Rab蛋白在囊泡转运中的作用及影响

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摘要 Rab蛋白是真核生物中保守的小GTP酶家族. Rab蛋白在细胞中普遍表达, 它的活性在细胞内受到严格的调控: 在活性形式Rab-GTP和无活性形式Rab-GDP之间转换, 这是由鸟嘌呤核苷酸交换因子(GEFs)和GTP酶活化蛋白(GAPs)调控的, 并在囊泡转运的调控中起分子开关的作用. 在囊泡运输中, Rab蛋白与不同的下游效应分子相互作用, 参与从供体膜选择货物、出芽形成囊泡、调控囊泡沿细胞骨架运动、囊泡与受体膜锚定融合. 当Rab蛋白功能受损导致囊泡转运途径障碍时, 则会表现出不同的疾病, 包括神经退行性疾病、癌症等. 本文将对近年来Rab的蛋白结构和功能、参与囊泡运输的分子机制、Rab蛋白的循环调控以及其异常导致的疾病进行综述.

关键词 Rab蛋白, GAPs, GEFs, 囊泡运输, 疾病

Rab蛋白是Ras超家族中成员最多的小GTP酶家族, 它们在进化上是保守, 且涉及包括生长、蛋白质运输、跨膜信号转导、膜结合细胞器的靶向和融合等各种细胞功能^[1,2]. 迄今为止, 在酿酒酵母(*Saccharomyces cerevisiae*)中发现11种^[3]、秀丽隐杆线虫(*Caenorhabditis elegans*)中29种、黑腹果蝇(*Drosophila melanogaster*)中33种^[4]、拟南芥(*Arabidopsis thaliana*)中57种^[2,5], 人类中则有约70种不同的Rab蛋白^[2,6,7](表1). 第一个Rab基因在酿酒酵母中被发现, 因其编码小囊泡蛋白, 功能与囊泡从高尔基体运输到质膜有关, 命名为*Sec4/Ypt*^[8,9]. 哺乳动物中第一个同源物于1987年被克隆并称为Rab^[10]. 后来的研究显示, Rab蛋白几乎存在于所有真核生物与膜相关的细胞器中, 表明这一类蛋白在真核生物体的普遍性和重要性.

大多数Rab基因的长度约为600 bp, 序列保守性

高, 不同物种间的序列同源性达到75%~95%, 常形成多个亚家族. Rab蛋白家族成员大约有200个氨基酸序列组成, 其相对分子量为21~25 kD, 氨基酸序列的相似性在55%~75%之间. 当序列相似性大于75%归为同一序列, 例如Rab6a, Rab6b和Rab6c. 这些高度相同的Rab蛋白是同一种的不同亚型^[11]. 此外, 目前已获得不同来源的Rab的高分辨率X射线晶体结构信息^[12]. Rab蛋白具有一些共同的结构特征, 由高度保守的G结构域和高度可变的N端和C端构成. G结构域由5个 α 螺旋、6个 β 片层和5个多态环结构组成, 并且在G结构域存在两个开关 I 和 II, 是其他调控因子与Rab相互作用的位点. Rab蛋白的羧基末端含有XXXCC, XXCCX, XCCXX, CCXXX或XXCXC基序(X代表任意氨基酸), 其中两个半胱氨酸是异戊烯化的底物, 这种修饰对该类蛋白与膜的结合至关重要^[13,14].

