刘佳佳, 中国科学院遗传与发育生物学研究所研究员, 博士生导师。于1991年获得武汉大学学士; 1994年获得中国科学院上海细胞生物学研究所硕士; 2000年获得芝加哥大学分子遗传及细胞生物学博士; 2000~2005年在斯坦福大学医学中心神经科学系从事博士后研究。2006年入选中科院“百人计划”。2013年获“国家杰出青年基金”资助及中国科学院优秀导师奖。刘佳佳团队的研究主要以培养细胞系、原代神经元以及小鼠为模型, 运用细胞生物学、生物化学、分子遗传学及影像学等多种研究方法, 探讨细胞内dynein-dynactin驱动的囊泡运输调控机制。此外, 还通过对于目标基因敲除小鼠的表型分析, 深入探讨神经元中膜运输及细胞骨架重塑调控神经发育与突触可塑性的作用机制及相关人类疾病的致病机理。

http://www.genetics.ac.cn/expert/liujiajia.htm

神经元细胞器和囊泡运输

刘佳佳*

(中国科学院遗传与发育生物学研究所, 分子发育生物学国家重点实验室, 北京 100101)

摘要 神经元是高度极化的细胞, 典型的神经元由胞体、轴突及树突构成。神经元的胞体和神经末梢之间的物质和信息传递以及神经元之间的通讯都依赖于胞内的细胞器和囊泡运输。神经元中的运输系统对于神经元形态和功能的建成和维持以及突触的功能和可塑性至关重要。胞内运输的调控机制是细胞神经生物学领域的重大科学问题。该文重点总结了近年来关于神经元内细胞器和囊泡运输的研究进展, 并对神经活性依赖的运输调控机制进行了初步探讨。此外, 该文还简要介绍了神经元胞内运输与人类疾病之间的关系。

关键词 神经元; 细胞骨架; 马达蛋白; 细胞器; 轴突运输; 树突运输

Organellar and Vesicular Transport in Neurons

Jia-Jia Liu*

(*State Key Laboratory for Molecular Developmental Biology, Institute of Genetics and Developmental Biology, Chinese Academy of Sciences, Beijing 100101, China*)

Abstract Neurons are highly polarized cells. A typical neuron is compartmentalized into an axon, several dendrites and cell body or soma. Intracellular transport is essential for the establishment and maintenance of the structural and functional polarity as well as synaptic transmission and plasticity. How the transport machinery is regulated to accommodate the needs of neuronal cells is a fundamental question in the field of neuronal cell biology. This review focuses on molecular motor-driven organellar and vesicular transport in neurons, and regulatory

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*通讯作者。Tel: 010-64806561, E-mail: jjliu@genetics.ac.cn

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*Corresponding author. Tel: +86-10-64806561, E-mail: jjliu@genetics.ac.cn

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mechanisms for neural activity-dependent transport in axon and dendrites. I also briefly discuss the involvement of vesicular transport in neurological diseases.

Keywords neuron; cytoskeleton; molecular motor; organelle; axonal transport; dendritic transport

