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驱动蛋白超家族在多种疾病的发生和发展中的作用

杨文星[1*], 刘鹤[1], 王力[2], 朱元军[3*]

1. Department of Organismic and Evolutionary Biology, Center for Brain Science, Harvard University, Cambridge MA02138, USA;
2. Department of Anesthesiology and Perioperative Medicine, University of Texas MD Anderson Cancer Center, Houston TX77030, USA;
3. 北京大学药学院分子与细胞药理学系, 北京 100191

* 联系人, E-mail: wenxingyang@fas.harvard.edu; zhuyuanjun@bjmu.edu.cn

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摘要 细胞内物质运输是细胞发挥正常生物学功能的基础. 驱动蛋白可作为运送细胞内物质的载体, 通过与不同的骨架蛋白结合以识别不同的分子货物, 从而参与这些分子货物下游的生物学效应. 没有运输活性的驱动蛋白也可以通过其自身对某些分子信号通路的调节而发挥其功能. 大量研究表明, 驱动蛋白广泛地参与了多种疾病的发生发展过程, 如神经性疾病、代谢性疾病、肾病、癌症等. 本文将对近年来诸多关于驱动蛋白与疾病的研究进行综述.

关键词 驱动蛋白, 细胞内物质运输, KIF, 分子马达, 微管

驱动蛋白超家族(kinesin superfamily proteins, KIFs)是一类分子马达, 在细胞内负责沿着微管, 向其正极运送不同的分子货物, 如蛋白质、细胞器、RNA等[1]. 1985年, Hirokawa等人[2]首次通过高精度显微技术(快速冷冻深度蚀刻)观察到在微管和细胞器之间有一些链接结构. 这些链接结构后来被证实可能是负责细胞内运输的分子马达蛋白, 如驱动蛋白(kinesin)、动力蛋白(dynein)、肌球蛋白(myosin)等. 驱动蛋白与其他的分子马达一起, 在细胞水平发挥运输工具的作用, 以微管等细胞骨架为依托, 将不同的分子货物运送到指定的细胞内位置, 从而发挥其生物学作用[3]. 因此, 驱动蛋白及其参与的细胞内物质运输对维持细胞的基本功能起到极其重要的作用[1]. 本文将着重综述驱动蛋白在多种疾病发生和发展过程中的作用.

1 驱动蛋白

就其结构而言, 驱动蛋白通常具有一个分子货物结合域和分子马达结构域. 分子货物结合域, 通过其自身或与其他连接蛋白(adaptor protein)或骨架蛋白(scaffold protein)形成特殊的结构, 识别不同的分子货物, 并与之结合(图1)[4~7]. 而分子马达结构域则通过水解三磷酸腺苷(adenosine triphosphate, ATP)获得能量, 带动驱动蛋白自身及与其结合的分子货物沿着细胞骨架运输. 1985年, Vale等人[8]首次命名驱动蛋白至今, 研究者已发现数10种驱动蛋白[1]. 这些驱动蛋白可根据其分子马达结构域位于蛋白的氨基端(N-terminal)、羧基端(C-terminal)或中间, 而分为3类[9]. 亦可根据其功能的不同分为常规的驱动蛋白(conventional kinesin)和非常规的驱动蛋白(unconventional kinesin). 前者具有明显的细胞内物质运输活性, 如KIF1A[10], KIF5B[11]等; 而后者则与之相反, 不具备ATP酶活性, 不能起到细胞内物质运输的作用, 如KIF26A[12]等.

