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评 述

VPS35在肿瘤发生与转移中的作用及机制研究

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摘要 VPS35是Retromer的重要组成部分, 在内吞体蛋白分选转运过程中有重要作用. 最近研究表明, *VPS35*作为一种新的致癌基因, 在多种肿瘤中高表达, 调控多种因子及通路, 从而影响肿瘤的发生发展和转移. 本文综述了目前VPS35调控肿瘤相关因子及通路进而促进肿瘤发生与转移的最新研究进展, 总结讨论了VPS35在肿瘤发生与转移中的作用机制, 为将来深入研究VPS35/Retromer组分在肿瘤发生转移中的作用及机制提供借鉴与参考.

关键词 VPS35, Retromer, 肿瘤发生, 肿瘤转移

Retromer(囊泡逆向转运复合体)最早由Seaman等人[1]在酵母中发现, 是由Vps35p, Vps29p, Vps26p, Vps17p和Vps5p五种蛋白质组成的复合物, 主要负责羧肽酶Y(carboxypeptidase Y, CPY)受体蛋白Vps10p从内吞体(endosome)回收到高尔基体(Golgi apparatus). 由于Vps5p-Vps17p二聚体能结合内吞体上的3-磷酸-磷脂酰肌醇(PtdIns(3)P), 因此Vps5p-Vps17p能作为膜结合组分在内吞体膜上组装并驱动囊泡形成[2], 而Vps35p-Vps29p-Vps26p亚复合体可选择性地识别货物蛋白(比如直接结合Vps10p), 因此作为货物识别组分, 将内吞体货物选择性地分选并逆向运输到高尔基体.

在哺乳动物中, Retromer由VPS26-VPS35-VPS29三聚体和分选连接蛋白(sorting nexins, SNXs)组成, 其中SNX1, SNX2, SNX3, SNX5, SNX6和SNX27参与Retromer的组装, 并且不同的SNXs介导不同货物蛋白从内吞体到高尔基体或细胞膜的运输过程[3]. 此外, 哺乳动物Retromer的功能受到多种相关因子的调控, 如TBC1D5, WASH复合体和WDR91[4], 但这些调控因子在酵母中并不保守. 由此可见, 酵母和哺乳动物的Retromer作用机制并不完全一致. 目前认为, 哺乳动物Retromer及其调控因子主要定位在内吞体回收亚区域, 从而保证货物蛋白被正确有序地识别、富集并得以分选转运[4,5].

Retromer参与多种重要受体和蛋白的胞内运输过程(如胚胎发育相关的Wnt信号蛋白运送受体, 细胞极性形成相关的顶端决定因子Crumbs和运输溶酶体蛋白水解酶的阳离子非依赖6-磷酸甘露糖受体), 因此Retromer在细胞的多种生理过程中发挥作用, 包括发育信号的传递、极性运输和溶酶体发生等[6~8]. VPS35是Retromer的重要组分之一, VPS35的突变体最初被

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发现与帕金森病(Parkinson disease, PD)息息相关, 这是一种功能缺失突变, 其与内吞体循环调节网络的相关性降低和内吞体受体分选的失调有关[9]. Zimprich等人[10]通过外显子组测序发现, VPS35中的D620N突变是导致PD的原因之一. Zavodszky等人[11]和McGough等人[12]研究表明, VPS35-D620N突变破坏了VPS35与其他转运蛋白的关联, 导致蛋白转运缺陷. Huang等人[13]的研究结果表明, VPS35-D620N突变破坏了由VPS35与多巴胺转运体(dopamine transporter, DAT), RAB5, RAB11和FAM21形成的蛋白相互作用复合物, 从而破坏了DAT从早期内吞体到循环内吞体的运输, 进而增加了突触间隙中的多巴胺(dopamine, DA), 导致多巴胺能(DAergic)神经元变性和运动功能障碍. 越来越多的证据表明, VPS35蛋白水平降低与多种神经退行性疾病密切相关, 如阿尔茨海默症[14]、渐冻症[15]、帕金森病[16]等.

除了神经退行性疾病, 癌症同样作为目前人们关注的健康问题, 也是医学上难以攻克的难题之一. 随着经济迅速发展, 人民生活水平日渐提高, 癌症已经成为中国最常见的死亡原因之一. 据中国国家癌症中心(Nastional Cancer Center China, NCC)估计, 2020年中国新发癌症病例457万例, 粗发病率为293.9/100000, 有241.35万人死于癌症. 统计表明, 中国最普遍的癌症是肺癌、乳腺癌、结直肠癌、胃癌、乳腺癌和甲状腺癌[17,18]. 根据国家卫生统计局的估计, 2000~2020年, 国人四个主要死亡原因是癌症、心脏病、脑血管疾病和呼吸系统疾病. 在城市地区, 癌症是主要死亡原因, 而在农村地区, 癌症也已经超过呼吸系统疾病, 成为主要死亡原因[19].