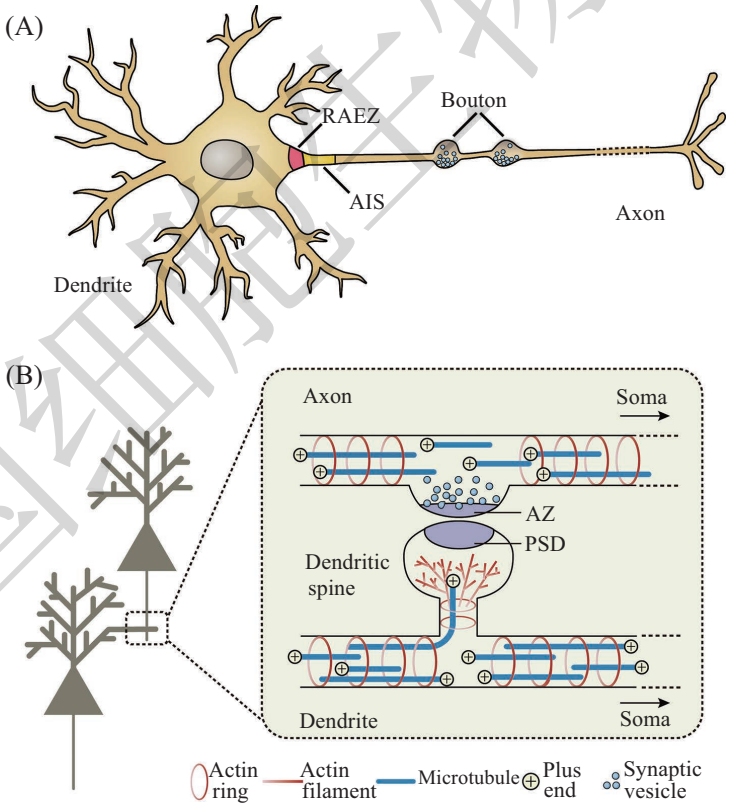
1 前言

神经元是在形态和功能上高度极性化和分区化的细胞。神经元的形态建成、轴树突特化和功能分区(包括细胞器的亚细胞差异分布、突触前和突触后功能蛋白的极性分布), 以及神经元的存活、稳态及突触可塑性等, 均高度依赖胞内运输系统。近二十年来, 细胞生物学技术手段(如亚细胞结构标记、活细胞成像和超高分辨显微成像)的丰富和发展, 极大地推动了神经元胞内运输领域的研究。限于篇幅, 本文将总结介绍迄今关于神经元细胞器/囊泡运输的研究进展, 包括从胞体到轴突和树突的极性运输以及轴树突细胞器/囊泡运输的作用机制、调控机制及其生理病理功能。

2 神经元的结构

2.1 神经元的细胞结构

一个典型的神经元由胞体(cell body or soma)和两种神经突起(process)组成: 一条细长的轴突(axon)和多条树突(dendrite)(图1A)。通常情况下, 轴突的功能是输出信号, 树突则接收信号。轴突和树突均通过分支生长形成复杂的网络结构, 并在神经元之间形成神经传递的基本单元——突触结构(synapse)。在以谷氨酸为神经递质的兴奋性神经元中, 突触结构由突触前神经元的轴突末梢或轴



A: 神经元的形态结构。PAEZ: 轴突前排斥区; AIS: 轴突起始节段; Bouton: 轴突结, 即位于轴突上的突触前结构。B: 神经元的突触结构及细胞骨架的分布; AZ: 作为神经递质释放位点的突触前活性区; PSD: 突触后致密物。

A: neuronal compartments include the cell body (soma), axon and dendrites. PAEZ: pre-axonal exclusion zone; AIS: axon initial segment; Bouton: synaptic vesicle-containing presynaptic structures formed along the axon shaft and at distal axon terminals. B: synaptic structure and cytoskeletal organization in axon and dendrites. AZ: the active zone for neurotransmitter release; PSD: the postsynaptic density.

图1 神经元的形态结构和细胞骨架

Fig.1 The morphology and cytoskeletal organization of a typical neuron

突结(bouton)与突触后神经元树突干质膜上的膜突起——树突棘(dendritic spine)构成(图1B)。

2.2 神经元的细胞骨架

2.2.1 微管细胞骨架(microtubules) 微管是由α-和β-tubulin组成的异源二聚体头尾相连组装而成的极性纤维(原丝, protofilaments)再通过侧面连接形成的外径约25纳米的中空管状结构。典型的微管由13条原丝组装而成。微管具有不断发生聚合和解聚的特性, 其聚合速率较快的一端被称作正端(plus end), 聚合速率较慢的一端则称作负端(minus end)。在大多数细胞如成纤维细胞、上皮细胞中, 中心体(centrosome)作为微管组织中心(microtubule organizing center, MTOC), 通过核化因子γTuRC复合体的作用使微管发生核化(nucleation)以聚合延伸。在成纤维细胞中, 由于中心体位于核周一侧, 所有的微管正端均指向细胞外周。在高等动物神经元轴突中, 几乎所有微管的正端都指向远离胞体的轴突末梢(正端朝外, plus-end-out); 而在树突中则呈现为混合极性, 在靠近胞体的近端大约一半的微管正端朝外, 在远端则多数正端朝外[1-2](图1B)。果蝇和线虫的神经元中, 轴突中所有微管的正端均朝外, 而靠近胞体的近端树突中绝大多数微管为负端朝外[3-5]。神经元胞体的中心体在发育过程中逐渐失去了作为微管组织中心的功能。利用果蝇对于树突发育和形态建成机制进行的研究发现, 在树突中一种被称为高尔基前哨(Golgi outposts, GO)的高尔基体相关结构能够作为微管组织中心, 促进微管的核化和聚合, 形成非中心体微管[6]。除了在微管组织中心发生的微管核化和聚合之外, 在微管侧面也可以发生微管的核化和聚合。在小鼠海马神经元中, 研究发现, augmin蛋白复合体和γTuRC介导轴突和树突中非中心体微管的核化和成束, augmin活性缺失导致轴突中微管的排列方向不再是正端一致朝向末梢[7]。

