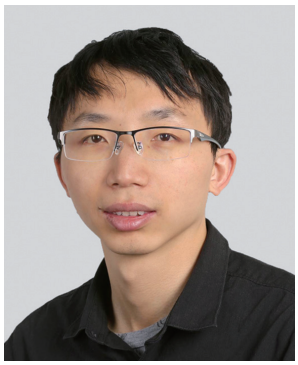

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哺乳动物中心体和初级纤毛的装配与功能

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摘要 中心体在细胞分裂过程中仅复制一次并被分配到子代细胞中, 其在细胞退出分裂周期时开始组装初级纤毛。该文总结了中心体和初级纤毛在哺乳动物细胞周期中的动态装配机制, 包括中心粒的结构变化与复制、中心体形成纺锤体极、初级纤毛的组装和去组装等过程。另外该文具体阐述了中心体作为微管组织中心和其在干细胞不对称分裂中的作用, 以及初级纤毛作为信号中心的功能。最后以肿瘤和纤毛病为例, 重点讨论了中心体和初级纤毛与疾病的关联。未来仍需深入研究和理解中心体和初级纤毛的基础生物学机制, 以及它们的生理和病理功能。

关键词 中心体; 初级纤毛; 细胞周期; 肿瘤; 纤毛病

Assembly and Function of Centrosome and Primary Cilium in Mammals

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Abstract Centrosomes are duplicated only once during cell division and distributed to daughter cells. They start to assemble primary cilia when cells exit the cell cycle. This article summarizes the dynamic assembly mechanisms of centrosomes and primary cilia in the mammalian cell cycle. These include centriole structural changes and duplication, centrosome formation of spindle poles, and primary cilia assembly and disassembly. This article also

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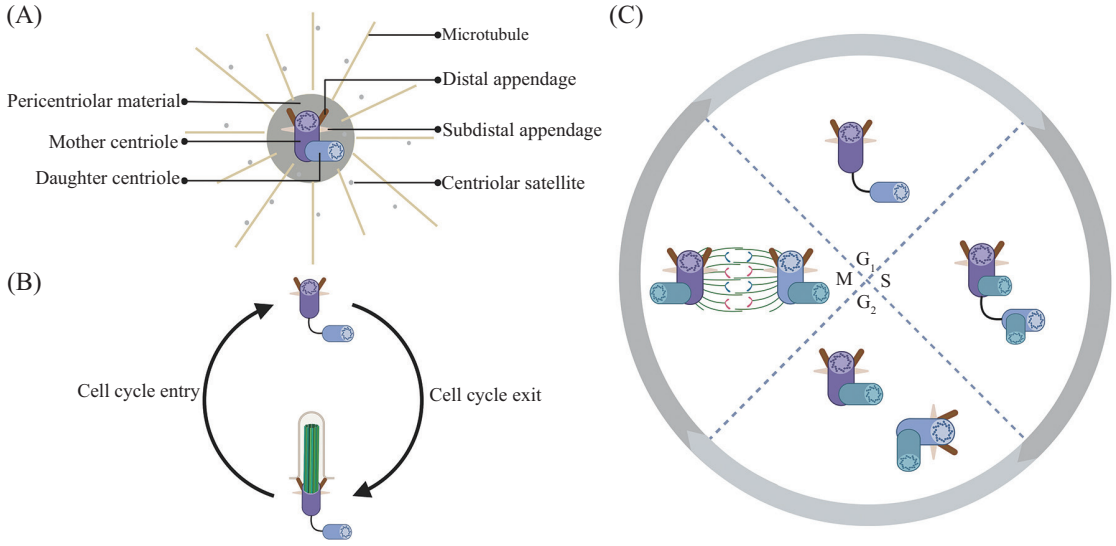
elaborates on the roles of centrosomes as microtubule organizing centers and their functions in stem cell asymmetric division. Moreover, it discusses the functions of primary cilia as signaling centers. This article then takes tumors and ciliopathies as examples to illustrate the association of centrosomes and primary cilia with diseases. In the future, it is essential to further study and understand the basic biological mechanisms of centrosomes and primary cilia, as well as their physiological and pathological functions.

Keywords centrosome; primary cilium; cell cycle; tumor; ciliopathy

作为微管组织中心, 中心体(centrosome)在微管的组装与解聚、细胞分裂等方面发挥着重要的作用[1-2]。一个成熟的中心体包含两个中心粒(centriole)和围绕中心粒的致密结构, 即中心粒外周物质(pericentriolar material, PCM)[3]; 中心粒卫星(centriolar satellite)是中心体外周散在分布的卫星样的颗粒结构, 有时也被称为中心体的“第三组分”(图1A)[4]。两个中心粒, 即母中心粒和子中心粒, 形成一个垂直排列的特殊的“L”形结构。每个中心粒都是由九组三联体微管组成的圆柱体, 但母中心粒与子中心粒在结构上有所不同, 包含远端附属结构(distal appendage)和亚远端附属结构(subdistal appendage)的突起[5-6]。PCM可能通过相分离的方式聚集微管蛋白来组织微管束, 在微管的成核和锚定中起着重要的作用[7-8]。

纤毛(cilium)是一种突出于细胞表面的“天线”样特化结构, 可分为动纤毛和静纤毛(也被称为初级纤毛)两类[9-10]。本文主要讨论哺乳动物中的初级纤毛, 初级纤毛是由中心体衍生而来的, 在有丝分裂期, 纤毛必须被解聚以允许中心体组装纺锤体。然而, 一旦细胞完成了有丝分裂并重新进入静息期(G_0期)或G_1期, 中心体就会转化为基体, 并开始组装新的纤毛(图1B)[11-12]。这种周期性的纤毛组装和去组装过程使得纤毛能够在细胞周期的不同阶段执行其



A: 中心体结构示意图。该图显示了母中心粒及其远端和亚远端附属结构、子中心粒、中心粒外周物质、中心粒卫星及微管。B: 中心体和初级纤毛的转换。当细胞离开细胞周期时, 初级纤毛一般开始组装, 随着细胞进入细胞周期, 初级纤毛逐渐去组装, 并在进入M期前被完全解聚。C: 中心体在细胞周期中的变化。G_1期时, 中心体的母中心粒和子中心粒稍微分开; 两个亲代中心粒在S期复制, 形成两个中心体; G_2期或M早期, 亲代子中心粒获得远端附属结构和亚远端附属结构, 形成两个成熟的中心体; M期发生有丝分裂, 中心体形成两个纺锤体极, 使得染色体被平均分配到两个子细胞中。