癌症引起的死亡90%以上都是由于肿瘤转移所导致的. 肿瘤转移经历一个繁琐的过程, 包括获得原发肿瘤的转移能力、血管生成、免疫抑制以及肿瘤细胞在宿主器官的定植和生长[20~22]. 肿瘤细胞可以通过扩散转移、血行转移、淋巴转移和种植转移, 对癌细胞胞外基质的重塑, 促进血管生成, 影响其脂质代谢、干细胞稳态等一些途径也可以促进肿瘤的转移. 此外, 通过特定因子和胞外囊泡(extracellular vesicle, EV)的分泌, 可以激活远端淋巴管生成, 招募骨髓来源细胞[23~25], 激活间质成纤维细胞促进胞外基质的重塑来帮助肿瘤细胞进行器官的远端定植[26,27]. 因此, 如何抑制肿瘤的转移, 提高肿瘤患者的生存期已成为当前国际社会研究的热点问题. 近几十年来临床肿瘤学的发展为肿瘤的治疗带来了一些进展, 但是肿瘤转移仍然是有效治疗癌症的关键阻碍. 因此, 揭示肿瘤转移的调控机制, 探寻肿瘤治疗靶点并研发相应药物是目前肿瘤治疗亟待解决的问题.

目前有许多研究揭示, VPS35在肿瘤中也发挥潜在影响. 近期, 一项单细胞和批量RNA测序数据揭露VPS35是癌症的潜在的治疗靶点[28], 它可通过PI3K-AKT[29]、Wnt[30]信号通路和KLF7/VPS35[31]等途径发挥其促癌作用, 以促进肿瘤生长、侵袭和转移. 本文将对VPS35在肿瘤发生与转移中的功能与机制进行综述.

1　VPS35在不同肿瘤中的表达水平升高

大量研究表明, VPS35广泛在人体组织中表达, 并且参与不同的生理生化反应. 根据TCGA数据库分析, VPS35在许多系统性恶性肿瘤, 如与消化系统相关的结肠腺癌、食管癌、胰腺癌、直肠腺癌、胃癌, 免疫系统肿瘤中的胸腺瘤中均有过度表达(图1), 并与肿瘤的病理分型、恶性程度、侵袭性和转移等都有相关性.

2　VPS35在肿瘤发生和转移中的作用

已有研究表明, VPS35在多种癌症(乳腺癌、肝癌、黑色素瘤癌等)中发挥重要作用, 哺乳动物VPS35/Retromer介导多种货物蛋白从内吞体到高尔基体或细胞膜的逆行转运[32], 譬如在生长因子受体转运[33,34]和细胞内信号转导[35,36]中发挥多种重要作用. 引起肿瘤病人死亡的一个首要因素是肿瘤转移的发生[37], 敲降*VPS35*可以抑制肿瘤细胞的迁移和侵袭, 过表达*VPS35*会促进肿瘤的侵袭和转移, VPS35/Retromer蛋白复合体对肿瘤发生与转移探索解析将会为肿瘤患者的治疗提供新的靶标和治疗策略.

2.1　VPS35与肿瘤发生

(1) VPS35调控N-Ras信号通路. *RAS*是目前研究最广泛的致癌基因[37]之一, Ras蛋白是一种外周膜蛋白, 其亚细胞定位取决于特定的脂质修饰、局部膜的组成以及C端19~20个残基形成的高可变区(highly

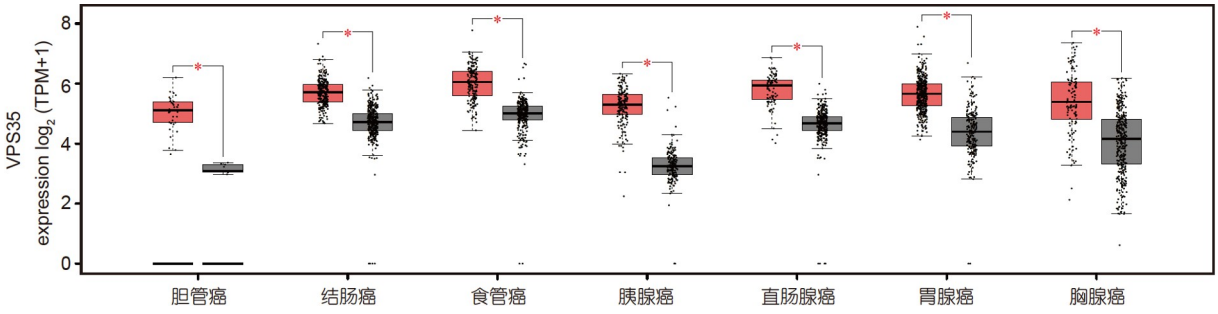

图 1 VPS35在不同肿瘤组织与配对正常组织中的表达水平(红色为肿瘤组织, 黑色为正常组织). 数据来自于 http://gepia2.cancer-pku.cn. *表示P<0.05

Figure 1 VPS35 expression in different tumors and matching normal tissues. (Red is tumor tissue; Black is normal tissue). The data come from http://gepia2.cancer-pku.cn. * represents P<0.05

variable region, HVR)[38]. Wright和Philips[39]发现, 所有Ras的HVRs都以CAAX序列结束, 该序列会被法尼基化(farnesylation)、AAX蛋白水解和戊基半胱氨酸羧甲基化修饰, 以运送Ras蛋白到质膜(plasma membrane, PM). Ras蛋白在细胞膜之间的运输需要额外的靶向元件, H-Ras和N-Ras被转运到高尔基体, 在高尔基体上HVR的半胱氨酸残基被DHHC9和GCP16棕榈酰化, 促进Ras与膜的结合, 然后通过囊泡运输到质膜, 激活下游信号通路[40,41].