2.2.2 微丝细胞骨架(actin cytoskeleton) 微丝(microfilaments or actin filaments)系两股由肌动蛋白(actin)单体聚合形成的螺旋状纤维交错扭结形成的直径6~7纳米的细丝状结构。微丝纤维也具有极性, 其延伸更快的一端为正端(barbed end), 延伸较慢的一端为负端(pointed end)。微丝在神经元中行使多种重要功能, 除了作为分子马达myosin驱动短程运输的轨道外, 还参与调控膜运输、胞吞/胞吐、突触发育和可塑性等生理过程。最近的超高分辨荧光显微成像研究显示, 在轴突和部分树突中, 微丝在质膜内表面沿轴突内径形成周期性环状结构, 微丝环(actin ring)之间为由spectrin四聚体形成的约190纳米的间隔[8-11], 这种膜相联的周期性骨架结构(membrane-associated periodic skeleton, MPS)被认为能为细长的神经突起提供结构支撑, 抵抗机械挤压或拉伸(图1B)。

2.2.3 中间纤维(intermediate filament) 被称作中间纤维的细胞骨架因其蛋白质多聚体的直径(10~15纳米)介于微管和微丝之间而得名。中间纤维在神经元中作为支架蛋白起到为轴突提供结构支撑的作用, 并且通过调控轴突直径影响神经冲动的传导速度。构成中间纤维结构的蛋白有六大类, 在神经元中特异表达的是peripherin, 以及被称作神经纤维(neurofilaments)的中间纤维亚基NF-H、NF-M、NF-L和α-internexin[12-13]。由于中间纤维没有极性, 因此, 不能充当分子马达定向运输货物的轨道。

2.3 神经元的主要细胞器

2.3.1 内质网 胞体是神经元细胞生物合成和降解的主要位点, 富集了核糖体附着的粗面内质网、高尔基体以及溶酶体。内质网在神经元中广泛分布, 形成连续的网络, 在树突中甚至能够进入树突棘[14-16]。在轴突中没有粗面内质网, 因此轴突主要依赖胞体合成提供蛋白质[17]。除了蛋白质和脂质合成及代谢功能外, 在神经元中内质网通过调控钙信号转导, 参与突触可塑性[18]。研究发现, 位于树突分支点和树突棘附近的内质网复杂度高, 通过限制膜蛋白如神经递质(neurotransmitter)受体AMPAR在内质网膜中的扩散, 调控树突棘突触后膜的递质受体数量和突触强度以及树突的分支生长[19]。

2.3.2 高尔基体 在轴突中没有发现高尔基体结构。在海马神经元的树突中, 虽然没有检测到完整的高尔基体片层, 却存在两种被称为高尔基前哨和高尔基卫星(Golgi satellite)的膜结构。高尔基前哨为管状囊泡状结构[20-21], 主要分布于海马神经元顶树突中, 为树突极性建立和分支状生长所需[6,22-23]; 高尔基卫星广泛分布于树突中, 是介于内质网–高尔基体中间结构(ER-Golgi intermediate compartment, ERGIC)和胞内体(endosome)之间的膜结构, 具有高尔基体的糖基化功能, 与树突中突触跨膜蛋白如谷氨酸神经递质受体NMDAR、AMPAR的合成及转运有关[24]。

2.3.3 线粒体 作为细胞的能量工厂, 线粒体将葡萄糖和丙酮酸转换为ATP, 对神经元的生长、存活、突触传递及再生至关重要[25-29]。此外, 线粒体通过吸收胞质中的钙离子参与维持细胞内钙稳态, 在神经元细胞的钙信号转导中具有重要的调控作用[18,30]。

2.3.4 胞内体、溶酶体和自噬小体 胞内体在胞内蛋白质分选和运输中具有重要作用。神经元中的胞内体不仅参与外界信号分子如神经营养因子(neurotrophins, NT)及其受体Trk形成的信号复合体的胞吞运输和信号转导[31-32], 在神经元形态发生和突触形成过程中, 还将胞体合成的物质通过囊泡运输途径转运至轴突和树突, 为树突分支和延伸提供原料[23,33]。胞内体还充当了突触蛋白等重要突触组分的转运载体, 不仅在突触前位点介导突触囊泡(synaptic vesicles)释放后的内吞再生[34], 而且还介导神经递质受体的内吞回收[35-36]。