A: schematics of the centrosome structure. It shows the mother centriole and its distal and subdistal appendages, the daughter centriole, the pericentriolar material, the centriolar satellites and the microtubules. B: the transition between the centrosome and the primary cilium. When the cell exits the cell cycle, the primary cilium usually starts to assemble, and as the cell enters the cell cycle, the primary cilium gradually disassembles and is completely depolymerized before entering the M phase. C: centrosome dynamics during cell cycle. During G_1 phase, the mother centriole and the daughter centriole are slightly separated; two parent centrioles duplicate in S phase, forming two centrosomes; in G_2 phase or early M phase, the parental daughter centriole acquires distal and subdistal appendages, forming two mature centrosomes; in M phase, mitosis occurs, and the centrosomes form two spindle poles, ensuring the equal distribution of chromosomes to two daughter cells.

图1 中心体和初级纤毛的动态装配

Fig.1 Dynamic assembly of centrosomes and primary cilia

多种功能。初级纤毛主要包括基体(basal body)、轴丝(axoneme)和纤毛膜(ciliary membrane)。基体由中心粒衍生形成, 亦由九组三联体微管构成; 初级纤毛的轴丝一般由缺少中央微管的九组二联体微管构成; 纤毛膜是纤毛的外部结构, 包裹纤毛的轴丝。纤毛膜和细胞膜相连, 都是由磷脂双层构成的, 但纤毛基底存在扩散屏障(diffusion barrier)[13], 两者的脂质和蛋白质组成均有明显差异。

1 中心体和初级纤毛的动态装配

1.1 中心体和细胞分裂周期

细胞分裂周期可以分为四个阶段: G_1期、S期、G_2期和M期, 细胞离开分裂周期时被称为静息期或G_0期。在分裂间期, 中心体精确地复制自身为有丝分裂做好准备, 这一过程被称为中心体复制。在每个细胞周期中, 中心体复制且仅复制一次[14-15]。有丝分裂结束后, 每个子代细胞获得一个中心体, 而在下次有丝分裂开始之前, 它又复制形成两个中心体。在高等动物细胞中, 中心体在细胞周期中呈现不同的形态和结构变化(图1C)。

1.1.1 中心粒的连接与成熟 细胞进入G_1期前逐渐完成母子中心粒的脱离(disengagement), 构成中心体的两个中心粒稍微分开, 为中心粒的各自复制做准备, 是中心体复制开始的征兆[16]。中心粒脱离依赖于Polo样激酶1(Polo-like kinase 1, PLK1)和分离酶(separase), 如果中心粒脱离失败, 则随后间期的中心粒复制也会被阻断[17]。当中心粒在S期开始复制时, 母子中心粒的连接也重新形成, 并持续到M期, 因此该现象也被称为S-M连接(S-M linker)[14,17]。两个亲代中心粒近端底部还存在一种松散连接被称为G_1-G_2栓(G_1-G_2 tether, GGT), 从G_1期开始形成并持续至G_2期[17-18]。由于只有一个亲代中心粒具有附属结构, 因此在G_2期未成熟的一个亲代中心粒完成成熟, 并形成远端和亚远端附属结构; 伴随着G_2期GGT的解聚, 中心体开始分离, 为M期纺锤体(spindle)组装做准备。

1.1.2 中心粒复制 中心粒复制是一个精确而复杂的过程, 受到一系列蛋白分子机制的调控[15]。中心粒复制发生在S期, 在每个亲代中心粒一侧会形成一个新的中心粒, 被称为原中心粒(procentriole)。PLK4是控制中心粒复制的核心激酶, 确保中心粒在正确的时间准确复制[19]。PLK4的过表达会促进中心粒过度复制和额外中心体的形成, 而PLK4的抑制会阻止中心粒复制[20]。在细胞从G_1期进入S期时, PLK4被招募到亲代中心粒近端的中心粒复制支架, 其主要包括中心体蛋白CEP152(centrosomal protein of 152 kDa)和CEP192, 这个过程可能依赖于PLK4自磷酸化导致的相分离[21]。PLK4还可以磷酸化NEDD1(neural precursor cell expressed developmentally down-regulated protein 1), 进一步招募SAS-6(spindle assembly abnormal protein 6 homolog)到中心体, 与STIL蛋白(SCL-interrupting locus protein)一起形成车轮状结构(cartwheel), 起始原中心粒的组装[22]。在S和G_2期, 原中心粒进一步招募CPAP(centrosomal P4.1-associated protein)促进中心粒微管的组装和中心粒的延伸, 并在远端形成一个包含CP110(centrosomal protein of 110 kDa)和CEP97蛋白的帽状结构[23-24]。

1.1.3 中心体和纺锤体极 在G_2晚期或者M早期, PCM进一步被招募和向外扩展, 形成两个独立的成熟中心体。在动物细胞有丝分裂过程中, 两个中心体会迁移到细胞的两端形成两个星体, 即纺锤体极(spindle pole), 进一步指导纺锤体的形成、染色体的列队和分离[25-26]。纺锤体极由微管束聚焦在中心体而形成, 其形成和运动依赖于微管以及与微管结合的马达蛋白。纺锤体极的形成和功能受到多种因素调控, 比如有丝分裂激酶Aurora A和PLK1是这一过程的关键激酶, 对于中心体的成熟、分离和纺锤体正常组装都至关重要[27] 。近期发现, 纺锤体装配因子NuMA(nuclear mitotic apparatus)发生液–液相分离凝集到纺锤体极, 并隔离驱动蛋白KIF2A(kinesin family member 2A)解聚微管的作用来控制纺锤体正常装配, 这一过程也受到了Aurora A的磷酸化调控[28]。

