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· 评述与综述 ·

浮舰蛋白flotillins在细胞生理和疾病中的作用

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摘　要：浮舰蛋白flotillin-1和flotillin-2参与多个细胞生理活动过程，包括调节细胞黏附、物质内吞、蛋白质分选与再循环和细胞迁移，同时也与一些退行性疾病和肿瘤的发生发展有密切联系。该文介绍了flotillins的结构与定位，综述了flotillins从发现至今影响个体形态发生、神经元生长和功能以及调控多个信号转导途径等几个方面的研究进展，并展望flotillins在疾病机制研究以及临床诊断治疗中的作用。

关键词：浮舰蛋白；脂筏蛋白；信号转导；肿瘤；阿尔茨海默病
中图分类号：Q423；Q51；Q89；R322.8；R741　　**文献标志码：**A

The effects of flotillins on cellular physiology and diseases

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Abstract: Flotillin-1 and flotillin-2 are involved in many cellular physiological processes, including regulation of cell adhesion, cargo endocytosis, protein sorting and recycling, and cell migration. Flotillins are also closely related to the occurrence and development of some degenerative diseases and tumors. In this review, we first introduced the structure and distribution of flotillins. Then, we summarized the recent progress of flotillins since its discovery, including the impact on morphogenesis, neural growth and function, as well as the regulation of multiple signal transduction pathways. Finally, the role of flotillins in the research of disease mechanism and clinical diagnosis and treatment was prospected.

Key words: flotillins; lipid raft protein; signal transduction; tumor; Alzheimer's disease

与哺乳动物不同，鱼和两栖类视网膜神经节细胞(RGC)受损后能够再生，并在视顶盖大脑重构视网膜投射[1]。Schulte等[2]使用单克隆抗体和分子克隆技术鉴定出金鱼RGC再生过程中表达上调的两种相对分子质量为47~48 kDa的蛋白，将其命名为reggie-1和reggie-2，来源于“再生”。同年，Bickel等[3]从鼠肺中分离出一类不溶于Triton X-100并能在蔗糖密度梯度上层中浮动的脂筏(lipid raft)蛋白，命名为浮舰蛋白(flotillins)。1998年，Lang等[4]研究表明，大鼠reggies(reggie-1和reggie-2)与flotillins(flotillin-1和flotillin-2)同源性高达99%，并且reggie-2与flotillin-1相同，reggie-1与flotillin-2相同。本文结合多年来的研究结果，统一使用flotillin-1和flotillin-2表示两种同源蛋白。

Flotillins是SPFH超家族(stomatin, prohibitin, flotillin, and HflK/HflC)成员[5]，其N端含质膜结合的SPFH结构域[6]，C端含α-螺旋的flotillin高度保守结构域，是形成同源或异源寡聚体的重要区域[7]。所有SPFH蛋白在其N端都有一个疏水结构域，通过棕榈酰基转移酶发生S-棕榈酰化，直接或间接地调节蛋白的稳定性、分子间的相互作用以及翻译后修饰，从而影响其质膜亚细胞定位和功能[8]。Flotillin-1的PHB (prohibitinlike domain)区半胱氨酸残基Cys-34的肉豆蔻酰化和/或棕榈酰化对其在肾细胞质膜的锚定是必不可少的[9]。

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Flotillin-1和flotillin-2虽为不同的基因产物，但二者mRNA同源性为50%，蛋白质同源性为44%，均由428个氨基酸组成，可以组成同源或异源二聚体[10]。二者分布非常广泛，几乎所有哺乳动物细胞类型都有表达，其序列从果蝇到人高度保守[11]。以哺乳动物为例，flotillin-1主要在神经系统中表达，而flotillin-2在不同组织中广泛分布[12]。在植物细胞中，flotillin-2复合物参与植物体水运输和细胞内物质运输过程[13]。逆转录病毒中的三结构域蛋白家族(tripartite motif, TRIM)成员TRIM5α与flotillin-1相互作用，调节逆转录病毒生命周期[14]。除了酵母和线虫不含flotillins外，其他真菌和细菌中均存在“flotillins样蛋白”同源物，虽然序列相似性低，但也具有flotillins蛋白的功能[10]。例如，枯草芽孢杆菌中的YuaG是真核生物flotillin的同源物，膜上YuaG在孢子形成的早期起信号级联反应作用，敲除*yuaG*会影响孢子的形成时期和出芽效率[15]；丝状真菌生长速率受到flotillins 同源物FloA的影响，敲低FloA会导致菌丝形状变得不规则，以及质膜结构受损[16]。Flotillins主要定位于细胞质膜和细胞内隔膜[4,17]，flotillin-1定位于胞内体[18]、高尔基体[19]、吞噬小体[20]、外泌体[21]，甚至与前列腺肿瘤过表达蛋白1 (prostate tumor overexpressed 1, PTOV1)结合，一起转移到细胞核内促进细胞增殖[22]。