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表 1 Rab蛋白在主要模式物种中的类型

Table 1 Types of Rab proteins in major model species

物种	Rab蛋白
酿酒酵母(<i>Saccharomyces cerevisiae</i>)	Ypt11, Sec4, Ypt31, Ypt32, Ypt51, Ypt52, Ypt53, Ypt6, Ypt7, Ypt10, Ypt11
秀丽隐杆线虫(<i>Caenorhabditis elegans</i>)	Rab14, Unc108, F11A5.3, F11A5.4, Rab11.2, Rab11.1, Rab39, Rab33, Rab30, Rab19, Rab18, Rab1, K02E10.1, Rab35, Rab8, Rab10, Tag312, 4R79.2, Rab37, Rab3, Aex6, Rab7, ZK669.5, Rab6.1, Rab6.2, Y71H2AM12, C56E6, Rab21, Rab5, Rab28
黑腹果蝇(<i>Drosophila melanogaster</i>)	Rab1, Rab2, Rab3, Rab4, Rab5, Rab6, Rab7, Rab8, Rab9, Rab10, Rab11, Rab14, Rab18/RP4, Rab19/RP3, Rab21, Rab23, Rab26, Rab27, Rab30, Rab32/RP1, Rab35, Rab39, Rab40, RabX1, RabX2, RabX3, RabX4, RabX5, RabX6, CG9807, CG32673, CG32671, Rab9D
拟南芥(<i>Arabidopsis thaliana</i>)	RabA1.a, RabA1.b, RabA1.c, RabA1.d, RabA1.e, RabA1.f, RabA1.h, RabA1.i, RabA2.a, RabA2.b, RabA2.c, RabA2.d, RabA3, RabA4.a, RabA4.b, RabA4.c, RabA4.d, RabA4.e, RabA5.a, RabA5.b, RabA5.c, RabA5.d, RabA5.e, RabA6.a, RabA6.b, RabB1.a, RabB1.b, RabB1.c, RabC1, RabC2.a, RabC2.b, RabD1, RabD2.a, RabD2.b, RabD2.c, RabE1.a, RabE1.b, RabE1.c, RabE1.d, RabE1.e, RabF1, RabF2.a, RabF2.b, RabG1, RabG2, RabG3.a, RabG3.b, RabG3.c, RabG3.d, RabG3.e, RabG3.f, RabH1.a, RabH1.b, RabH1.c, RabH1.d, RabH1.e
人类 (<i>Homo sapiens</i>)	RabF2a, RabF2b, RabL3, RabL5, Rab1A, Rab1B, Rab35, Rab13, Rab8A, Rab8B, Rab10, Rab12, Rab3A, Rab3C, Rab3B, Rab3D, Rab15, Rab44, Rab27A, Rab27B, RasEF, Rab27, Rab37, Rab2, Rab2B, Rab4A, Rab4B, Rab14, Rab11A, Rab11B, Rab9, Rab39B, 201475, Rab42, Rab19, Rab43, Rab30, Rab33A, Rab33B, Rab40A, Rab40B, Rab40C, Rab18, Rab17, Rab5A, Rab5B, Rab5C, Rab22A, Rab31, Rab21, Rab20, Rab24, Rab6A, Rab6B, Rab6C, Rab41, Rab34, Rab36, Rab7L1, Rab29, Rab32, Rab38, RabL4, Rab7

在所有真核细胞的膜转运系统中Rabs起着重要的作用, 控制着不同的转运途径和细胞器生物发生, 对于细胞内囊泡出芽、囊泡转运以及与靶膜融合的准确协调是必不可少的, 可以确保囊泡内物质准确递送到胞内不同区域. 囊泡运输是由Rab蛋白介导的主动转运过程. 近年来, 研究Rabs在膜运输中的作用取得了巨大进展. 本文概述了近期Rab蛋白家族在囊泡转运中的功能及其调控方面的研究进展, 并叙述了Rab功能受损和转运途径异常可能引起的疾病.

1 Rab蛋白在囊泡运输中的功能

Rab蛋白在所有真核细胞膜转运系统中起着重要作用, 控制不同的转运途径和细胞器的生物发生, 在时间和空间上与不同阶段的效应分子相互作用, 调控从供体膜侧选择货物进入囊泡、囊泡在肌动蛋白和细胞骨架上运动以及与靶膜锚定融合等过程(图1).