1.2 初级纤毛的组装和去组装

1.2.1 纤毛关键蛋白运输复合物 哺乳动物初级纤毛的组装和去组装是一个复杂的过程, 与细胞周期的进程和分化状态紧密相关, 涉及到大量蛋白复合体和调控因子[29-30], 其中被研究最多的就是鞭毛内运输(intraflagellar transport, IFT)复合物[31]。IFT复合物最早在衣藻中被发现, 主要介导“货物”在纤毛基部和顶端的双向运输, 其可分为IFT-A和IFT-B[32]。IFT-B首先在纤毛基底处组装并进入纤毛, 接着结合驱动蛋白-2(kinesin-2)并将货物朝纤毛顶端运输, 即正向运输(anterograde transport); 货物在纤毛

顶端被释放作为纤毛组分, IFT重建, IFT-A与动力蛋白(dynein-2)结合将货物从纤毛顶端朝纤毛基部运输, 即反向运输(retrograde transport), 同样IFT组分得以被运输至纤毛基部并发生重建, 保证IFT的循环进行[33]。IFT-A包括3个核心亚基(IFT122、IFT140、IFT144)和3个非核心亚基(IFT43、IFT121、IFT139); IFT-B包含2个亚复合物IFT-B1和IFT-B2, 它们又分别至少包括10个亚基(IFT22、IFT25、IFT27、IFT46、IFT52、IFT56、IFT70、IFT74、IFT81、IFT88)和6个亚基(IFT20、IFT38、IFT54、IFT57、IFT80、IFT172)。不同IFT亚基精细的相互作用及调控保证了运输的准确进行, 近期一系列结构生物学研究解析了IFT复合体在不同物种、类型纤毛内的分子构象, 为我们理解IFT的装配机制、货物招募、运输以及进化差异提供了更深层次的见解[34]。除了纤毛内的运输外, IFT-A也控制包括GPCR在内的一系列膜蛋白从纤毛外进入纤毛[35]; 在此过程中, IFT-A聚合形成的一系列β-螺旋桨和TPR结构域使其得以与TULP结合并介导这些膜蛋白的纤毛定位[36]。

BBSome复合物包含8个被发现在巴尔得–别德尔综合征(Bardet-Biedl syndrome, BBS)中存在突变的蛋白, 其至少包括BBS1、BBS2、BBS4、BBS5、BBS7、BBS8、BBS9和BBS18。BBSome主要调控纤毛膜信号分子进入纤毛并将其偶联到IFT, 这个过程依赖于GTP酶ARL6(ADP ribosylation factor like 6)与BBS1的结合[37-38]。近期也发现BBSome对于将激活的信号受体移出纤毛是必需的, 小GTP酶RABL2(Rab-like protein 2)和ARL3的GTP/GDP结合形式的转换可以介导BBSome将这些膜蛋白通过过渡区(transition zone)[39-40]。

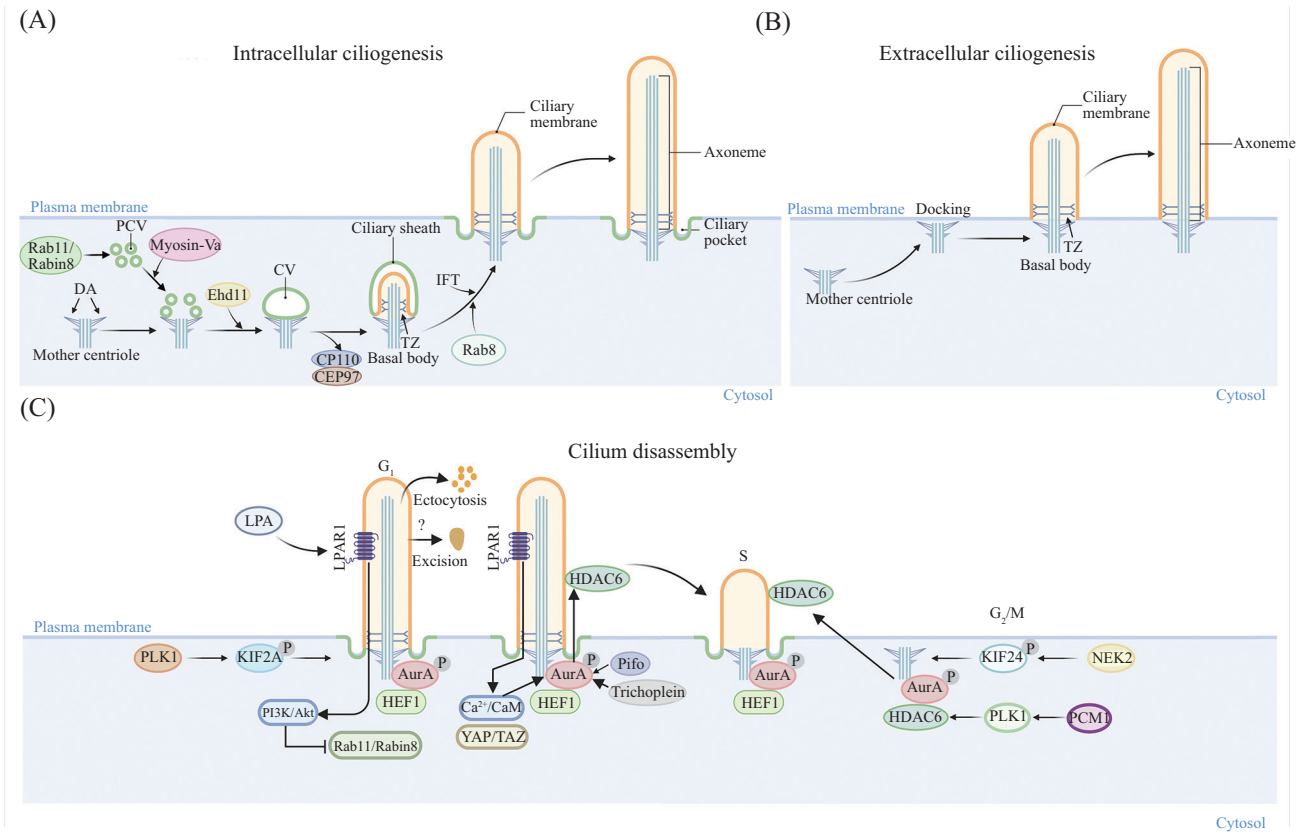
磷酸二酯酶6δ(phosphodiesterase type 6δ, PDE6δ)和Unc119是一些脂化修饰的货物蛋白的载体并将其运送到初级纤毛, 而ARL3-GTP将货物蛋白从Unc119上释放至纤毛。RP2(retinitis pigmentosa 2)和ARL13b分别是ARL3的GTP酶激活蛋白(GTPase-activating protein, GAP)和鸟苷酸交换因子(guanine nucleotide exchange factor, GEF), 进而介导了这类脂化蛋白及其载体在纤毛的循环运输[41-42]。