Flotillins的亚细胞定位是动态分布的，取决于细胞分化状态和细胞类型。由于其独特的结构与生理特性，flotillins作为脚手架蛋白与本身异源寡聚化、肌动蛋白的结合以及和膜的结合有关[8]，调节蛋白质复合物的局部聚集与组装，并直接或间接地影响脂筏信号转导过程，调节多种细胞生理功能。

1 Flotillins参与个体形态发生

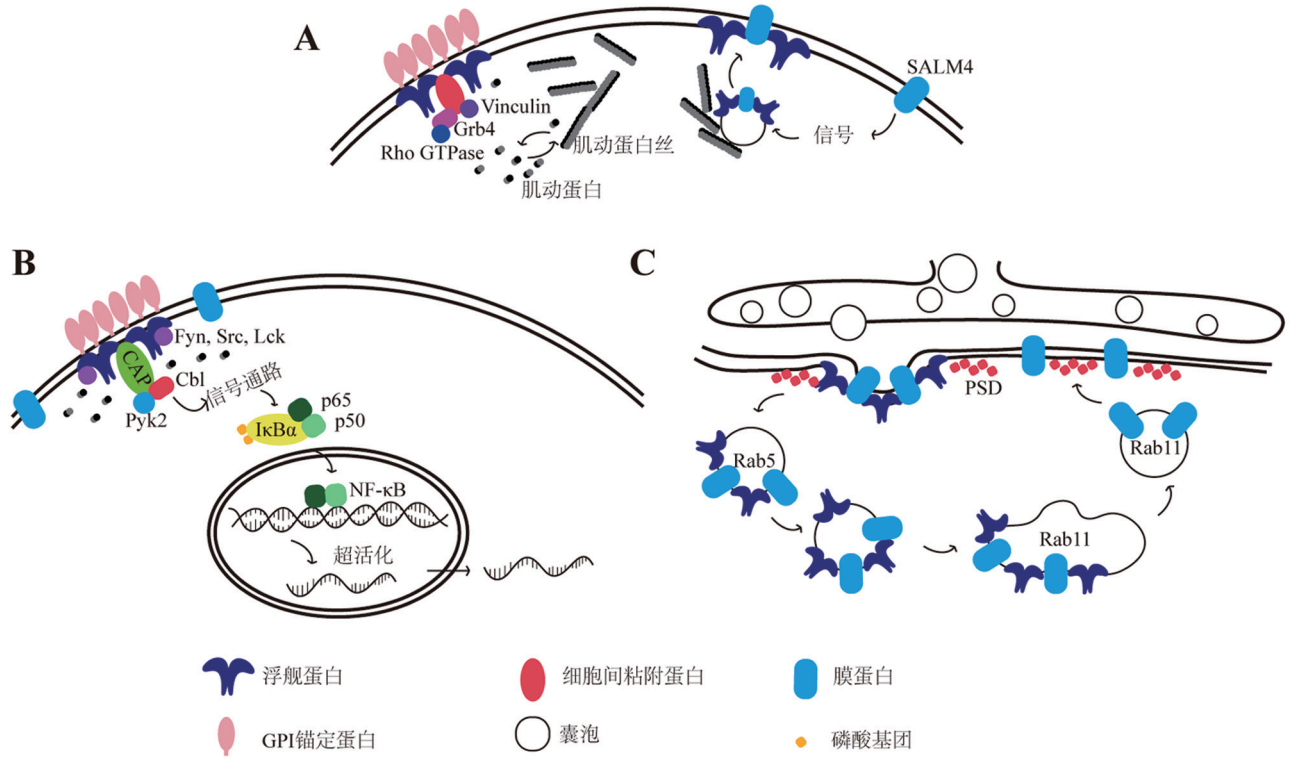
通过原位杂交、在体成像等技术，在非洲爪蟾、果蝇、斑马鱼以及小鼠等模式动物中均可检测到flotillins的表达。2004年，Pandur等[23]从非洲爪蟾cDNA文库中克隆了flotillin-1的两个旁系同源基因(paralogous gene)*flotillin-1a*和*flotillin-1b*，检测了*flotillin-1*基因从受精卵到蝌蚪期的表达模式。在早期发育阶段，即受精卵发生和卵裂期，flotillin-1的mRNA高度表达，首先在外胚层中表达，并随着神经板的形成，在神经外胚层逐渐增强。随着神经管的形成与分化，flotillin-1在胚胎背侧表达增多，在尾芽期的轴旁中胚层表达增高。Flotillin-1a在鳃弓间充质、鳃外胚层和背侧中胚层均有表达，而flotillin-1b主要在背侧神经管和头部感觉器官中表达。在果蝇胚胎发育过程中，flotillin-2参与神经系统翻译后调节[24]。在斑马鱼胚胎发育过程中，flotillin-1a、flotillin-1b和flotillin-2a从受精卵开始到整个发育早期都有表达，发育后期会产生组织特异性分布[17]，并对原肠期的外包(epiboly)形成至关重要[25]。