1.1 Rab蛋白调控运输囊泡的组装

Rab蛋白可以与跨膜蛋白/受体的细胞质区域相互作用, 以促进它们包装成运输囊泡. 囊泡货物的选择, 是由每个表层复合体的组件识别要运输货物的特定元

素所决定, 尽管Sar/Arf家族的GTP酶在募集外壳复合物以及促进囊泡形成的效应物中起主要作用^[16], 但近年来的实验证据也已证明几种Rab蛋白参与该过程. 早期内吞途径中的Rab5和Rab21直接与 β 1整联蛋白的 α 亚基结合, 促进其内吞作用和循环, 重塑细胞表面迁移和胞质分裂^[17]. 此外, Rab5还与血管紧张素II 1A型受体(angiotensin II receptor type 1A, AT1AR)直接相互作用, 促进其内吞运输^[13]. 在胞吐途径上, Rab3b直接与多聚免疫球蛋白受体(polymeric immunoglobulin receptor, pIgR)结合, 以调节其在极化上皮细胞中的转胞吞作用^[14]. 此外, 一些Rab蛋白还可通过与衔接蛋白的相互作用参与将货物蛋白包装到运输囊泡的过程中. 譬如, Rab9通过其效应物TIP47促进货物蛋白(甘露糖-6-磷酸受体)募集到晚期内体衍生的转运囊泡中^[18].

1.2 Rab蛋白与细胞骨架蛋白的相互作用促进囊泡运输

已知Rab蛋白与肌动蛋白、微管运动蛋白等(如肌球蛋白、驱动蛋白和动力蛋白)相互作用以促进运输囊泡在肌动蛋白和微管细胞骨架上的运动. V类肌球蛋白是肌动蛋白, 由N末端肌动蛋白结合运动结构域和C末端货物结合球状尾结构域(globular tail domain,

图 1 Rab参与囊泡运输的示意图(根据参考文献[15]绘制)

Figure 1 Schematic diagram of Rab involvement in vesicle trafficking (modified from reference [15])

GTD)组成, 可结合后高尔基体分泌囊泡上的许多Rab或再循环内体, 并被招募到这些胞吐隔室^[19]. 哺乳动物细胞的研究提示, Rab11通过其效应物Rab11家族相互作用蛋白2(Rab11-FIP2)与肌球蛋白Vb相互作用, 以调节质膜再循环^[20]. Rab27a通过募集其效应物黑色素/Slac2-a, 再与肌球蛋白Va结合, 从而调节黑素细胞中发现的黑素小体向质膜的转运^[21]. 因此, Rab-肌球蛋白V相互作用将运输囊泡与肌动蛋白相关联, 并促进它们向细胞表面移动.

此外在动物细胞中已被证明Rab还可以通过与以微管为基础的马达蛋白相互作用来调节众多膜通路. 微管通常在微管组织中心(如中心体)以负端排列, 正端直接进入细胞质并朝向细胞外周^[22]. Rab蛋白可以通过与肌动蛋白(正端定向马达)或动力蛋白(负端定向马达)家族成员相互作用来调节两个方向的运动. 例如Rab6直接结合驱动蛋白(KIF20A)和动力蛋白(DYNLRB1和Dynactin)^[23]; Rab14也直接与驱动蛋白-3(KIF16B)结合^[24].

1.3 Rab蛋白参与囊泡与靶膜的锚定融合

Rab蛋白另一个重要的功能则是帮助运输囊泡定位, 以与靶膜锚定融合. 为了确保囊泡运输的准确性, 大多数膜运输途径需要在囊泡融合之前将囊泡“束缚”

到靶膜上, 此过程需要束缚因子的参与. 这些束缚因子分为两类: 长卷曲螺旋链或多蛋白复合物, 它们也都是Rab蛋白的效应分子. 其中已经发现的Rab蛋白与束缚因子多蛋白复合物的相互作用包括: SEC4/Rab8效应Exocyst复合体^[25]; Rab5/Vps21效应CORVET复合体^[26]; Rab7/Ypt7效应HOPS复合物(图2)^[27]; Rab1/Ypt1效应TRAPPI和TRAPPII复合体^[28]. 这些束缚因子通常由Rabs募集, 再与SM(Sec1-Munc18)蛋白质相互作用以促进SNARE复合物的组装, 用于膜融合^[29].