1.2.2 *初级纤毛的组装* 初级纤毛的组装大致可分为细胞内途径和细胞外途径两种, 成纤维细胞和间充质细胞一般采用胞内途径而极性上皮细胞往往采用胞外途径[12,43-44]。

胞内纤毛组装途径(图2A)如下。 Rab8(Ras-related protein 8)是参与哺乳动物细胞内囊泡运输和膜融合的小GTP酶, Rabin8是一种鸟嘌呤核苷酸交换因子(guanine nucleotide exchange factor, GEF)并激活Rab8, 而Rab11与Rabin8相互作用促进了Rab8起始的纤毛组装[45-46]。细胞在退出分裂周期时, Rabin8开始招募高尔基体囊泡和内吞循环体, 随后被Rab11激活, 对接在母中心粒的远端附属结构, 被称为纤毛前囊泡(preciliary vesicle, PCV), 这是纤毛发生的一个最初和关键的步骤。肌球蛋白Myosin-Va是一种马达蛋白, 对PCV运输至母中心粒以及后续纤毛组装起重要作用[47]。EHD1(Eps15 homology domain-containing protein 1)介导PCV融合产生纤毛囊泡(ciliary vesicle, CV)[48-49]。在此基础上, 母中心粒的远端帽CP110和CEP97的移除是纤毛起始发生的前提和标志性事件, 这依赖于TTBK2(Tau tubulin kinase 2)[50]。另外近期发现M期磷酸化蛋白9(M-phase phosphoprotein 9, MPP9)[51-52]、自噬受体NudC样蛋白2(NudC-like protein 2, NudCL2)[53]、线性泛素链组装复合物(linear ubiquitin chain assembly complex, LUBAC)[54]、Enkurin结构域蛋白1(enkurin domain-containing protein 1, ENKD1)[52]等介导了CP110从母中心粒上的移除和降解。纤毛过渡区(transition zone, TZ)接着开始组装[55], IFT接着促进轴丝组装, CV持续融合并延伸形成初级纤毛膜。初级纤毛膜通过与质膜融合形成一个凹陷的纤毛口袋, 最后突出细胞表面形成成熟的初级纤毛。

胞外纤毛组装途径(图2B)如下。同胞内途径一样, 膜组分与母中心粒的对接启动了母中心粒帽状结构的移除, 中心粒转变为基体, 并起始了纤毛轴丝的组装。不同于细胞内途径, 母中心粒直接向质膜迁移并通过远端附属结构锚定在质膜, 随后形成轴丝突出细胞表面组装纤毛[43]。中心粒如何迁移到质膜附近并启动纤毛装配的机制目前仍不清楚, 例如Rab34仅参与胞内纤毛组装途径[56-57], 但Rab19似乎可同时参与胞内和胞外两种途径[58]。

1.2.3 *初级纤毛的去组装* 当细胞离开G_0期进入细胞周期时, 纤毛逐渐去组装, 有多种分子机制共同抑制纤毛组装, 并确保在纤毛进入细胞周期期间不会发生异常纤毛组装(图2C)。活化的Aurora A激酶介导的组蛋白去乙酰化酶6(histone deacetylase 6, HDAC6)磷酸化和激活是导致纤毛解聚的核心因



A: 胞内纤毛组装途径。胞内途径由纤毛前囊泡(PCV)被招募并对接到母中心粒的远端附属结构开始, 接着形成纤毛囊泡(CV)。随后母中心粒的帽被移除, 基体形成, 过渡区(TZ)也被组装。接下来, IFT复合物被不断地招募到纤毛基部以允许轴丝的延伸, 而Rab8被招募以促进纤毛膜的延伸, 最后纤毛膜和质膜融合, 形成一个凹陷的纤毛口袋。B: 胞外纤毛组装途径。母中心粒通过远端附属结构迁移并锚定在质膜上, 而后形成轴丝。C: 初级纤毛的去组装。激活的Aurora A和PLK1激酶导致HDAC6介导的微管去乙酰化, 其中Ca^{2+}/CaM、HEF1、Pifo、Trichoplein等多因子激活Aurora A; PLK1和NEK2激酶可分别激活驱动蛋白KIF2A和KIF24介导的微管解聚; 血清中的溶血磷脂酸(LPA)可能通过其纤毛受体诱导纤毛去组装; 纤毛还可以通过核外粒体分泌或顶端的剪切来实现纤毛蛋白的移除。

A: intracellular cilogenesis. The intracellular pathway starts with the recruitment and docking of PCVs (preciliary vesicles) to the distal appendages of the mother centriole, followed by the formation of CVs (ciliary vesicles). Then, the cap of the mother centriole is removed, the basal body is formed, and the TZ (transition zone) is also assembled. Next, IFT complexes are continuously recruited to the ciliary base to allow axoneme extension, and Rab8 is recruited to promote ciliary membrane extension. Finally, the ciliary membrane and the plasma membrane fuse, forming a depressed ciliary pocket. B: extracellular cilogenesis. The mother centriole migrates and anchors to the plasma membrane through its distal appendages, and then an axoneme is formed. C: cilium disassembly. Activated Aurora A and PLK1 kinases cause HDAC6-mediated microtubule deacetylation, in which multiple factors such as Ca^{2+}/CaM, HEF1, Pifo and Trichoplein activate Aurora A; PLK1 and NEK2 kinases can respectively activate the kinesin KIF2A and KIF24-mediated microtubule depolymerization; LPA (lysophosphatidic acid) in serum may induce ciliary disassembly through its ciliary receptor; ciliary protein removal can be achieved by ectocytosis or ciliary excision.