VPS35蛋白参与Ras蛋白的分选和运输. Goodwin等人[42]和Rocks等人[43]研究表明, N-Ras可以通过Retromer介导的囊泡运输途径从内吞体逆行到高尔基反面管网结构和质膜, 对Ras信号的释放、回收、重分配有调节作用. Zhou等人[44]通过荧光共振能量转移技术观察到完整细胞中N-Ras有一种亚型选择性, 表明正是N-Ras独特的HVR对脱棕榈酰化特别敏感, 有利于其与VPS35的相互作用, 而VPS35与N-Ras结合的方式依赖于法尼基化, 通过Preyl依赖的方式结合N-Ras, 并调节其亚细胞定位, 此外, 他们还发现沉默VPS35可以增加N-Ras与细胞质囊泡的联系, 减少Ras的GTP负载, 抑制促分裂素原活化蛋白激酶信号通路(mitogen-activated protein kinase signaling, MAPK)和N-Ras依赖性黑色素瘤细胞的生长, 为黑色素瘤患者的治疗提供新的靶标和治疗策略.

已有的研究表明, VPS35对Ras信号的释放、修饰、回收、重分配有调节作用, 且经修饰后的N-Ras高可变区与VPS35可以相互作用, 调节细胞定位. VPS35对MAPK信号通路也有一定的影响, MAPK通路是细胞增殖的主要途径之一, 且位于许多生长因子受体的下游, MAPK与成纤维细胞生长因子受体(fibroblast growth factor receptor, FGFR)也有一定的关系, 所以探讨VPS35对肿瘤的调控很有必要.

(2) VPS35对Wnt信号通路的影响. 在胚胎发育过程中, Wnt/非典型平面细胞极性(non-canonical planar cell polarity, PCP)对于细胞迁移是必不可少的[45,46]. 此外, Wnt/PCP核心成分在各种实体肿瘤中都存在调节失调的现象, 且它们都直接参与促进了肿瘤细胞迁移和转移[47], 如乳腺癌[48~50]、脑癌[51]、卵巢癌[52]、前列腺癌[53]、胃癌[54]和结直肠癌[55]等. Liu等人[56]通过RT-PCR观察到*VPS35*过表达会通过诱导上皮-间质转化(epithelial-emesenchymal transition, EMT)相关基因表达, 如基质金属肽酶14(matrix metalloproteases14, *MMP14*)、基质金属肽酶9(matrix metalloproteases9, *MMP9*)和Ⅰ型胶原α2(collagen type Ⅰ alpha 2 chain, *COL1A2*)等上调, 同时也会降低RhoA Ser188位点、Rac Ser71位点和p62 Serine 403位点的磷酸化, 增加p62和Rock1的表达和JNK的磷酸化来增强肝癌(hepatocellular carcinoma, HCC)细胞侵袭和转移, VPS35的缺失也会减少裸鼠肝癌的肺转移概率, 通过转录组分析, 确定VPS35通过调节肝癌细胞中卷曲蛋白2(frizzled class receptor 2, FZD2)和ROR1的膜分选和转运机制激活Wnt/PCP通路, 加速EMT的进展, 促进了HCC细胞在体内和体外的迁移, 从而为肝癌提供一个潜在的预后标志物和治疗靶点.

George等人[57]通过GST融合蛋白pulldown实验, 确定了LRP6细胞内结构域和VPS35之间可能的间接相互作用, 且VPS35的N端缺失突变体减少了表达外源性Wnt-1的HEK-293细胞中典型的Wnt信号. Chiu等

人[58]通过构建杂合子*VPS35*$^{D620N/+}$敲入小鼠生成了常染色体显性和晚发型PARK17动物模型，发现VPS35 D620N突变导致VPS35功能失常，使Wnt/β-catenin通路活性受损，16月龄*VPS35*$^{D620N/+}$敲除小鼠黑质致密部(substantia nigra pars compacta, SNpc)中Wnt1和核β-catenin显著下降，下调抗凋亡蛋白Survivin的表达活性，导致Caspase-8和Caspase-9的蛋白水平上调，研究表明VPS35 D620N突变会引起线粒体碎裂和线粒体功能障碍，使SNpc多巴胺能(DAergic)神经元细胞发生神经退行性病变，导致线粒体ROS过量产生和线粒体凋亡通路激活，证明Wnt/β-catenin级联的活性需要含有VPS35的逆转运复合体的正常功能，该级联信号也参与黑质致密部多巴胺能神经元的保护和存活，对线粒体形态功能维持有重要作用，所以靶向VPS35-线粒体研究将对研究肿瘤发生提供重要的理论依据.