图 2 Rab7/Ypt7参与晚期内体-液泡的束缚(根据参考文献[27]绘制). 晚期内体上活化的Rab7/Ypt7-GTP与其效应复合物HOPS结合以促进晚期内体-液泡的束缚, 完成后GAP使Rab7/Ypt7-GTP的活性形式转变为无活性形式Rab7/Ypt7-GDP

Figure 2 Rab7/Ypt7 is involved in late endosome-vacuole tethering (modified from reference [27]). The activated Rab7/Ypt7-GTP localized on the late endosomes binds to its effector—the HOPS complex for tethering the late endosomes with vacuoles. After finishing this process, GAP will inactivate Rab7/Ypt7-GTP to form Rab7/Ypt7-GDP

2 Rab蛋白循环调控

和Ras家族的其他小GTP酶一样, Rab蛋白对鸟嘌呤核苷酸GTP和GDP有较高的亲和力, 但是在GTP水解过程中GTP酶的活性较弱. 因此, 需要催化因子GEFs和GAPs促进细胞中GTP/GDP交换过程和GTP水解反应^[30]. 但是要实现Rab的GTP/GDP交换功能的先决条件是Rabs要先定位到细胞内膜上, 下面将概述Rab蛋白是怎样定位的以及GEFs和GAPs是如何调控Rab蛋白循环的.

2.1 Rab蛋白质膜定位

Rab蛋白在膜上的定位作为GTP/GDP循环功能的先决条件, 此过程中需要在Rab蛋白的C-末端半胱氨酸残基处发生不可逆的异戊烯化^[11]. 1991年发现Rabs异戊烯化^[31,32]是由三种酶催化法尼基焦磷酸盐(farnesyl pyrophosphate, FPP)或香叶基香叶基焦磷酸盐(geranylgeranyl pyrophosphate, GGPP)修饰靶蛋白, 法尼基转移酶(farnesyltransferase, FTase)或香叶基香叶基转移酶(geranylgeranyltransferase I, GGTase I)识别C末端的CaaX基序, 通过硫醚键把单个的farnesyl-或geranylgeranyl-基团连接至半胱氨酸上^[33,34]. 相反地, 香叶基香叶基转移酶(geranylgeranyltransferase II, GGTase II, 也称为RabGGT酶)识别不同基序内的C-末端半胱氨酸残基(如CC, CXC), 并且通常修饰Rab蛋白的C-末端的2个半胱氨酸残基^[35]. mRNA经核糖体翻译合成Rab蛋白后, 首先需要与Rab护送蛋白(Rab escort protein, REP)结合形成稳定的复合物, 后者才将Rab蛋白呈递给RabGGTase进行异戊烯化. 然后再把新的GGPP分子与RabGGT酶的活性位点结合后, 双重异戊二烯化的Rab与REP从RabGGTase分离, 把Rab蛋白传递到目标膜^[36].

2.2 GEF和GAP催化的GTP/GDP循环

鸟苷酸交换因子(GMP exchange factor, GEFs)在囊泡运输中是正调控因子, 在供体膜侧促进核苷酸的交换, 刺激Rabs与GTP结合发生构象变化^[37,38], 其机制是通过改变开关 I (Rab-GDP结合状态)和破坏Mg²⁺的配位, 稳定Rab蛋白的无核苷酸形式^[29]. 两者相互作用主要发生在GEF和开关 I 的C-末端半部分之间(其中 γ -磷酸和Mg²⁺结合G2-motif Thr定位), 从而将开关 I 拉入开放构象. 该构象改变还导致Rab蛋白中与鸟嘌呤

碱基相互结合Phe或Tyr残基的构象发生移位, 因此降低了核苷酸的亲和力^[39]. 由于GEF催化双向核苷酸交换(即从GDP-到GTP-结合状态, 反之亦然), 这些结果表明, 取决于GEF催化反应Rab:GDP或Rab:GTP的比例, GEF对GTP酶的初始识别可能是通过与开关 I 或开关 I (Rab-GTP结合状态)结合^[36]. 含Vps9结构域的GEF, 特异于Rab5家族成员并且在早期内吞运输中发挥作用^[40]. 含DENN(differentially expressed in normal and neoplastic cells)结构域的GEF在正常组织和肿瘤中表达是有差异的, 如Rab3, Rab9, Rab10, Rab11, Rab12, Rab27, Rab28, Rab35 和Rab39^[41]. SAND1/Mon1复合物是Rab7/Ypt7在晚期核内体特定GEF, 通过激活Rab5和Rab7促进内吞作用(图3)^[42]. 对于胞吐作用, TRAPP复合物^[43]和Sec2/Rabin8蛋白^[44]分别是Rab1/Ypt1和Rab8/Sec4促进ER向高尔基体转运和后高尔基体向质膜转运的GEFs. 近年来, 发现秀丽隐杆线虫蛋白REI-1及其人类同源蛋白SH3BP5对Rab11具有GEF活性^[45].