图2 初级纤毛的组装和去组装

Fig.2 Assembly and disassembly of primary cilia

素, 而Aurora A的这种作用完全独立于它在有丝分裂中的作用[59]。Aurora A的激活依赖于钙内流诱导的Ca^{2+}/钙调蛋白(calmodulin, CaM)与Aurora A及其伙伴人丝化增强子1(human enhancer filamentation 1, HEF1)的结合[60], 以及蛋白Pifo(Pitchfork)[61]和Trichoplein[62]。近期发现*Aurora A*的mRNA稳定性依赖于m^1A去甲基化酶ALKBH3(α-ketoglutarate-dependent dioxygenase alkB homolog 3)[63]。另一种有丝分裂激酶PLK1在进入有丝分裂期前被招募到中心粒外周基质, 结合并激活HDAC6, 促进微管去乙酰化和纤毛解聚[64]。PLK1还能磷酸化并激活驱动蛋白家族成员KIF2A促进微管解聚, 而NEK2(NIMA related kinase 2)激酶则通过磷酸化并激活KIF24[65], 触发纤毛分解所需的微管解聚[66]。另外, 血清中的溶血磷脂酸(lysophosphatidic acid, LPA)可以通过LPA受体1(LPAR1)激活磷脂酰肌醇3-激酶(phosphoinositide 3-kinase, PI3K)/Akt信号通路, 阻断Rab11-Rabin8的结合, 并抑制纤毛前运输和纤毛发生[67]; 另一项研究证明LPA及其受体是通过G蛋白激活YAP/TAZ(yes-associated protein/transcriptional coactivator with PDZ-

binding motif)和Ca^{2+}/CaM通路促进Aurora A的转录和磷酸化, 并进一步导致纤毛去组装的[68]。

纤毛在低等生物中可以通过核外粒体(ectosome)释放介导细胞间的通讯[69], 近期发现哺乳动物初级纤毛上的GPCR等信号受体也可以通过核外粒体的形式从纤毛中移除, 这个过程依赖于微丝骨架[70]。另一项研究则表明血清刺激介导的纤毛解聚可以通过膜的重构和纤毛顶端的剪切(excision)来实现纤毛蛋白的去除[71], 潜在机制涉及Aurora A的激活, 其降低INPP5E(inositol polyphosphate-5-phosphatase E)水平, 导致磷脂酰肌醇-4,5-二磷酸[$PI(4,5)P_2$]的再分配。$PI(4,5)P_2$与肌动蛋白调节因子一起, 通过局部诱导纤毛内肌动蛋白聚合导致纤毛膜的切除和释放, 限制纤毛生长, 间接促进纤毛解体。信号分子依赖的核外粒体分泌和血清介导的纤毛剪切机制的异同仍待进一步研究[70-71]。

2 中心体和初级纤毛的功能

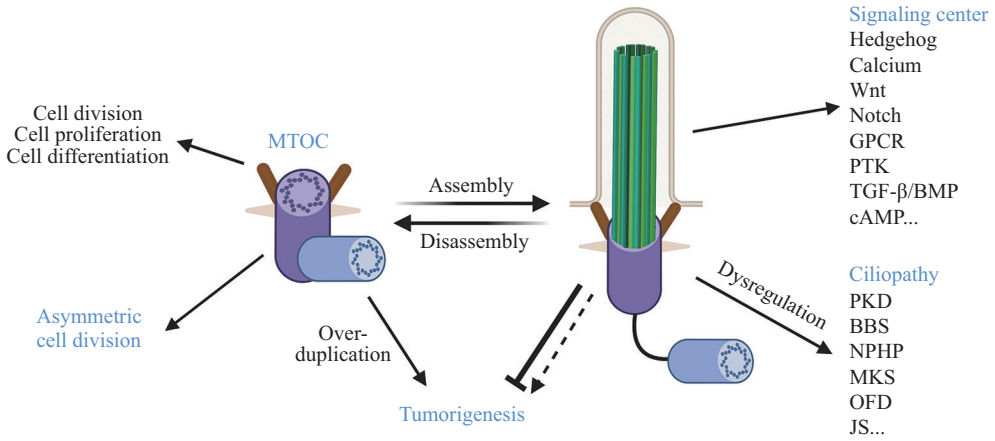
中心体和初级纤毛介导细胞内大量生命活动, 本文将选择性地对中心体作为微管组织中心、调控干细胞不对称分裂, 以及初级纤毛作为信号中心的功能作介绍。进一步我们讨论了它们的异常在肿瘤和纤毛病中的调控(图3)。

2.1 中心体的功能

2.1.1 *中心体是微管组织中心* 中心体作为微管组织中心在细胞分裂、增殖和分化中起重要的作用, 对于个体发育至关重要[72]。在间期细胞中, 中心体作为微管组织中心, 对于细胞微管骨架的构建具有重要影响, 调控细胞形状以及细胞运动。中心体调控微管的数量、稳定性、极性和空间分布, 结合马达蛋白的运动方向, 决定细胞内部大量物质的运输。近期发现中心体还可以作为微丝组织中心, 而聚合态的微丝可以拮抗微管的组装[73-74]。

在细胞分裂期, 中心体会迁移到细胞的两极形成纺锤体。纺锤体是主要由微管组成的结构, 微管一端连接中心体, 另一端连接着染色体的动粒(kinetochore)。中心体微管组装的动态变化确保了染色体携带的遗传物质能够准确、对称地被分配到两个子细胞中。在有丝分裂后期, 纺锤体微管会逐渐缩短, 将姊妹染色单体拉向细胞的两极。这个过程对于染色体的准确分离至关重要, 而如果这个过程发生错误, 可能会导致细胞凋亡或者突变而致癌[75]。

2.1.2 *中心体调控干细胞不对称分裂* 在增殖细胞中, 中心体在S期之前或开始时进行复制, 形成两



中心体和初级纤毛的功能是多样的, 本文总结了中心体作为微管组织中心的功能, 并重点讨论了中心体在特定干细胞不对称分裂中的作用。初级纤毛是一个信号中心, 其异常会引起多种纤毛病。中心体过度复制导致肿瘤发生, 而初级纤毛可能抑制或者促进肿瘤发生。纤毛介导的信号包括Hedgehog、钙、WNT、Notch、GPCR、RTK、TGF-β/BMP、cAMP等; 纤毛病包括PKD、BBS、NPHP、MKS、OFD、JS等。

The functions of the centrosome and the primary cilium are diverse. This article summarizes the function of the centrosome as a MTOC (microtubule organizing center) and focuses on the role of the centrosome in asymmetric division of specific stem cells. The primary cilium is a signaling center, and its dysregulation causes various ciliopathies. Centrosome overduplication leads to tumorigenesis, while the primary cilium may either inhibit or promote tumorigenesis. Cilia-mediated signaling includes Hedgehog, calcium, WNT (wingless-type), Notch, GPCR (G-protein coupled receptor), RTK (receptor tyrosine kinase), TGF-β/BMP (transforming growth factor-β/bone morphogenetic protein), cAMP, etc. Ciliopathies include PKD (polycystic kidney disease), BBS, NPHP (nephronophthisis), MKS (Meckel syndrome), OFD (oral-facial-digital syndrome), JS (Joubert syndrome), etc.