溶酶体(lysosome)作为细胞中的降解机器, 在分解代谢中利用多种水解酶分解蛋白质、脂类、核酸、糖原和黏多糖等底物。在神经元中, 溶酶体与自噬小体(autophagosome)融合, 清除通过胞吞进入细胞的胞外物质、细胞内错误折叠的蛋白质和受损伤的细胞器, 通过自噬作用维持细胞稳态[37]。溶酶体还在突触可塑性中发挥作用。研究发现, 神经活性依赖的溶酶体胞吐释放半胱氨酸水解酶Cathepsin B, 通过活化基质金属蛋白酶MMP9(matrix metalloproteinase 9)消化/重塑细胞外基质, 促进树突棘的结构可塑性[38]。

3 神经元的胞内运输

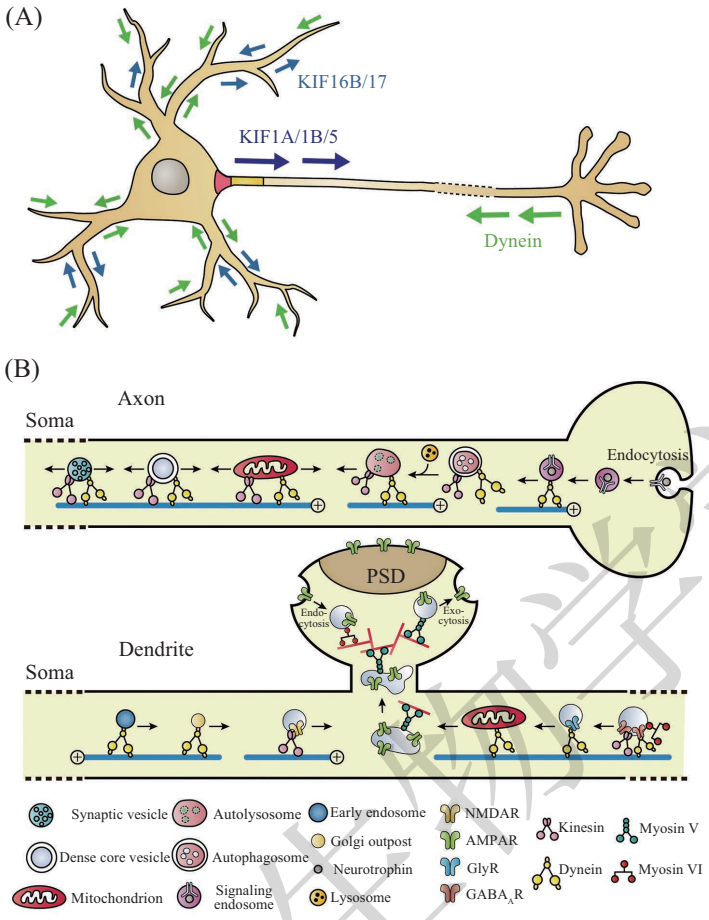
3.1 轴突运输和树突运输

在神经元胞体和神经突起之间以及轴突、树突内的长程运输由基于微管的分子马达(molecular motors)kinesin和dynein驱动。在轴突中, kinesin-1家族成员KIF5和kinesin-3家族成员KIF1A/KIF1B驱动从胞体到轴突远端的正向运输[39-43], dynein则驱动朝向胞体的逆向运输[44]; 而在树突干(dendritic shaft)中, 由于微管呈混合极性排列, 同一马达蛋白能够驱动双向运输(图2A)。在树突远端, 多数微管的正端朝外, 主要由kinesin-2家族成员KIF17和kinesin-3家族成员KIF16B将货物从胞体运输到树突, 在树突末端, dynein则负责货物朝向胞体方向的逆向运输[45-46](图2A)。值得注意的是, 在轴突和树突中微管不仅是分子马达驱动长程运输的轨道, 微管蛋白的翻译后修饰对于分子马达选择性运输货物到轴树突也具有调控作用。最近的研究发现, 在树突中大部分乙酰化微管的正端指向胞体, 因此, 识别乙酰化微管的kinesin-1沿着微管回到胞体而不能进入树突驱动运输; 同时, 树突中酪氨酸化微管的正端指向树突远端, 使得kinesin-2家族成员能够驱动从胞体到树突方向的运输[47]。