(3) VPS35受KLF7调控并影响肿瘤发生. Krüppel-like因子(Krüppel-like factors, KLFs)是一类高度保守的含锌指结构的转录因子，通过与靶基因启动子序列结合调节基因转录活性，广泛参与人体重要的生物过程[59]，在许多生理和病理过程中都是必不可少的[60,61]. 根据KLF7的转录活性, KLF7调节多种基因的表达, 参与癌症的发展. Wang等人[62]研究发现，在子宫内膜癌(endometrial cancer, UCEC)中, KLF7促进UCEC细胞增殖、集落形成，加速细胞周期进展和细胞迁移，*KLF7*敲低会抑制UCEC细胞的异种移植肿瘤发生. 通过RNA测序、免疫印迹分析发现，KLF7在UCEC细胞和组织中正向调控透明质酸合成酶2(*HAS2*)，HAS2的下调可以抑制KLF7在肿瘤发展中的促癌作用. Rahman等人[63]构建表达*VPS35*或*VPS35 D620N*的转基因SH-SY5Y细胞系，并进行RNA-Seq转录组分析，发现VPS35-D620N突变会影响透明质酸(hyaluronic acid, HA)介导的运动受体(hyaluronan mediated motility receptor, HMMR)对自噬相关PI3K-AKT通路的调节，PI3K-AKT通路也在卵巢癌[64]、胃癌[65]、肿瘤血管生成[66]中有许多研究. Guo等人[31]的qRT-PCR结果显示，*KLF7*在癌组织中过表达，表明KLF7是HCC分化和转移的预测因子，他们的研究也证实了KLF7-VPS35调控轴在HCC细胞生长、细胞侵袭、细胞周期和细胞凋亡中的重要作用, 并发现KLF7在HCC细胞中作为转录因子调控VPS35的表达，与VPS35表达量呈正相关，通过CHIP-qPCR发现KLF7与*VPS35*启动子结合，KLF7通过KLF7-VPS35轴激活CCDC85C介导的β-catenin通路，促进肝癌细胞增殖、侵袭和细胞周期进程，并阻断肿瘤细胞凋亡，且VPS35, KLF7, β-catenin呈强正相关, 因此靶向KLF-VPS35-β-catenin是值得研究的肿瘤治疗靶点.

KLF7作为转录因子，在多种癌症中都有研究，前文指出VPS35可以与其相互协作调节β-catenin通路，KLF7也与Akt信号通路有关并促进前脂肪细胞的增殖[67]，那么KLF7与VPS35之间是否还存在其他信号通路的调节，对肿瘤的发生又有何作用，需要进一步去探索.

(4) VPS35调控FGFR促进肿瘤发生. FGFR是一类具有单次跨膜结构的受体酪氨酸激酶(receptor tyrosine kinases, RTK)蛋白，由胞外结构域(extracellular domain, EC)、跨膜区(transmembrane domain, TM)和胞内结构域(intracytoplastic domain, IC)构成[68]. FGF和FGFRs在血管生成、组织稳态、胚胎发生和伤口修复等基本生物学过程中发挥重要作用，而且在肿瘤发展中也发挥重要作用[69]. FGFR3突变促进膀胱癌[70]、宫颈癌[71]、鳞状细胞肺癌[72]、前列腺癌[73]、横纹肌肉瘤[74]等发生发展，FGFR2突变促进子宫内膜癌[75]和非小细胞肺癌[76]的发生发展.

Zhang等人[77]在肝细胞癌中发现了VPS35突变, 该研究发现VPS35激活的PI3K/AKT信号通路与FGFR3有关，FGFR3通过PI3K/AKT通路参与下游信号传递. 对VPS35-KO肝癌细胞中膜、细胞质和总细胞裂解物中FGFR3的测定发现其显著减少，证明VPS35对于FGFR3的分选和运输到质膜至关重要，表明VPS35可以通过增加FGFR3的分选和转运发挥其致癌作用. Zanazzi等人[78]在胶质瘤中通过DNA甲基化阵列、癌症全外显子组和转录组测序发现，*FGFR2*的17号外显子与*VPS35*的外显子2融合，融合蛋白保留FGFR2激酶结构域和伴侣基因*VPS35*的几乎整个编码序列，这种新型融合有望激活FGFR信号，并可通过使用FGFR抑制剂进行靶向治疗. Laederich等人[79]发现，FGFR3与HSP90分子伴侣紧密结合，并且会受其稳定性和功能的影响. Tan等人[80]研究表明，N端HSP90抑制剂(STA9090)上调Bclaf1和VPS35的水平，会增加EV的分泌，促进HepG2细胞的侵袭，Bclaf1可以通过bZIP结构域促进*VPS35*的转录，而敲低*Bclaf1*或*VPS35*可减轻STA9090诱导的EV的促转移能力，揭示了Bclaf1-

VPS35-EVs轴在肝细胞癌(Hepatocellular carcinoma, HCC)转移中的作用, 为抑制N端Hsp90 Inhibitor诱导的胞外囊泡转移提供了一种新的联合治疗策略.

FGFR2和FGFR3在报道中都发现和VPS35有关系, 作为Retromer的核心组分, VPS35对FGFR的分选和转运有关键作用, 且可以通过胞外囊泡的分泌增加来促进肿瘤细胞的侵袭, 故靶向VPS35将为肿瘤治疗提供新的治疗手段.