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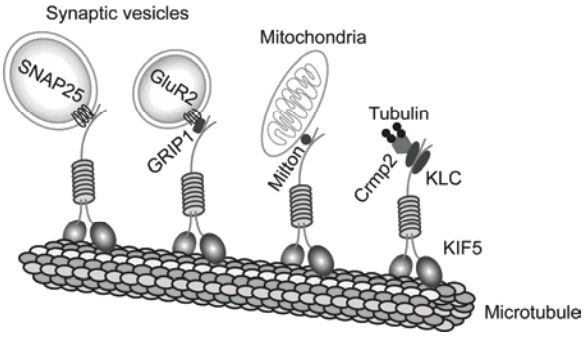

图 1 KIF5 与不同分子货物的结合. KIF5 可以直接识别突触小泡(synaptic vesicle)上的SNAP25, 可以通过GRIP1 识别突触小泡上的GluR2 受体, 可以通过Milton结合并运输线粒体(mitochondria), 还可以通过驱动蛋白轻链(kinesin light chain, KLC)与Crmp2 结合, 由此运输与后者结合的微管蛋白(tubulin)二聚体

Figure 1 Binding between KIF5 and its different cargos. KIF5 can directly recognize SNAP25 on the synaptic vesicles, and recognize GluR2 receptor on the synaptic vesicles via GRIP1, and bind with Milton to transport mitochondria, and form complex with kinesin light chain and Crmp2 to transport tubulin dimer

2 驱动蛋白与神经退行性疾病

2.1 阿尔茨海默症

阿尔茨海默症(Alzheimer's disease), 俗称早老性痴呆, 是一种主要危害老年人的神经退行性疾病[13]. 65岁以上的老人中, 有6%患有阿尔茨海默症, 并且该病发病率伴随年龄的增加呈上升趋势[14]. 阿尔茨海默症的一个主要发病机理在于β-淀粉样肽(amyloid β peptides, Aβ)的产生和过度沉积; 沉积的β-淀粉样肽形成斑块, 对神经元产生毒性作用而引起退行性的脑功能障碍[15~17]. β-淀粉样肽是由淀粉体前体蛋白(amyloid precursor protein, APP)经酶裂解后产生. APP广泛分布于多种组织的细胞膜中, 其生物学作用还有待进一步阐明[18]. APP可通过骨架蛋白c-Jun氨基末端激酶相互作用蛋白1 (c-Jun N-terminal kinase-interacting protein 1, JIP1)和驱动蛋白轻链(kinesin light chain, KLC)与KIF5结合, 在细胞内沿轴突运输[19,20]. 因此, APP的轴突运输又受到JIP1的严格调控[21]. APP可作为受体参与β-分泌酶(β-secretase)和早老素(presenilin-1)的轴突运输[22], 后两者与Aβ的形成紧密相关. 由此可推测, KIF5的缺陷可能引起APP的轴突运输异常, 从而导致Aβ在特定位置的堆积, 由此参与阿尔茨海默症的发生. 另外, Aβ堆积导致阿尔茨海默症的过程也与驱动蛋白相关. Ari等人[23]发现, Aβ或kinesin 5 (Eg5, KIF11)抑制剂, 或过表达APP均可减少细胞表面的神经生长因子/神经营养因子受体(nerve growth factor/neurotrophin receptor, NGF/NTR] p75和*N*-甲基-*D*-天门冬胺酸(*N*-methyl-*D*-aspartate, NMDA)受体. 这些实验说明, Aβ可以通过抑制kinesin 5, 降低神经营养因子和神经递质受体向细胞表面的运输, 而阻断特定的神经功能. 这些发现进一步证明阿尔茨海默症的认知障碍可能部分源于Aβ对神经元kinesin 5的抑制. 因此预防Aβ对kinesin 5或其他驱动蛋白的抑制, 可能成为治疗阿尔茨海默症的一种新方案.

2.2 亨廷顿舞蹈症

亨廷顿舞蹈症(Huntington's disease)是一种常染色体显性的遗传性神经退化疾病. 严重的病患可发生痴呆, 甚至死亡. 即使亨廷顿舞蹈症相关基因*HTT* (*huntingtin*)发生单突变, 患者中年也会100%出现病症. 研究表明, 突变的*HTT*可以通过激活轴突内c-Jun氨基末端激酶(c-Jun N-terminal kinase, JNK), 而抑制神经细胞内的快速轴突运输. *HTT*对快速轴突运输的抑制作用是由神经元特异性的JNK3来实现的. JNK3可以磷酸化驱动蛋白kinesin 1分子马达结构域内176位上的丝氨酸残基, 导致后者空间构象发生改变, 从而降低其与微管的结合能力, 最终影响快速轴突运输[24]. 此外, 与*HTT*广泛分布于人体各处相异, HTT结合蛋白1 (huntingtin-associated protein 1, HAP1)富集于神经元内, 提示它的异常可能参与亨廷顿舞蹈症的发生. 研究表明, HAP1可与KLC直接结合, 并共表达于神经元生长锥. 抑制HAP1表达, 可以抑制PC12细胞神经突起的生长, 进而抑制驱动蛋白依赖性的细胞内转运机制[25]. 这可能是亨廷顿舞蹈症的另一机制.