Myosin家族成员利用微丝纤维作为轨道, 主要负责驱动胞内货物的局部、短途运输。例如, Myosin Va将内质网从树突干转运到树突棘中[48], 在长时程突触增强(long term potentiation)中, 受到钙信号激活的Myosin Vb将携带递质受体AMPAR的循环胞内体从树突棘基底部转运到树突棘中, 促进其插入突触后膜[49](图2B)。然而有研究发现, Myosin V也介导突触囊泡在海马神经元轴突的突触结(synaptic bouton)之间的长程运输和交换[50]。

3.2 轴树突极性运输的调控

神经元的轴突和树突在形态和功能上的分化依赖于极性运输。在胞体树突区(somatodendritic domain)和轴突之间是被称作轴突起始节段(axon initial segment, AIS)的区域(图1A)。AIS是动作电位起始的部位, 电压门控离子通道(voltage-gated ion channels)在AIS质膜中通过与质膜内表面的ankyrin G(AnkG)及β-IV spectrin结合而高度富集[51]。同时, 不仅AIS质膜作为物理屏障防止胞体树突区和轴突之间的跨膜蛋白和脂类分子的扩散, 在AIS中还存在微丝纤维, 其正端朝向胞体, 充当了胞质中囊泡货物穿越的物理屏障[52]。研究发现, kinesin-1家族成员KIF5能够驱动货物穿过微丝屏障, 而kinesin-2家族成员如KIF17则不能, 因此被KIF17特异性识别的囊泡货物如NMDA受体亚基NR2B不能进入轴突[53]。被kinesin错误转运到AIS的树突货物还能由向微丝正端运动的Myosin Va运回到胞体, 从而避免这些货物被运输到轴突[54-55]。另有研究发现, AIS质膜内表面的AnkG招募dynein活性调控因子NDEL1和Lis1, 激活dynein将靶向树突的货物从AIS逆向运输回到胞体[56]。最近发现, 在胞体和AIS之间还存在一个轴突前排斥区(pre-axonal exclusion zone, PAEZ)(图1A), 多数位于胞体树突区的细胞器及囊泡如高尔基体、粗面内质网和AMPAR囊泡都不能进入



A: 驱动神经元轴突和树突运输的分子马达, 箭头指示运输的方向。B: 轴突和树突(树突干和树突棘)中的细胞器和囊泡运输。

A: molecular motors responsible for axonal and dendritic transport, arrows indicate the directionality of motor-driven movement. B: schematic representation of molecular motor-driven organellar/vesicular transport along cytoskeletal tracks in axon, dendritic shaft and spines, respectively.

图2 神经元胞内的细胞器和囊泡运输

Fig.2 Organellar/vesicular transport in a typical neuron

PAEZ[57]。将kinesin-1和树突囊泡货物相联使得这些货物囊泡进入轴突, 提示极性运输的主要决定因素是货物与驱动轴突/树突定向运输的分子马达之间的识别[57]。

3.3 细胞器和囊泡运输

3.3.1 高尔基体运输 Dynein驱动高尔基前哨在树突中的运输(图2B)。对果蝇神经元树突树状分支的机制研究发现, 树突分支生长依赖于高尔基前哨和dynein[23,33,58], 随后发现dynein调控因子NudE也为树突分支生长所需, 推测它和另一个调控因子Lis1可能介导dynein识别高尔基前哨[58-59]。位于高尔基体膜表面的Lava lamp介导dynein驱动高尔基前哨到树突远端的运输[60], 丝氨酸/苏氨酸激酶Lrrk(Leucine-rich repeat kinase)通过抑制Lava lamp和dynein的相互作用调控高尔基前哨的运动和树突分支生长[61]。

3.3.2 线粒体的运输及其神经活性依赖的锚定(anchoring) 线粒体为神经元的轴树突分支生长、突触形成和可塑性、动作电位产生、突触囊泡转运与回收等重要生理功能提供能量[25,27,29,62-63]。正在发育的神经元轴突和树突中, 20%~30%线粒体沿着微管轨道双向运输(图2B), 而在成熟的神经元树突中几乎所有的线粒体相对静止, 富集于突触位点和树突分支处[25,64]。TRAK蛋白家族(果蝇中同源蛋白为Milton)是介导分子马达识别线粒体的货物适配因子(cargo adaptor)。TRAK1可以结合kinesin-1和dynein, TRAK2则通过特异性结合dynein介导线粒体转运至树突中。研究发现, 另外一个蛋白分子Syntabulin也在神经突起中介导kinesin-1驱动的线粒体运输[65]。能量水平和神经活性调控线粒体的运动。由电压门控的钙离子通道(voltage-gated calcium channel, VGCC)或谷氨酸受体NMDAR开放产生的