(5) VPS35通过SLC4A的转运调控肿瘤发生. 胞内和胞外pH(intracellular and extracellular pH, pHi和pHe)稳态是细胞微环境的重要组成部分, 是细胞功能正常的前提. 过去十年的研究表明, pHi稳态在癌症的发生中有明显改变[81,82]. George等人[57]通过使用液泡质子ATP酶(vacuolar proton ATpase)抑制剂阻止其对内吞体的酸化作用, 从而抑制由Wnt配体启动的典型Wnt信号转导途径. 溶质连接共转运蛋白4(solute linked co-transporter 4, SLC4)家族由十个成员组成(SLC4A1~5; SLC4A7~11), 它们在pHi缓冲中起着关键作用[83,84]. SLC4A11是这个家族中最分化的成员, 最近被描述为Na^+/OH^-和$NH4^+$转运蛋白[85], 故SLC4家族成员的失调可能与某些癌症的病理发展有关.

SLC4A7可以促进乳腺癌组织中的酸排出, 维持碱性细胞的内环境并促进侵袭性肿瘤的生长. Lee等人[86]研究发现, 通过干扰*SLC4A7*表达可延长乳腺癌潜伏期, 抑制肿瘤细胞增殖, 减缓肿瘤生长. Boedtkjer等人[87]也发现, Na^+和HCO_3^-的共转运蛋白SLC4A7在人原发性乳腺癌和转移灶中相对于正常乳腺组织均有表达上调. Parks和Pouyssegur[88]发现, *SLC4A4*上调促进结肠癌和乳腺癌细胞的生长和迁移. Qin等人[89]发现, *SLC4A11*高表达是3/4级浆液性卵巢癌OS差的独立预测因子, 在卵巢癌中, DNA扩增和低甲基化都有助于其上调. Liu等人[90]发现, VPS35在角膜细胞增殖, 特别是基底上皮细胞增殖中是必要的, SLC4A11是VPS35/Retromer的识别货物, 其靶向细胞表面依赖于VPS35的功能. 力学研究表明, VPS35是促进角膜内皮膜运输蛋白SLC4A11的细胞表面靶向作用所必需的. 由此可以推断, VPS35对于与SLC4A相关的肿瘤可能是一个潜在的靶点.

SLC4A与细胞微环境调控有关, SLC4A的排酸作用对维持促进肿瘤生长侵袭的碱性环境有所助益. 肿瘤与细胞微环境的关系目前也是肿瘤生物学的研究热点, 而在前文所述SLC4A11可能是VPS35/Retromer的识别货物, VPS35在肿瘤微环境中的调控作用目前还是未知的, 所以很有探讨的前景和必要性.

2.2 VPS35与肿瘤转移

(1) VPS35通过调控线粒体的功能来影响肿瘤转移. 作为细胞的能量工厂, 线粒体与肿瘤转移的关系一直以来都是肿瘤研究热点. VPS35可以与线粒体相关蛋白相互作用来调节线粒体的稳态及功能, 也与由线粒体引发的内源凋亡途径息息相关.

线粒体的融合/裂变不仅对控制线粒体的形状、大小和数量至关重要, 而且对调节线粒体功能(如呼吸和细胞死亡/存活)、清除(如线粒体分裂)和分布也至关重要. Tang等人[91]发现, VPS35是线粒体E3泛素蛋白连接酶1(mitochondrial E3 ubiquitin protein ligase 1, MUL1)转运和降解的关键调节因子, 可以增加线粒体融合蛋白2(mitochondrial fusion protein, MFN2)的稳定性, 促进MFN2介导的线粒体融合, VPS35/Retromer的异常调控损害MUL1降解和线粒体融合, 这可能是引发线粒体疾病的基础. Wang等人[92]发现, VPS35突变体可以通过增强的VPS35-DLP1相互作用引起线粒体碎裂, 在线粒体动力样蛋白(dynamin-like protein 1, DLP1)的C末端发现了一个高度保守的FLV基序, 其突变显著降低了VPS35-DLP1相互作用, 从而影响线粒体的稳定性. Farmer等人[93]证明, 哺乳动物Eps15同源结构域蛋白1(Eps15 homology domain protein 1, EHD1)及其相互作用分子Rabankyrin-5通过与Retromer相互作用可以影响线粒体动力学, 可能是通过诱导VPS35从线粒体膜上去除失活的动力蛋白相关蛋白1(dynamin-relatedprotein 1, Drp1)来影响线粒体稳态. 线粒体的形态与肿瘤也有关系, 例如线粒体裂变增加是一种促瘤表型[94].

VPS35除了调节线粒体融合分裂相关因子外, 也对由线粒体引发的内源途径的细胞凋亡因子(B-cell lymphoma-extra large, Bcl-xl)有重要影响. Farmer等人[95]确定VPS35和VPS26这两种Retromer的核心成分是Bcl-xl的新型调控因子, 当VPS35耗尽时, 非线粒体Bcl-xl水平增加. 此外, Retromer缺失细胞表现出更快的Bax激活和凋亡, 揭露了Retromer通过促进Bcl-xl运输到线粒体外膜来调节细胞凋亡. Bcl-xl除了与细胞的凋亡相关, 还在一些肿瘤细胞的侵袭、迁移、上皮

间质转化、转移中发挥作用，这些生物学功能已在不同类型的肿瘤中被观察到，如胶质瘤[96]、乳腺癌[97]、结肠直肠癌[98]和胰腺癌[99]. 因此, VPS35可以是肿瘤转移调控中一个良好的潜在治疗靶点.