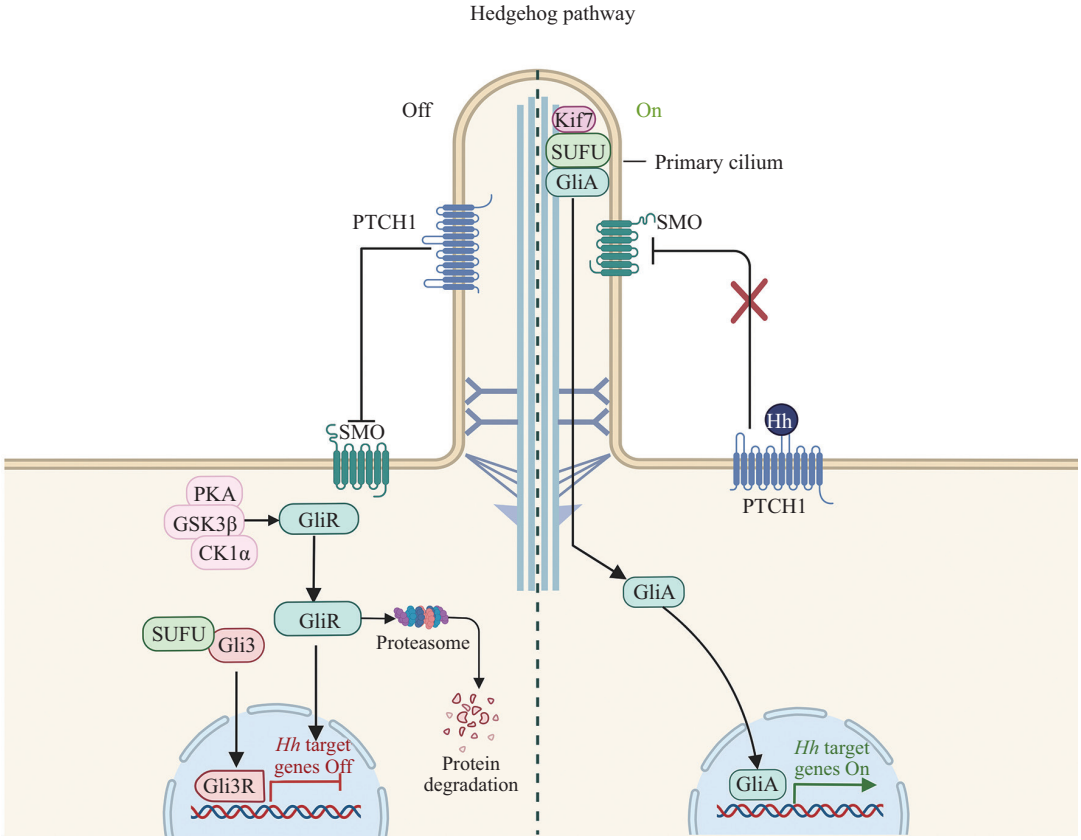
图3 中心体和初级纤毛的功能

Fig.3 Functions of centrosomes and primary cilia

个新的中心体。中心体的复制过程确保了在有丝分裂期间, 每个子细胞都能获得一个完整的中心体对, 从而保证了细胞分裂的正确进行[75]。每个中心体由两个中心粒组成, 一个是成熟的母中心粒, 另一个是在细胞周期中新组装的未成熟的子中心粒, 亲代的母中心粒和子中心粒分别复制形成两个中心体。在细胞分裂过程中, 亲代母中心粒组装成的中心体能够吸引更多的胞内组分, 在形成纺锤体时往往表现出更强的微管组织能力, 通过这种机制, 细胞可以在分裂过程中实现不对称性[76]。干细胞可以通过对称分裂进行自我更新, 也可以通过不对称细胞分裂产生两个具有不同细胞分化命运的子细胞, 这两种分裂形式之间的平衡对于维持组织稳态至关重要, 而在干细胞不对称分裂中, 往往子代干细胞获得亲代母中心粒复制产生的中心体。小鼠皮层放射状胶质祖细胞中心体与顶端膜的锚定对于不对称分裂和皮层的形成至关重要[77], 分裂后子代干细胞获得母中心粒而分化的细胞获得子中心粒[78]; 在整个有丝分裂过程中, 母中心粒附着残留的纤毛膜组分, 可以在子细胞中快速起始初级纤毛组装[79]。类似地, 人前脑类器官模型也证实子代能自我更新的神经前体细胞更倾向获得母中心粒[80], 同样鼠胚胎干细胞不对称分裂也是干细胞获得母中心粒[81]。但目前也发现一些反例, 如小鼠脑颗粒神经元前体细胞不对称分裂中母子中心粒的差异似乎并不影响子代细胞的命运[82]。

2.2 初级纤毛是一个信号中心

初级纤毛是细胞的一个信号中心, 能够接收环境中的多种信号, 并将其传递到细胞内部, 能协调各种信号通路, 包括Hh(Hedgehog)(图4)、钙信号、Wnt(wingless-type)、Notch、GPCR(G-protein coupled receptor)、RTK(receptor tyrosine kinase)和TGF-β/BMP(transforming growth factor-β/bone morphogenetic protein)信号通路等[83-84], 这里选择性地介绍。



Hh配体释放PTCH1对SMO的抑制作用, 从而诱导SMO转位到纤毛, 进而导致Gli激活子(GliA)启动*Hh*基因的表达。反之, 没有Hh配体时, 细胞则产生Gli抑制子(GliR)关闭Hh信号。详见文字描述。

Hh ligand releases the inhibition of PTCH1 on SMO, thereby inducing SMO to translocate to the cilium, and then causing Gli activator (GliA) to initiate *Hh* gene expression. Conversely, in the absence of Hh ligand, Gli repressor (GliR) is produced to shut down Hh signal. See text for details.