3 驱动蛋白与糖尿病

随着生活水平的提高, 糖尿病的发病率逐渐升高. 我国成年人糖尿病发病率已高达11.6%, 对于糖尿病的预防和治疗, 已成为一个受关注的公共健康问题[26]. 糖尿病主要分为Ⅰ型和Ⅱ型. Ⅰ型糖尿病多由遗传因素引起, Ⅱ型糖尿病多由后天形成. 糖尿病早期表现为胰岛素分泌升高. 长期的高胰岛素刺激, 会逐渐导致患者机体对胰岛素不再敏感, 进而出现高胰岛素、高血糖的症状. 终末期患者的胰岛细胞因为长期高强度的工作而逐渐出现功能异常, 胰岛细

胞分泌胰岛素的能力大幅下降，胰岛功能逐渐丧失[27]. 因此，对于糖尿病的研究也主要集中在两个方面：刺激胰岛素分泌和降低胰岛素抵抗(胰岛素耐受). 最新研究表明，胰岛β细胞内高表达了一种驱动蛋白KIF12[28]. KIF12可以与热休克蛋白70 (Hsc70)及其转录因子Sp1形成三聚体，从而稳定新生成的Sp1免于蛋白降解. 由此Sp1维持Hsc70的表达，进而维持正常的过氧化物酶体功能，降低细胞内氧张力，维护β细胞分泌胰岛素的功能[28]. 而在*KIF12*基因敲除小鼠(*Mus musculus*)内，Hsc70表达下降，过氧化物酶体内的蛋白转运机制失调，导致细胞水解氧自由基的能力下降，造成细胞内氧张力升高，最终损害β细胞功能，导致胰岛素分泌异常[28]. 另外，高脂饮食可以显著降低胰岛β细胞内的*KIF12*的表达. 因此，无论是先天性的KIF12表达异常，还是后天因高脂饮食引起KIF12的表达异常，都有可能通过上述机制而引起糖尿病[28]. 因此由KIF12介导的抗氧化通路，可能参与了特定的Ⅰ型及Ⅱ型糖尿病的发生，可作为治疗糖尿病的新靶点[28].

在β细胞内，胰岛素颗粒形成于反式高尔基体网络(*trans*-golgi network)，再由驱动蛋白超家族成员kinesin-1 (如KIF5B等)沿着微管进行细胞内的长距离运输，直至运送至临近浆膜的细胞边缘区域[29,30]. 在此区域内有密集的微管分布，诺考达唑(nocodazole)引起的微管解聚几乎完全阻断了β细胞内胰岛素颗粒的方向性运输，进一步说明kinesin-1依托微管转运胰岛素颗粒[31]. Cui等人[32]发现*kif5b*敲除并未改变小鼠胰岛形态、胰岛细胞组成和β细胞大小，但其胰岛体积缩小、胰岛数量增加，并伴随β细胞内胰岛素颗粒增加. *kif5b*敲除小鼠不仅生长缓慢，还呈现出高血糖症状. 这些小鼠在糖耐受实验中表现出明显的糖耐受性，这种糖耐受源于胰岛素分泌障碍而非胰岛素抵抗. KIF5B还参与了胰岛素诱导的葡萄糖转运子蛋白4 (glucose transporter type 4, GLUT4)的运输，从而参与由胰岛素调节的糖代谢过程[33~35]. 此外，长期的高糖处理可以改变海马细胞及视网膜细胞的KIF1A和KIF5B的表达水平，由此提示驱动蛋白还可能参与了糖尿病引起的神经病变[36,37]. 这些体内体外的实验证明，驱动蛋白广泛地参与了胰岛素的生成、转运和分泌及糖代谢，由此提示驱动蛋白和糖尿病的发生、发展有着紧密的联系.