(2) 调控MT1-MMP转运回收促进肿瘤转移. 膜1型基质金属蛋白酶(membrane type 1 matrix metalloproteinase, MT1-MMP)最初被发现为存在于肿瘤细胞表面的基质金属蛋白酶[100]. 在人类蛋白质图谱中的MT1-MMP亚细胞图谱显示，该蛋白酶主要定位于细胞质和细胞骨架[101]的微丝中, 它除了在细胞表面积聚外, 还定位于细胞质[102]、高尔基体[103]和细胞核[104]等. 它的表达与多种肿瘤的生长发展息息相关，Hao等人[105]通过文献整理分析发现，MT1-MMP在许多系统性恶性肿瘤中，如消化系统肿瘤中的肝细胞癌、胃癌, 泌尿系统肿瘤中的肾癌，神经系统肿瘤中的神经胶质瘤等均过度表达，并与肿瘤的病理分型、恶性程度、侵袭性和转移等都有相关性. Szabova等人[106]和Tomari等人[107]研究发现，在肿瘤细胞中增加MT1-MMP的表达量可以通过影响细胞外基质重塑[108]、血管生成[109]、脂质代谢[110]、炎症反应[111]等途径促进肿瘤的转移. Strongin[112]和Zhang等人[113]发现，MT1-MMP在肿瘤组织中的表达和活性明显升高，MT1-MMP的高水平量与细胞迁移能力增强和肿瘤区域侵袭、肿瘤细胞远程转移直接相关. Sharma等人[114]研究表明，在乳腺癌细胞系中，VPS35/Retromer和SNX27通过直接与MT1-MMP细胞质尾部的最后三个氨基酸DKV相互作用选择性地识别MT1-MMP，并帮助其从内吞体中分选, 促进MT1-MMP蛋白酶在细胞表面循环, 从而介导ECM降解，调节基质侵袭活性，在肿瘤转移中发挥重要作用. 由此可见，VPS35/Retromer可以参与并通过调控MT1-MMP的胞内转运, 影响肿瘤的转移.

3　讨论

VPS35目前在神经退行性疾病中研究颇多，在肿瘤的发生与转移方面较为单薄. 本团队通过TCGA数据库分析发现, VPS35广泛在人体组织中表达, 且与许多系统性恶性肿瘤都有密切关系. 本文从FGFR、N-Ras信号通路、Wnt信号通路、SLC4A、线粒体调控、MT1-MMP转运回收以及KLF7因子等方面着手, 论述VPS35在肿瘤发生和转移中的作用，并绘制了相关总结图(图2和3). 在肿瘤细胞中, 这些信号分子都对肿瘤的发生发展起关键作用，所以VPS35调控肿瘤相关信号通路的总结和归纳对于肿瘤预防和治疗具有深远意义. FGFR作为成纤维细胞生长因子受体，与FGF一起调控诸多与细胞生成、分化、增殖等相关的信号通路, FGFR3与HSP90分子伴侣紧密结合, 并且会受其稳定性和功能的影响. Bclaf1可以通过bZIP结构域促进VPS35的转录，而敲低*Bclaf1*或*VPS35*可减轻STA9090诱导的EV的促转移能力，*Bclaf1*和*VPS35*的上调也会通过增加胞外囊泡的分泌对细胞增殖有促进作用. *RAS*是致癌基因，它的修饰与肿瘤的发生相关, 通过抑制*VPS35*可以沉默由其介导的MAPK信号通路, 对黑色素瘤生长有抑制作用. KLF7是转录因子，通过调控VPS35可以激活β-catenin通路来促进肝癌的发生. Wnt信号在胚胎发育中有重要作用，它所介导的三个分支通路也在细胞生理生化功能中必不可少. 过表达*VPS35*可以诱导EMT相关基因表达来调控Wnt信号通路. VPS35通过调节肝癌细胞中FZD2和ROR1的膜分选和转运机制激活Wnt/PCP通路，并通过激活EMT细胞加速EMT的进展，促进HCC细胞在体内和体外的迁移. 此外，它与Notch对维持干细胞活性及分化平衡的负向调节有着重要的生理意义. VPS35可以与线粒体相关蛋白相互作用来调节线粒体的稳态，也与由线粒体引发的内源凋亡途径息息相关，且研究报道有指出, VPS35的缺陷会导致Wnt级联引发的线粒体凋亡, 因此VPS35与线粒体之间的关系对肿瘤的影响有极为重要的研究意义. SLC4A与细胞微环境调控有关, SLC4A11可能是VPS35/Retromer的识别货物，肿瘤与细胞微环境之间的关系目前也是肿瘤生物学的研究热点，VPS35在肿瘤微环境中的调控作用目前还是未知的.