图4 初级纤毛控制Hedgehog信号

Fig.4 Primary cilia control Hedgehog signaling

2.2.1 纤毛调控Hedgehog信号 纤毛介导的Hh信号通路是在发育过程中用于细胞间通信的关键信号通路之一, 对细胞的增殖、分化和命运决定, 以及器官的发育、体内平衡和再生都至关重要。例如初级纤毛调控成肌细胞和肌肉干细胞Hh信号以及肌肉分化过程[85-86], 初级纤毛和Hh还调控成体神经干细胞的形成[87], 通过促进对称分裂扩增神经前体细胞库[88]。近期一项研究发现大脑视交叉上核初级纤毛的节律变化介导了Hh通路的节律变化, 并决定了该区域神经元的同频共振[89]。

脊椎动物的Hh信号通路依赖于初级纤毛(图4)[90-91], 主要是通过其受体PTCH1(patched 1)和跨膜蛋白SMO(smoothened)来调节转录因子Gli(glioma-associated oncogene homolog)的[92]。纤毛是产生Gli抑制子(Gli repressor, GliR)和Gli激活子(Gli activator, GliA)的地方[93]。在没有Hh配体(如Shh)的情况下, PTCH1受体定位于初级纤毛, 可以阻止SMO积累在纤毛且抑制SMO活性。数个蛋白激酶能磷酸化Gli2/3, 导致全长Gli2/3剪切为截短形式并作为*Hh*靶基因(如*Gli1*)表达的阻遏物, 即GliR。在存在Hh配体的情况下, Hh配体与PTCH1结合, 解除了PTCH1对SMO的抑制作用, 导致了SMO在纤毛上的积累和激活, 形成了Gli2/3激活态形式(GliA), 然后GliA迁移到细胞核并激活了靶基因的表达[94]。SUFU(suppressor of fused homolog)是Hh信号通路的一个负调控因子, 可以通过与细胞质中的Gli3结合并促进Gli3R的加工[95]。此外, GPR161(G-protein coupled receptor 161)通过在纤毛内产生cAMP从而抑制Hh信号通路, 而Hh配体可通过SMO将其移除纤毛[96]。

2.2.2 纤毛与钙信号 在胚胎发育过程中, 纤毛在一小群被称为左右组织者(left-right organizer, LRO)的细胞中起到关键作用, 并能感受液体流动, 但液体流动决定胚胎左右不对称性的机制是长久以来存在争议且尚未解决的问题[97-98]。初级纤毛与钙信号以及机械感受的关系存在较大争议[99-100], 但直到最近, 两项研究结合光镊和先进成像技术, 在小鼠和斑马鱼中揭示LRO左侧的初级纤毛是一种机械感受器, 能感受胞外的液体流动并将其转变成钙信号, 并建立胚胎期的左右不对称性[101-102]。PKD2(polycystic kidney disease 2 protein)是一种存在于所有LRO纤毛的蛋白, 这种机械感应能力与之有关。初级纤毛还能介导其他方式的钙信号调节, 例如γ-氨基丁酸(γ-aminobutyric acid)受体$GABA_{B1}$是一种定位于胰岛β细胞初级纤毛上的GPCR, 通过激活电压依赖的钙通道促进钙离子内流[103]。

2.2.3 纤毛参与Wnt等其他信号调节 Wnt信号通路可以分为经典和非经典Wnt信号通路, 初级纤毛可能介导两者的平衡。多种Wnt通路核心组分被发现存在于纤毛, 证实初级纤毛可以介导Wnt信号[104]。一些研究认为纤毛抑制经典Wnt信号通路。NPHP2(Nephrocystin-2)被发现能抑制DVL1(dishevelled homolog 1)介导的Wnt激活[105], 另外小鼠纤毛基因*Kif3A*的缺陷导致初级纤毛丢失并增强了Wnt3A配体的敏感性[106]。另有研究则认为初级纤毛不影响小鼠胚胎的经典Wnt通路[107]。纤毛和Wnt的调控关系在果蝇、斑马鱼等其他物种中也有研究, 但它们的联系仍存在争议。

初级纤毛还介导了其他信号通路的调控。在胚胎期皮肤发育过程中, 表皮的纤毛能激活Notch信号, 从而平衡细胞增殖和分化过程[108]; 角膜上皮细胞中的纤毛也可通过Notch信号维持细胞增殖[109]。另外, 初级纤毛还参与其他GPCR、RTK、TGF-β/BMP信号通路来调节细胞功能。近期发现脑干血清素能的轴突和海马CA1区锥体神经元的初级纤毛能形成一种新的突触, 而纤毛上的5-羟色胺受体可能介导非经典$G_{\alpha q/11}$-RhoA信号通路改变染色体开放状态[110]。ω-3脂肪酸可以通过激活定位于前脂肪细胞初级纤毛上的FFAR4(free fatty acid receptor 4), 激活纤毛内cAMP的产生来触发有丝分裂和脂肪形成[111]。值得注意的是, 只有纤毛内而不是细胞质产生的cAMP才能抑制Hh信号, 这个过程依赖于PKA[112]。

3 中心体、初级纤毛和疾病

3.1 中心体、初级纤毛与肿瘤

中心体在细胞生命活动中起着重要作用。如果中心体丢失或功能异常, 则可能会引发一系列的细胞功能障碍和疾病。在正常情况下, 中心粒的数量在细胞中受到严格控制, 但在肿瘤中常常发生异常[17]。中心粒复制失控导致细胞内中心粒数量超过正常值, 从而引发细胞周期紊乱和染色体不稳定。癌细胞有丝分裂常表现为中心粒数量增多伴随的多极纺锤体或异常双极纺锤体形成, 这可能是由于中心粒过度复制、有丝分裂失败以及细胞异常融合等

多种因素导致的[113]。研究揭示, 中心体数量的过度增加导致细胞分裂时染色体的错误分离和染色体不稳定性[114]。中心体异常, 特别是中心粒过度复制, 不仅是肿瘤发生的副产物, 而且在促进和加速肿瘤进展中起直接作用[115-116]。近期发现, 抑制PLK4或中心粒复制因子可以选择性靶向TRIM37(tripartite motif-containing protein 37)高表达的乳腺癌细胞, 此过程能作为潜在的治疗手段[117-118]。