4 驱动蛋白与肾病

前期研究表明，KIF3A和多囊肾的形成有关[38]. 特异性地敲除肾脏的KIF3A可使小鼠在出生后5 d就发生肾脏纤毛的丧失和肾内囊泡的形成，在出生后21 d出现肾功能衰竭. 该小鼠肾囊泡上皮细胞缺乏初级纤毛，呈现出高于正常水平的细胞分化和细胞凋亡、异位表达的表皮生长因子受体、升高的β链蛋白(β catenin)和c-Myc表达等. 这些结果尚不能明确地解释KIF3A如何诱导多囊肾的发生，但至少表明初级纤毛在多囊肾的形成中发挥重要作用[38]. Duangtum等人[39]研究表明，人肾阴离子交换蛋白1 (human kidney anion exchanger 1, kAE1)和KIF3B共表达于人肾组织，并通过其羧基端的双亮氨酸基序(dileucine motif)与KIF3B结合. 在HEK293T细胞中，抑制KIF3B可抑制细胞膜上的kAE1含量，从而引起细胞内kAE1的堆积. 这些结果提示，KIF3B可能在人肾α闰细胞中负责kAE1向细胞膜的转运，由此参与了远端肾小管性酸中毒(distal renal tubular acidosis)的形成. 本课题组[28]前期实验发现，肾脏高表达了驱动蛋白KIF12. Mrug等人[40]通过对461只多囊肾小鼠的数量性状基因座(quantitative trait loci)的分析发现，KIF12是先天性多囊肾的一个修饰基因(modifier gene)，并受到HNF-1b的调节[41]. 初级纤毛上表达了众多多囊肾相关基因(包括*Cys1*)，因此，KIF12表达于肾脏初级顶纤毛更进一步提示其在多囊肾发生过程中可能发挥着重要作用[42]，但其具体机制尚需进一步研究. 此外，还有研究表明，KIF12与肾脏和泌尿道先天性异常(congenital anomalies of the kidney and urinary tract)的形成有关[43].

5 驱动蛋白与肿瘤发生

很多研究表明，驱动蛋白广泛地参与了多种肿瘤的发生、发展[44]，其表达水平的变化和很多肿瘤的发生、发展有直接关联[45~51]. 所有类型的肿瘤都有一个基本特征就是过度的细胞增殖，后者源于细胞周期失控[45]. 异常的驱动蛋白表达可以通过染色体过度凝集、纺锤体形成异常、细胞分裂缺陷、形成后期桥或非整倍体及有丝分裂阻滞改变细胞内遗传物质的分布；遗传物质的增加或减少都会引起子代细胞的众多功能异常，最终可能渐进性地导致肿瘤发生[52~58].

6 驱动蛋白与其他疾病

6.1 KIF26A与巨结肠

KIF26A不具有ATP酶活性, 是一种非常规的驱动蛋白. Zhou等人[12]研究表明, KIF26A敲除小鼠呈现出巨结肠的表型. 通过对敲除小鼠的分析, 他们发现, 在正常情况下, KIF26A可与肠神经系统中生长因子受体结合蛋白2 (growth factor receptor-bound protein 2, Grb2)结合. 这种结合阻止了Grb2与SHC转化蛋白(SHC-transforming protein 1, SHC)结合, 由此减弱了胶质细胞源神经营养因子-*RET*原癌基因(Glial cell line-derived neurotrophic factor-*RET* proto-oncogene, GDNF-*RET*)信号通路. 在敲除小鼠中, 由于KIF26A的缺失, Grb2与SHC的结合不再受到抑制, 由此激活了其下游的GDNF-*RET*信号通路, 引起肠神经系统的过度生长.