相比之下, GTP酶活化蛋白(GTPase-activating protein, GAP)含有的TBC(Tre-2/bucdc16)结构域, 用于催化GTP水解, 在人类中发现40多种不同的成员^[29]. Gyps于20世纪90年代首先被发现于酵母中, 其TBC结构域包含保守的催化基序IxxDxxR和YxQ. 2000年解析出第一个GAP——Gyp1^[46]. 与其他只提供Arg-手指(Arg finger)的GAPs与小GTP酶G3-基序中的谷氨酰胺参与水解活性相比, Gyp1还能提供一个额外的、反向的Gln-手指(Gln-finger)来取代G3-基序中的谷氨酰胺. 这即是GAP作用Rabs的双指机制: Arg和Gln侧链插入Rab上的GTP结合位点稳定GTP水解的过渡态^[47]. 但是还有一些GAP缺乏Arg和Gln或两者, 因此可能通过不同的机制起作用^[48]. 更有意思的是, 在人类Rab3-GAP复合物由两种不同的蛋白质组成, 但不包含保守的TBC结构域^[49].

3 Rab蛋白介导的膜转运失调与疾病的关系

3.1 神经退行性疾病

有研究发现, Rab蛋白异常所导致的膜转运失调与几种常见的神经性疾病有关, 包括帕金森综合征(Parkinson's disease, PD)、阿尔茨海默症(Alzheimer's disease, AD)和亨廷顿舞蹈症(Huntington's disease,

图3 Rab5和Rab7促进内吞作用模式图(根据参考文献[42]绘制)

Figure 3 SAND-1/Mon1 activates Rab5 and Rab7 to promote endocytosis (modified from reference [42])

HD)等^[50].

帕金森综合征是最常见的神经运动障碍, 主要影响锥体外运动系统. 富含亮氨酸重复激酶2(LRRK2)基因的突变被认为是常染色体显性遗传和迟发家族性PD的最常见致病因素之一^[51]. 目前至少在LRRK2中发现7个突变: N1437H, R1441 C/G/H, Y1699C, G2019S, I2020T, 被认为是家族性PD的致病因素^[52]. LRRK2具有激酶活性, 能与小GTP酶Rab家族的Rab7L1相互作用, 调控神经突起的外向生长和细胞内运输^[53]. 先前研究表明, LRRK2在细胞内运输和维持亚细胞结构(如高尔基体、溶酶体)有重要作用^[54]. 而且Rab7L1已经被确定位于PD相关风险位点PARK16的候选基因^[55]. Rab7L1蛋白主要定位于细胞中的高尔基体或其附近^[56]. 先前研究已表明, 其在调节反式高尔基体聚类和完整性方面具有作用^[57,58]. Rab7L1敲低对反式高尔基体结构的损伤导致甘露糖6-磷酸受体(M6PR)的异常分布, 而M6PR是溶酶体蛋白细胞内转运的介质^[59]. Rab7L1的Ser72位点是LRRK2激酶原位活性的靶点, Rab7L1的Ser72位于分子开关II区域的中部, 该区域与效应分子结合, 从而导致Ser72磷酸化可能调节与细胞内转运相关的细胞功能^[60]. PD相关的LRRK2致病突变体在Ser72位点显著增强了其磷酸化Rab7L1的能力, Rab7L1中Ser72磷酸化的调控导致了跨高尔基体网络的形态和分布的改变^[60]. 这些研究共同表明了Rab7L1磷酸化参与Lrrk2介导的细胞运输和PD发病

机制.