初级纤毛可以通过调节细胞周期、细胞增殖、细胞凋亡等方式影响细胞的生长和分化[119], 其还能通过调节信号通路等影响肿瘤细胞的转化。在许多类型的癌症如肾癌、肠癌、卵巢癌等中, 相比周围健康细胞而言, 癌细胞中总会明显缺乏初级纤毛结构, 因此纤毛发生障碍一般被认为是癌症发生的先决条件。初级纤毛需在有丝分裂前去组装, 而癌细胞中纤毛的丢失可能激活了一些细胞增殖相关信号[120]。EZH2(enhancer of zeste homolog 2)在黑色素瘤中高发扩增, 进一步促进纤毛的丢失, 并增强Wnt/β-catenin信号及促进黑色素瘤发生[121]。根据肿瘤起始因素, 初级纤毛可能通过激活或者抑制Hh信号来促进或抑制肿瘤发生[122-123]。近期在Notch1过表达的脉络膜瘤模型中也发现初级纤毛可能通过激活Hh信号促进细胞增殖和肿瘤发生[124]。总之, 初级纤毛在肿瘤发生中的作用是复杂且多样的。

3.2 纤毛病

纤毛普遍存在于人体细胞中, 纤毛相关基因突变、纤毛的结构或功能缺陷导致的器官病变, 从而引起的疾病被称为纤毛病(ciliopathy)。纤毛病患者常表现出肝肾囊肿、内脏异位、嗅觉或听觉缺陷、肥胖、不育不孕、智力障碍、复发性呼吸道感染和骨骼异常等临床症状。结合人类遗传学的研究, 细胞和模式生物中的突变体表型分析和遗传筛选也为我们理解纤毛缺陷的生物学功能以及纤毛病的发病机理提供了重要参考[90,125-127]。目前已经发现的纤毛病超过40种, 涉及的致病基因超过300个[9,84]。

多囊肾病(polycystic kidney disease, PKD)典型特征为肾脏内形成许多囊肿, 并可分为常染色体显性遗传性多囊肾病(autosomal dominant PKD, ADPKD)和常染色体隐性遗传性多囊肾病(autosomal recessive PKD, ARPKD)[128]。大多数ADPKD患者有*PKD1*或*PKD2*基因突变, 这两个基因分别编码PC-1(polycystin 1)和PC2(polycystin 2)[129]。PC1和PC2在初级纤毛上可以形成同源或异源二聚体, 对于初级纤毛感受液体流动至关重要。ARPKD比ADPKD要少见, 被认为主要是由*PKHD1*(polycystic kidney and hepatic disease 1 protein)或*DZIP1L*(DAZ-interacting zinc finger protein 1-like)基因突变导致的。*PKHD1*基因编码纤维囊肿蛋白[(fibrocystin), 也称多管蛋白(polyductin)], 是一种定位于初级纤毛和基体的单通道跨膜蛋白[130]。DZIP1L蛋白是一种可溶性锌指蛋白, 定位于基体和纤毛过渡区, 对于PC1和PC2转位到纤毛是必需的[131]。

BBS因医生Bardet和Biedl描述该遗传症状而得名, 主要表现为视觉低下、多指(趾)畸形、肥胖、肾异常、智力落后等, 为常染色体隐性遗传。目前已至少鉴定出22个BBS的致病基因, 主要为纤毛蛋白, 包括BBSome复合体亚基、IFT-B亚基[132]、纤毛过渡区蛋白[133]等。

还有一些其他纤毛病包括肾消耗病(nephronophthisis, NPHP)[134]、朱伯特综合征(Joubert syndrome, JS)[135]、梅克尔综合征(Meckel syndrome, MKS)[136]和口–面–指综合征(oral-facial-digital syndrome, OFD)[137]等。纤毛病的遗传致病原因以及发病机理有待挖掘, 而纤毛病的临床干预手段目前仍然十分有限且需要进一步探索。

4 展望

中心体和初级纤毛是细胞的关键组成部分, 我们期待未来针对该超微结构取得更多的突破。

4.1 显微结构的精细分辨

近年来超分辨成像[138]、冷冻电镜[139]等技术的发展大大加深了我们对中心体和纤毛在亚细胞甚至原子水平的理解, 中心体和纤毛的超精细结构以及这些精细结构的动态变化仍值得进一步探索。

4.2 中心体和纤毛的组成解析及调控机制

我们需要清晰知道中心体和纤毛的蛋白组成, 更好了解中心体和纤毛的基础生物学调控机制和功能。之前有一些蛋白组学的研究以及基于功能基因组学的筛选探索, 但仍不完全, 特别是纤毛膜蛋白的鉴定仍有较大探索空间, 有助于我们明确纤毛介导的信号和功能。

4.3 中心体和纤毛的生理调控和功能

中心体是多样的, 纤毛更是多样的。不同细胞、组织、器官、物种中它们的结构、装配过程和功能

都不同, 在生理水平上这些差异的决定机制和功能效应有较大空白。例如在小鼠脑室管膜多纤毛内存在大量核糖体和翻译因子, 这样微管蛋白等蛋白质能在纤毛内被活跃翻译[140], 其他类型的纤毛是否存在类似机制仍待探索。最近发现在斑马鱼和小鼠生殖细胞减数分裂过程中, 存在一种偶线期纤毛可能介导染色体组装和遗传重组[141-142]。

4.4 中心体和纤毛的病理调控和功能

我们仍然知之甚少, 例如中心体和纤毛与癌症的关系仍充满争议且不清晰。另外, 同种纤毛基因的突变为什么可能导致不同的纤毛病？这些不同基因突变可能产生特定的生物学效应。近期以线虫为主要模型, 发现DYF-5激酶持续活化型突变反而导致与DYF-5缺失类似的纤毛缺陷表型, 这依赖于RNA编辑介导的蛋白翻译抑制[143]。

4.5 靶向中心体和纤毛相关蛋白的临床药物

一方面, 在基础研究中亟需更加深入解析其中的调控机制, 并明确潜在靶点; 另一方面, 需开展相应的临床前和临床研究, 以探索中心体和纤毛作为临床诊断、预防和治疗的潜在可能。

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