6.2 KIF1B与2A型进行性神经性腓骨肌萎缩症

杂合子的KIF1B (*kif1b*$^{+/-}$)小鼠因丧失转运突触小泡前体(synaptic vesicle precursors)的功能, 导致突触外周的突触小泡前体数量减少, 引起神经元死亡, 而发生CMT (Charcot-Marie-Tooth disease)病, 表现为渐进性的肌无力. KIF1B (*kif1b*$^{-/-}$)敲除神经元的存活能力明显低于野生型的神经元细胞; KIF1Bβ, 而非KIF1Bα, 可以恢复KIF1B (*kif1b*$^{-/-}$)敲除神经元的存活能力. 这些实验结果说明, 相对于KIF1Bα, KIF1Bβ可能在维持神经元存活能力上起到更大的作用. 人KIF1Bβ的Q98L突变可以使KIF1Bβ丧失其分子马达的活性, 并与CMT病在临床上具有直接关联性[59].

7 结语

驱动蛋白广泛地分布于各组织细胞, 对于维持细胞的正常形态和功能发挥重要作用. 因此, 驱动蛋白及其参与的分子机制发生异常, 与很多疾病的发生发展有着直接关联. 经过30年的努力, 对驱动蛋白的功能已经有了很多认识. 与此同时也应看到, 对于完全阐述驱动蛋白的功能, 还需继续努力.

由于驱动蛋白是负责细胞内运输的主要分子马达之一, 很多细胞功能都需要由驱动蛋白来完成, 因此对于特定的细胞, 仅靠一种驱动蛋白, 并不能完成其生物学功能. 例如, 不同的神经元内表达了KIF1A/Bβ[59,60], KIF5A/B/C[36,61,62]等, 肾脏表达了KIF3B[39]和KIF12[28]等, 胰腺表达了KIF5B[32]和KIF12[28]等. 这些具有多种驱动蛋白表达的细胞内, 不同驱动蛋白之间的功能可能具有互补性. 因此, 除了一些遗传性疾病, 很多单基因的驱动蛋白表达异常不能在整体水平引起明显的表型. 因此, 多基因敲除的小鼠可能对进一步分析驱动蛋白的功能有重要意义.

一种驱动蛋白一般可以运送多种不同的分子货物, 但对于分子货物的鉴定具有难度. 由于基因测序技术的发展[63,64], 对于单个驱动蛋白基因敲除的小鼠, 如果结合基因测序的方法, 应该可以知道单个驱动蛋白的敲除可以导致下游哪些蛋白的表达异常. 通过对这些蛋白的功能进行解析, 可能有助于进一步了解驱动蛋白参与的分子机制.

此外, G蛋白在功能上和驱动蛋白有一定的相似性, 两者在发挥功能时都需要消耗生物能. G蛋白水解三磷酸鸟苷(guanosine triphosphate, GTP), 通过激活不同的下游通路、产生第二信使(环腺苷酸(cyclic adenosine monophosphate, cAMP)、肌醇三磷酸(inositol trisphosphate, IP3)和甘油二酯(diacylglycerol, DAG)), 而发挥进一步的生物学效应. 驱动蛋白水解ATP, 将获得的生物能转化为机械能, 从而转运与之结合的分子货物沿着细胞骨架移动. 二者在功能上也有相关性. 驱动蛋白通过转运第二信使下游的结合蛋白[65]或含有第二信使的突触小泡[66,67], 而参与到G蛋白介导的信号通路中. G蛋白偶联受体[68,69]已被作为药物开发的潜在靶点进行广泛研究. 对于与之相关的驱动蛋白的研究, 可进一步深化对某一G蛋白下游通路的认识, 有利于开发精确靶向某一特定G蛋白信号通路的药物, 促进特定疾病的精准治疗.