钙内流使线粒体锚定在突触位点[64,66]。研究发现, 位于线粒体外膜的GTPase Miro是一个钙感应蛋白(Calcium sensor)[67], 并参与调控轴突和树突中线粒体的双向运输[67-69]。Miro通过与TRAK1/2相互作用, 介导kinesin-1和线粒体的结合。当运动中的线粒体经过一个活化的突触时, 局部高浓度的钙离子结合Miro并改变其构象, 使其能直接与kinesin-1的马达功能域(motor domain)结合, 致使kinesin-1从微管解离, 从而使线粒体停留在突触部位, 增强对突触的能量供应[70]。此外, Miro能被损伤线粒体表面积累的丝氨酸/苏氨酸激酶PINK1磷酸化, 再由被PINK1招募并激活的泛素连接酶Parkin通过泛素化介导的蛋白酶体降解, 从而使线粒体与kinesin-1解离而停止运动[71]。这一机制被认为有利于损伤线粒体, 从而使其被自噬体吞噬并清除。另有研究发现, 位于线粒体外膜的syntaphilin是轴突中线粒体的锚定蛋白, 高钙促进syntaphilin和kinesin-1结合并抑制其ATPase活性, 使线粒体停止运动[72]。

最近的研究发现, PINK1通过激活蛋白激酶A(protein kinase A, PKA)调控线粒体在树突中的运输。活化的PKA通过磷酸化Miro2增强由TRAK2-Miro2介导的线粒体运输, 促进树突的分支生长[73]。也有研究发现, 与主要精神疾病相关的蛋白分子DISC1通过与Miro结合, 也和TRAK-Miro形成蛋白复合体调控轴突和树突中线粒体运输以及树突的形态发生[74]。此外, 除了基于微管的长程运输, 对神经元局部施加神经生长因子(nerve growth factor, NGF)能使线粒体停留在信号分子的刺激位点, 提示线粒体有可能通过微丝细胞骨架发生局部的转运[75]。

3.3.3 溶酶体和自噬体运输　位于胞体的溶酶体通过Arl8 GTPase与kinesin-1介导因子SKIP的相互作用被kinesin-1正向运输到轴突中[76]。另有研究报道, 与kinesin和dynein均能结合的支架蛋白JIP3参与介导轴突中溶酶体的逆向运输[77]。轴突中存在大量的晚胞内体/溶酶体, 然而它们的酸化程度低于胞体中成熟的溶酶体, 也缺少多种成熟的溶酶体水解酶[78]。同时, 无需外界刺激(如饥饿导致的细胞应激反应诱导), 神经元中的自噬小体在轴突末端从内质网膜持续组成型生成[79-81], 以清除受损的线粒体、突触囊泡、失活蛋白质等, 从而维持细胞和突触稳态。自噬小体产生后与晚胞内体/溶酶体融合形成自噬溶酶体(autolysosome), 由dynein驱动从轴突末梢逆向运输至胞体(图2B), 在运输途中逐渐酸化/成熟, 在胞体部位成为成熟的溶酶体发挥降解功能[79-80,82-83]。对大鼠背根神经节细胞(感觉神经元)的研究发现, 自噬溶酶体通过晚胞内体膜表面的Snapin介导与dynein的识别[80]。利用果蝇幼虫运动神经元作为研究体系, 研究者通过遗传筛选发现, STRIPAK复合体中的支架蛋白CKA分别与自噬小体蛋白Atg8a以及dynein-dynactin动力蛋白复合体亚基p150^{Glued}相互作用, 促进神经轴突中dynein驱动的自噬小体逆向运输[84]。有趣的是, 尽管溶酶体和轴突末端新生的自噬小体在轴突中的运动都是双向的, 而且kinesin和dynein都能和自噬小体结合[85-86], 但多数自噬小体很快转为朝向胞体的逆向运输(图2B)[85]。研究发现, 与kinesin-1和dynactin p150^{Glued}均能结合的支架蛋白JIP1通过和自噬小体蛋白LC3结合被募集到从轴突末端进入轴突干的自噬小体上[87]。JIP1的S421位磷酸化促进其结合并激活kinesin, 而去磷酸化的JIP1与p150^{Glued}结合, 抑制其与kinesin的结合及正向运输[88]。体外实验表明, JIP1与LC3的结合抑制其激活kinesin, 提示JIP1通过调控分子马达活性决定自噬小体的运动方向[87]。另外, 定位于自噬小体的磷酸酶MKP1也可能通过使JIP1去磷酸化抑制其激活kinesin[87]。研究还发现, 另一个支架蛋白Huntingtin(Htt)及其互作蛋白HAP1也定位于自噬小体。由于Htt和HAP1均能与kineisin-1和dynein-dynactin结合, 而且降低它们的表达抑制自噬小体的逆向轴突运输, 因此推测它们也参与调控自噬小体轴突运输的方向性[89]。