4　总结与展望

由VPS35作为核心成分组成的Retromer是一种进化上保守的多聚体蛋白复合物，协调许多跨膜受体从内吞体到高尔基体和质膜分选. 最近的研究表明, *VPS35*是一种新的癌基因，与许多致癌因子息息相关, 可通过多种途径参与各种实体肿瘤的生长与转移，影响到关键的肿瘤进程，例如本文中所描述的FGFR、SLC4A、N-RAS信号通路、Wnt信号通路等与VPS35

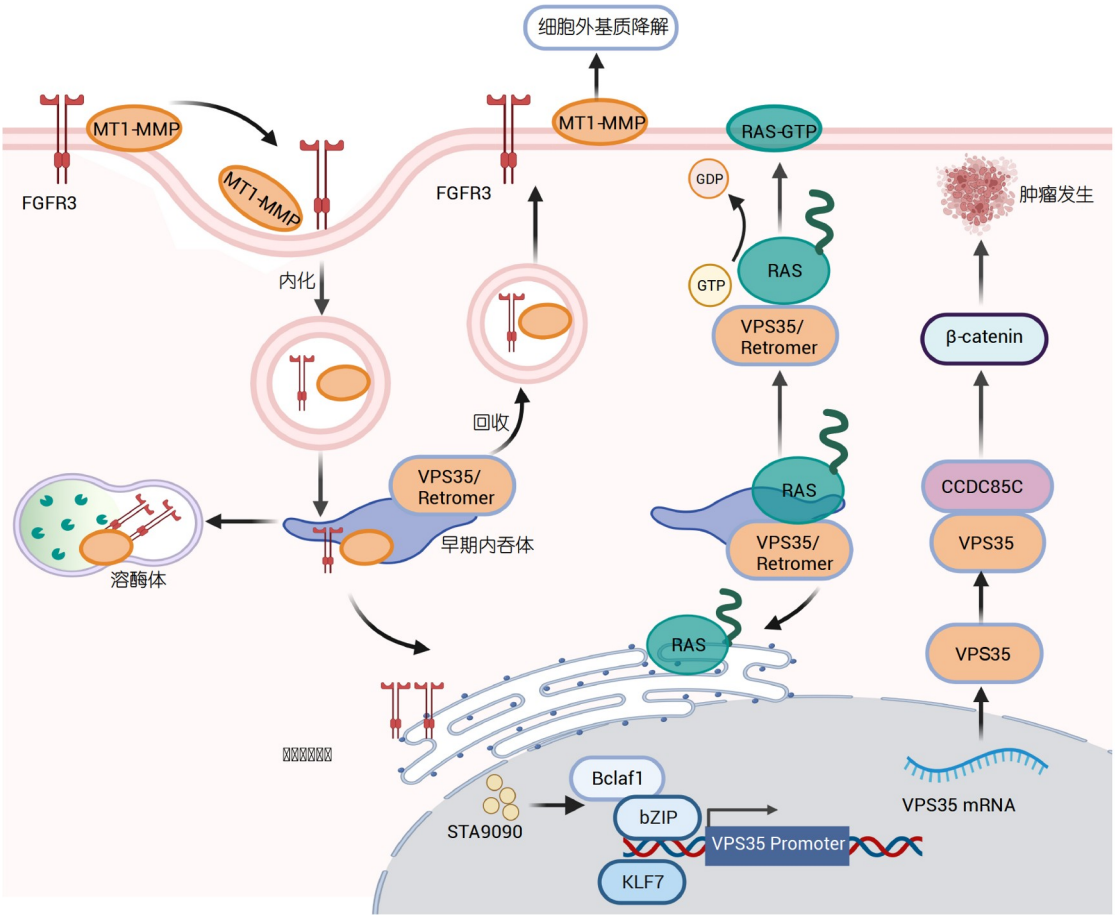

图 2 VPS35与FGFR, Ras, CCDC85C的作用机制图
Figure 2 Diagram showing VPS35 interacting with FGFR, Ras and CCDC85C

都息息相关，且里面的分子机制在一定程度上都有相交联系，例如，VPS35的突变体与Wnt/β-catenin通路相关，且KLF7也参加β-catenin通路，而且该突变体也会影响线粒体碎裂和线粒体功能障碍，从而导致线粒体ROS过量产生和线粒体凋亡通路激活.

PLA2G6(PARK14)突变导致人类神经退行性疾病, Lin等人[115]通过研究PLA2G6的果蝇同源物iPLA2-VIA，发现iPLA2-VIA可以通过结合Retromer亚基VPS35和VPS26促进蛋白质和脂质循环, 而iPLA2-VIA的缺失会损害Retromer功能, 使神经酰胺升高, 影响膜流动性并损害Retromer和神经元功能, 表明PLA2G6调节Retromer的稳定性，用药物(包括肉豆蔻素或地昔帕明)减少神经酰胺，可缓解溶酶体应激并抑制神经变性. Vos和Klein[116]描述了体内鞘脂是循环利用的，它们可以通过内吞囊泡，由Retromer介导完成从质膜到TGN的转运，一小部分被运送到溶酶体，通过酸性鞘磷脂酶降解为神经酰胺，故Retromer对神经酰胺的影响也是极为关键的. Morad和Cabot[117]论述了神经酰胺是一种肿瘤抑制因子，它可以驱动细胞发生凋亡、自噬和影响细胞周期进程，而肿瘤细胞因神经酰胺生成和代谢缺陷有助于其存活和耐药性的产生，通过神经酰胺疗法即神经酰胺信号和靶向特定的代谢接合点来放大神经酰胺的抑瘤活性在癌症治疗中具有极大潜力. Eleuteri和Albanese[118]研究表明, Parkin缺陷的小鼠大脑中与Retromer相关的WASH复合物货物减少, FAM21-WASH复合物可以与Retromer相互作用，控制WASH复合物向核内体的募集，保证其正确定位, WASH复合物的错误定位会导致自噬体形成缺陷，扰乱蛋白质的分选. 细胞竞争是一种保守的稳态机制, 上皮细胞通过这种机制消除一些坏细胞. Liu等人[119]