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Summary for “驱动蛋白超家族在多种疾病的发生和发展中的作用”

The role of the kinesin superfamily proteins in the pathogenesis and progression of multiple diseases

YANG WenXing[1*], LIU He[1], WANG Li[2] & ZHU YuanJun[3*]

[1] *Department of Organismic and Evolutionary Biology, Center for Brain Science, Harvard University, Cambridge MA02138, USA;*
[2] *Department of Anesthesiology and Perioperative Medicine, University of Texas MD Anderson Cancer Center, Houston TX77030, USA;*
[3] *Department of Molecular and Cellular Pharmacology, School of Pharmaceutical Sciences, Peking University, Beijing 100191, China*
* Corresponding authors, E-mail: wenxingyang@fas.harvard.edu; zhuyuanjun@bjmu.edu.cn

Intracellular transportation serves as the basis of various cell functions. As the molecular motors responsible for the intracellular transportation, kinesin superfamily proteins (KIFs) recognize diverse molecular cargos, such as proteins, organelles, synaptic vesicles, and RNA granules, via their unique binding structures. KIFs have motor domain, which usually convey ATPase activity. KIFs gain energy from ATP hydrolysis, and transport their cargos moving along the microtubules, thus play important role in biological processes of those cargos. KIFs can be divided into 3 classes, according to the motor domain location on the N-terminal, the C-terminal or the middle of the proteins. Meanwhile, some KIFs lack motor function, which can still play important roles by regulating certain molecular pathways, through their binding proteins. Abundant evidence has shown that the KIFs are widely involved in the pathogenesis and progression of many diseases, such as neuronal diseases, metabolic diseases, kidney diseases, etc. In the present review, we summarize recent research findings which explore the relationship between the KIFs and the diseases.

Amyloid β peptides (Aβ) drives Alzheimer’s disease and is derived from the amyloid precursor protein (APP). APP is transported by binding with KIF5 through c-Jun N-terminal kinase-interacting protein 1 (JIP1) and kinesin light chain (KLC) in the axons. APP can also function as a receptor for the transportation of β-secretase (BACE1) and PS1. Thus, the dysfunction of KIF5 may impair the axonal transport of APP, induce the accumulation of Aβ, lead to Alzheimer’s disease.

Huntingtin mutation can suppress the fast axonal transport by activating axonal c-Jun N-terminal kinase (JNK). Huntingtin-associated protein 1 (HAP1) is enriched in the neurons, which directly binds with KLC *in vitro*, and colocalizes with KLC in growth cones of the neurons. Knocking down HAP1 suppresses neurite outgrowth of PC12 cells, and inhibits the kinesin-dependent transport of APP vesicles. This may serve as a pathological mechanism of Huntington’s disease.

KIF12 forms a complex with Hsc70 and Sp1, and maintains the proper expression of Hsc70 through a transcriptional mechanism in pancreatic beta cells. Defect in KIF12, either by knockout or high fat diet intake, can reduce the expression of Hsc70, and impair the peroxisomal targeting of anti-oxidative enzymes, lead to the increase of intracellular oxidative stress. Abnormal accumulation of oxidative stress eventually impairs the insulin secretion of the beta cells, and facilitates diabetes progression. In addition, KIF5B knockout mice shows glucose tolerance and hyperglycemia, which is caused by impaired insulin secretion.

Mice, with tissue-specific knockout of KIF3A in renal tubular epithelial cells, begin to develop cysts in the kidney at postnatal day 5 and show renal failure by postnatal day 21, suggesting the association of KIF3A with polycystic kidney disease. Human kidney anion exchanger 1 (kAE1) binds with KIF3B through its C-terminal dileucine motif, and co-expresses with KIF3B in human kidney. Suppressing KIF3B in HEK293T cells results in the reduction of kAE1 on the cell membrane and the accumulation of kAE1 in cytoplasm. These findings suggest that KIF3B may be responsible for the transportation of kAE1 towards the membrane, thus involve in the pathogenesis of distal renal tubular acidosis.

It is well accepted that KIFs serve as one of the bases for the intracellular transportation. Although they have been widely studied, their functions are still largely unknown. Usually multiple KIFs are expressed in one cell. Their functions may be distinct or overlapping with each other. Therefore, double, even triple, knockouts of these KIFs in specific tissues may help us to further explore their biological functions. In addition, next generation sequencing is highly developed in recent years. It must be informative using this novel technique to analyze the kinesin knockout mice for identifying more cargos.

kinesin, intracellular transport, KIF, motor protein, microtubule

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