阿尔茨海默症是中枢神经系统退行性疾病, 特征在于由淀粉样蛋白 β (A β)以及细胞内神经纤维缠结组成的斑块的细胞外积累^[61]. 家族性AD(familial AD, FAD)与淀粉样蛋白前体蛋白(amyloid precursor protein, APP)、早老素1(presenilin 1, PSEN1)和早老素2(PSEN2)的突变相关, 这三种基因的突变与A β 的生成直接相关, 而由A β 蛋白积累成的斑块是造成AD的一个因素^[62,63]. 在人死后的胆碱能基底前脑神经元和散发性AD中的CA1锥体神经元中, 均报道了Rab4, Rab5, Rab7和Rab27转录物和蛋白质水平的上调^[64,65]. 因此通过上调Rab GTP酶导致的内吞机制过度活跃, 这可能导致内体信号传导和蛋白质更新失衡. 有研究提出, PSEN1是内质网/高尔基体网络中Rab GDI的膜受体, 以调节与网络相关的活性Rab6的量. PSEN1的功能丧失导致Rab GDI的量减少, 引起膜相关的活性Rab6水平降低^[66]. 在AD患者的大脑中, Rab6的表达水平显著增加了5倍, 并且在PSEN1突变细胞中Rab6和Rab4的总蛋白水平增加^[67]. 与广泛分布的PSEN1不同, PSEN2限制性地位于晚期内体/溶酶体中, PSEN2中FAD相关突变增加晚期胞内体和溶酶体中易聚集的A β 42的水平, 这可能导致溶酶体功能障碍和细胞死亡^[68]. 这些研究表明, 膜泡运输缺陷可能是造成AD的一个原因.

亨廷顿舞蹈症是一种常染色体显性遗传病, 病因是三个核苷酸CAG重复扩增, 使翻译的多肽链延长了至少36~40个谷氨酰胺残基, 导致亨廷顿蛋白突变^[69]. 亨廷顿蛋白(Htt)是一个膜相关的大分子蛋白, 主要位于高尔基体以及胞吞和胞吞囊泡上^[70]. 亨廷顿蛋白的突变与Rab5, Rab8, Rab11相关. Htt通过卷曲螺旋蛋白FIP2与Rab8或Rab8/optineurin复合物相互作用在后高尔基体转运中发挥作用^[71], Htt功能丧失导致该Rab8/optineurin复合物错误定位, 损害高尔基体和溶酶体之间的囊泡运输^[72]. Htt与相关蛋白HAP40形成复合物, 作为Rab5效应分子调控早期内体的运动性^[73]. 所以在HD中, Htt-HAP40复合物形成被破坏, 导致HAP40上调和早期内体运动下降. Htt通过与含有Rab11 GDP复合物的相互作用激活Rab11. 在HD的小鼠模型中, 原代皮层神经元显示转铁蛋白受体的再循环减少回到质膜, 表明HD发病机制至少部分与回收内体中Rab11活性降低有关^[74].

3.2 肿瘤生物学

由于Rab是膜泡转运的主要调节因子, 而膜转运在癌症生物学中有重要作用, 因此一些Rab与癌症的发生有关, 主要是肿瘤细胞的侵袭转移. Rabs调控囊泡运输的功能障碍可以促进癌症的侵袭. 人类肿瘤测序数据库中发现一些Rabs可以激活癌细胞存活的重要酶: 磷脂酰肌醇3-激酶(PI3K)和蛋白激酶B(AKT). Rab35被证明在HeLa细胞中生长因子介导的AKT的磷酸化和激活是必需的^[75]. Rab35与内吞和再循环相关, 可通过调节内吞作用和再循环利用促进生长因子介导的PI3K/AKT通路活化^[76]. Rab 35以GTP依赖的方式与p53相关蛋白激酶(p53-related protein kinase, PRPK)相互作用, 并抑制PRPK诱导p53表达^[77]. 众所周知, p53是肿瘤抑制因子, 其下调通过绕过细胞凋亡检测点来促进肿瘤细胞的发育. Rab25通过循环内涵体控制 $\alpha 5 \beta 1$ 整联蛋白的运输, 促进侵袭性细胞迁移, 其在高度增殖和转移的癌细胞中是过表达的^[78,79]. Rab11是膜蛋白再循环和蛋白质从反面高尔基体网(trans Golgi network, TGN)转运到质膜的重要组成部分, 已发现Rab11介导的 $\alpha 6 \beta 4$ 整联蛋白运输有助于增加乳腺癌中癌细胞的侵袭^[15,80]. 热休克蛋白90a被鉴定为Rab27b调控的囊泡的组成部分, 作为激活基质金属蛋白酶2(matrix metalloproteinase 2, MMP2)所需的一种前侵入性生长调节剂. Rab27B表达的增加与雌激素受体阳性乳腺癌患者预后不良有关, 支持了Rab27B在肿瘤发展中的作用^[81].