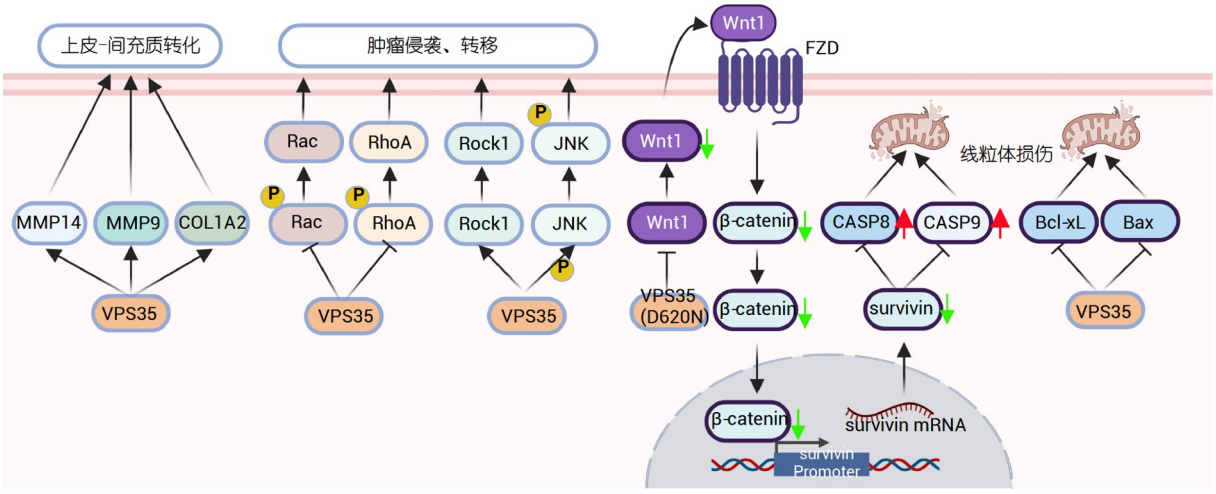

图 3　VPS35与Wnt、线粒体的相互作用
Figure 3　Interaction of VPS35 with Wnt and mitochondria

通过*scrib*$^{-/-}$细胞竞争模型中的遗传实验揭示了内吞体肌动蛋白调节因子WASH的激活状态是连接EGFR和Hippo信号激活的中心节点, 对维持细胞竞争有关键作用, 而WASH活性与Retromer循环途径息息相关. Muzio等人[120]针对Retromer稳定剂药理性可能有助于延缓渐冻症发生的退行性过程, 设计并合成了一个小阵列的苯基双胍基腙伴侣2a, 其可以在VPS35-VPS29界面与货物识别核心(cargo recognition core, CRC)复合物相互作用, 因为它能够穿过血脑屏障, 通过STD-NMR和WL-NMR实验证明了2a与VPS29-VPS35异源二聚体的结合, 并可以增加Neuro2a细胞中的VPS35水平. Retromer的不稳定可能会导致溶酶体缺陷, 接受2a驱动的Retromer稳定的G93A小鼠显示出高分子量SOD1聚集物的大幅减少, 多泛素化蛋白水平维持稳定, 这表明靶向VPS35/Retromer的药物对肌萎缩侧索硬化(amyotrophic lateral sclerosis, ALS)的治疗有重要作用.

目前许多药物都是基于Retromer设计, 以治疗神经性退行性疾病, 对于靶向VPS35抑制肿瘤转移的治疗并没有成药, 且相关的机制研究也并不充分. Retromer在肿瘤的发生和转移中起到至关重要的作用. 此外, Retromer对细胞和组织代谢方面的研究也处于起步阶段, 鉴于肿瘤患者中有很高比例的代谢合并症, 故研究靶向VPS35/Retromer的治疗方案具有很好的转化意义[121]. 因此, 可以根据神经性退行性疾病中与Retromer相关的药物来探索解析VPS35/Retromer组分在肿瘤发生转移中的作用及机制, 这将为肿瘤患者治疗提供新的策略与靶标.

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The roles and mechanism of VPS35 in tumorigenesis and metastasis

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VPS35 is an important component of the Retromer complex and plays an important role in the sorting and transporting of endocytic proteins. Recent studies have shown that *VPS35* is a new oncogene, and it is highly expressed in a variety of tumors and affects the development and metastasis of tumors by regulating a variety of factors and pathways. In this review, we summarize the latest research progress on how VPS35 regulates tumor-related factors and pathways to promote tumorigenesis and metastasis, and the mechanism of VPS35 in tumorigenesis and metastasis. We aim to provide a reference for further research and application of VPS35 in the cancer biology field.

VPS35, Retromer, tumorigenesis, metastasis

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