溶酶体和自噬活性与突触发育和稳态以及突触可塑性密切相关[38,90-96]。尽管如此, 对于溶酶体和自噬小体在树突中运输的行为及其调控研究较少。最近研究报道, 溶酶体在树突中呈双向运输, 突触活性增强使溶酶体转运到树突棘[97]。据推测, 溶酶体的降解活性有利于突触后组分(如递质受体和突触后结构蛋白)的更替和突触重塑。未来的研究将探讨神经活性依赖的溶酶体转运是如何被调控的。

3.3.4 胞内体运输　对果蝇感觉神经元树突发育的研究发现, dynein驱动早胞内体从胞体进入树突, 为树突生长和分支提供膜组分(图2B)[33]。在大鼠海马神经元中, dynein-dynactin通过与Rab5下游效应

因子FHF结合, 驱动早胞内体从轴突逆向运输到胞体和树突, 防止转铁蛋白受体(transferrin receptor)和谷氨酸受体被错误靶向到轴突中[98]。kinesin-3家族成员KIF16B在树突中通过其羧基端的PX结构域直接与早胞内体膜结合, 介导其双向运输, 促进早胞内体携带的AMPAR和神经营养因子受体$p75^{NTR}$转运到树突质膜[45]。另外, 在树突中SNX6通过与dynactin $p150^{Glued}$结合, 介导dynein驱动的早胞内体双向运输[99]。在轴突中, Snapin通过与dynein亚基DIC(dynein intermediate chain)互作, 介导晚胞内体/溶酶体的逆向运输[100]。

神经营养因子[如NGF、BDNF(brain-derived neurotrophic factor)]与神经元细胞质膜上的Trk受体结合形成信号复合体, 激活受体自磷酸化, 并通过细胞内吞形成早胞内体, 进入内吞运输途径, 这种携带了信号复合体的胞内体膜表面活化的受体通过招募效应因子, 在从神经末梢向胞体转运过程中激活轴树突生长、存活、突触组装和可塑性以及神经损伤修复所需的下游信号通路, 因此被称作信号胞内体(signaling endosome)[101-102]。研究发现, DIC的IB亚型特异性结合Trk胞内体[103]。当Trk受体被NT家族成员NGF激活, 继而被激活的下游效应因子Erk1/2磷酸化DIC-1B, 增强dynein与携带Trk的信号胞内体结合并驱动其逆向运输(图2B)[104]。在皮层神经元中, Snapin也介导dynein驱动的BDNF-TrkB信号胞内体/晚胞内体轴突逆向运输[105]。另有研究发现, Htt-HAP1通过与dynactin亚基$p150^{Glued}$互作, 也介导NT家族成员BDNF的囊泡运输[106]以及其受体TrkB信号胞内体在纹状体神经元树突中的逆向运输[107]。另外, 在初级感觉神经元轴突中, kinesin-3家族成员KIF1A驱动由Rab3介导的TrkA囊泡正向运输, 使在胞体合成的TrkA被转运到轴突质膜上以接收NGF信号[108]。

4 突触囊泡、递质受体囊泡和神经肽致密囊泡的运输

突触囊泡是神经元特有的囊泡结构。在化学突触的突触前膜, 突触囊泡释放神经递质, 通过突触间隙与位于突触后膜的递质受体结合, 实现突触传递。在轴突中, kinesin-3家族成员KIF1A和KIF1B驱动突触囊泡前体向轴突远端突触位点的运输[41-43], KIF1A/KIF1B通过与Rab3活性调节因子DENN/MADD互作识别Rab3相联的突触囊泡[109]。有趣的是, 突触囊泡在中枢神经元轴突中双向运动, dynein-dynactin驱动其逆向运输(图2B)[110]。膜蛋白Ankyrin-B与dynactin亚基p62结合, 介导突触囊泡、早胞内体、溶酶体和线粒体在轴突中的逆向运输[110]。