3.3 免疫相关疾病

Rab是细胞内运输的主要调控者, 因此也可通过调节免疫受体的运输来调节免疫应答. Rab蛋白的直接功能障碍或间接Rab蛋白调节因子或效应分子缺陷引起与免疫相关的疾病. 目前Rab27a被证明是与人类免疫功能障碍相关的GTP酶^[82]. Rab27a缺陷型T细胞

表现出降低的细胞毒性和细胞溶解颗粒胞吐作用, Rab27a似乎是细胞毒性颗粒胞吐作用的关键效应分子, 这是免疫稳态所必需的途径^[83]. Griscelli综合征的特征是由于黑素细胞中黑素的积累而导致毛发和皮肤色素减退, 细胞毒性T淋巴细胞分泌的裂解颗粒受损, 引起血细胞综合征激活, 导致免疫缺陷^[83,84]. Rab27a依赖型黑素细胞内黑素体的转运缺陷会影响黑色素向角质形成细胞转移, 这与Griscelli综合征有关.

3.4 其他疾病

除了以上介绍的疾病, Rab也参与了其他疾病的发生发展. Rab10和Rab14促进含有GLUT4的囊泡与质膜对接和融合, 它们介导的GLUT4(葡萄糖转运蛋白)易位过程的功能障碍与II型糖尿病有关^[15]. Rab39a突变导致的功能丧失可引起其中一种X连锁智力障碍(X-linked intellectual disability, XLID)的发生^[85].

4 总结和展望

综上所述, Rab蛋白家族在时间和空间上与多个效应分子相互作用, 是囊泡运输的主要调控因子. 但是因为Rab蛋白家族成员众多, 广泛分布且功能多样, 以及在时空上调控质膜运输发生还处于初步了解阶段, 所以不同Rab蛋白是如何协同运作完成复杂的膜转运过程还需要进一步阐明. 最近的研究表明, 马达蛋白的激活可能与它的肌动蛋白在囊泡周围轨道的成核有关, Rab结合控制着一种促进肌动蛋白分解的酶^[86,87]. 这些发现为Rabs和细胞骨架调节因子之间的交叉研究开辟了新的方向, 有助于揭示Rabs调控囊泡与细胞肌动蛋白骨架之间的联系. 与此同时, 膜转运失调与疾病的发生密切相关, 故Rab蛋白的研究也为开发新的疾病治疗分子靶点提供了新的思路和方案.

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Roles of Rab proteins in vesicle transport

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Rab proteins are a part of a conserved small GTPase family in eukaryotes that are widely expressed in cells, and their activities are strictly regulated within the cell: the transition between the active Rab-GTP and inactive Rab-GDP forms is regulated by guanine nucleotide exchange factors (GEFs) and GTPase-activated proteins (GAPs). Functioning as important molecular switches in vesicle transport, Rab proteins interact with several different downstream effector molecules that are involved in cargo selection from the donor membrane, bud development, movement along the cytoskeleton, and anchor of the vesicles to the receptor membrane. In addition, the impaired roles of Rab proteins and disturbed vesicle trafficking caused by abnormal Rab proteins may lead to various diseases, including cancer and neurodegenerative and immune diseases. This article will review the recent research progress on Rab proteins, molecular mechanisms involved in vesicle trafficking, regulation of the Rab protein cycle, and diseases caused by abnormal vesicle transport.

Rab proteins, vesicular transport, GAPs, GEFs, disease

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