤毛类疾病机理及其治疗方法的研究必将长期持续。

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