神经递质受体是突触传递功能的执行者, 递质受体的突触转运依赖于神经元胞体和树突中的囊泡运输。已知mLin-10介导KIF17驱动兴奋性递质谷氨酸受体NMDAR亚基NR2B的囊泡运输[111]。突触后蛋白CASK和SAP97也介导KIF17驱动的携带NMDAR的高尔基前哨转运[112]。另一个谷氨酸受体AMPAR从胞体到突触位点的长程囊泡运输机制尚不明晰。突触后支架蛋白Gephyrin通过与dynein轻链亚基(dynein light chain, DLC)结合介导抑制性递质甘氨酸受体GlyR的囊泡运输(图2B)[113-114]。货物介导分子muskelin与Myosin VI及dynein均能结合, 分别调控另一个抑制性递质γ-氨基丁酸受体$GABA_AR$由Myosin VI驱动的内吞运输以及dynein驱动的长程运输(图2B)[115]。另外, Myosin Vb驱动由Rab11-FIP2介导的携带AMPAR的循环胞内体从树突干到树突棘的运输(图2B)。

神经元分泌神经肽用于调节神经活性, 神经肽在胞体合成并被包装入致密核心囊泡(dense core vesicles, DCVs), 转运到轴突和树突中的释放位点。致密核心囊泡在轴突和树突中双向运输, kinesin-1家族成员KIF1A、kinesin-3和dynein是驱动其运输的分子马达(图2B)[116-120]。在高钙条件下, 钙离子激活的钙调蛋白与KIF1A结合使之构象改变, 解除了KIF1A的分子内自抑制, 从而能够结合并转运致密核心囊泡[119]。

5 神经元囊泡运输的生理功能及其与疾病的关系

如前所述, 细胞器和囊泡运输对于神经元细胞的生长发育、突触形成和可塑性至关重要。最近的研究还发现, 增强线粒体运输能为损伤部位提供ATP以弥补受损神经中线粒体去极化造成的能量缺失, 从而促进神经轴突再生[28]。此外, 运输障碍与多种神经退行性病变密切相关, 例如运动神经元病[121]、脊柱肌萎缩(spinal muscular atrophy)和遗传性痉挛性截瘫(hereditary spastic paraplegia)[122]、

2B型腓肌萎缩症(Charcot-Marie-Tooth type 2B)[123]、佩里综合征(Perry syndrome)[124]等。

6 总结与展望

通过近年的研究, 我们对神经元囊泡运输的特点和调控机制的认识不断加深。然而, 鉴于神经元形态结构的高度极性化、分区化及神经突触结构和功能的可塑性, 囊泡运输如何被神经活性调控, 以及突触可塑性如何通过膜运输实现, 是亟待解答的重要科学问题。钙内流及其诱导的信号转导是触发长时程突触增强和抑制的核心机制, 胞内运输如何被钙信号调控是进一步研究的重要切入点。已知轴突中kinesin-1驱动的线粒体和致密核心囊泡运输都受到钙调控[70,119]; 发生长时程突触增强时, 在树突棘内NMDA受体介导的钙内流增强Myosin Vb与携带AMPAR的循环胞内体膜表面Rab11-FIP2之间互作, 将AMPAR从树突干转运到树突棘内, 促进其通过胞吐到达突触后膜[49]。有研究发现, 钙信号转导的核心效应因子CaMKII通过磷酸化KIF17, 抑制其与NMDAR囊泡的货物介导因子Mint1结合, 从而使分子马达释放其货物[125]。鉴于其他kinesin(如KIF1B)也含有进化保守的钙调蛋白结合位点, 钙离子/钙调蛋白有可能参与其他分子马达的运输调控。在神经轴突和树突中, 尤其是在突触位点, 是否马达蛋白对货物的识别和卸载都是神经活性依赖的? 介导钙信号的核心调控因子钙调蛋白(calmodulin)及其下游效应因子CaMKII是否通过调控运输系统的组分(如分子马达及其调控因子)的功能, 调控分子马达的活性、马达–货物的相互作用及运输的方向性? 除了钙信号, 还有哪些调控因子参与神经活性依赖的突触转运? 这些都是神经细胞生物学领域重要的科学问题。

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