过表达和(或)敲除flotillins会导致动物个体形态发生和发育缺陷。在果蝇中敲除flotillin-2引起Wnt和Hedgehog这两种形态发生相关因子减少，而过表达flotillin-2则诱导Wnt和Hedgehog的分泌和扩散[26]，导致果蝇翅膀、眼睛和刚毛异常，免疫球蛋白超家族成员(IgCAMs)的细胞黏附分子定位错误[24]。单细胞时期注射吗啉基敲低flotillin-2后，斑马鱼胚胎从16细胞期到至少1000细胞期表现出明显的组织缺陷。随着发育的进行，敲低组个体出现外骨骼发育缺陷，个体生长明显延迟或完全停滞[25]。在哺乳动物发育过程中也能检测到类似现象[16]。神经元突触前的粗面内质网附近的flotillin-1表达水平在3周龄大鼠的视皮层中达到高峰，三个月后表达量显著降低[27]。在出生后7天和14天的大鼠睾丸中发现，flotillin-1的表达水平较高，但在出生后21天显著下降[28] 。这些实验结果表明，flotillins的表达和分布与发育时期相关，并在一定程度上影响胚胎发生与个体发育。

2 Flotillins影响神经元生长和功能

最初在受损的金鱼视网膜神经节修复过程中检测到flotillins，表明flotillins影响神经元形态发生、再生和功能。突触黏附样分子(synaptic adhesion-like molecules, SALMs)是一类可以诱导哺乳动物海马区的神经突生长的分子，可以诱导轴突形成和分支。Flotillin-1是SALM4介导的轴突分支的必需分子，这一过程也需要胞体合成膜蛋白，以及SoHo蛋白对肌动蛋白细胞骨架的调节[29] (图1A)。Flotillins对神经元轴突、树突形成后的延伸与分支，以及神经网络的形成至关重要。

在轴突发育的起始、生长、修剪和分支等一系列形态发生过程中，flotillins通过膜转运系统参与突起结构调节和功能发生。Flotillins形成的聚合体能够与糖基磷脂酰肌醇(glycosylphosphatidylinositol, GPI)锚定蛋白结合，通过协同激活flotillins依赖性Src酪氨酸激酶Fyn、丝裂原激活蛋白激酶(MAPK)、Rho家族GTP激酶、磷酸肌醇3激酶(PI3K)以及下游效应因子(如肌动蛋白解聚因子Cofilin)等[30-33]，通



(A) 通过SALM4调节细胞骨架锚定和膜蛋白运输。(B) 通过NF-κB转录因子，参与分子信号转导通路，激活基因转录。 (C) 参与Rab5和Rab11介导的胞内体转运。

图1　Flotillins参与的部分信号转导和运输途径

过Rab5和Rab11介导的胞内体将神经型钙黏蛋白(N-cadherin)募集到质膜的特定区域(如轴突的生长锥)，调节蛋白质募集和再循环以及细胞骨架肌动蛋白动态变化[34]。敲除*flotillin-1/-2*基因后，斑马鱼和小鼠等神经元轴突生长受阻，导致神经元发育缺陷；而体外培养成年大鼠RGC，过表达*flotillin-2*后，产生的轴突要比对照组的轴突长40%~60%[32]。当激活的朊蛋白(Prion protein, PrP)和膜上flotillins微区(microdomain)形成共聚体富集在细胞的生长锥时，Fyn和MAPK等激酶信号被激活，调节轴突中胞外分泌复合体(exocyst)关键亚基Exo70和神经型钙黏蛋白的转运，最终促使轴突生长。GTPase TC10突变可以阻止PrP-flotillins诱导的神经型钙黏蛋白募集和转运，表明PrP-flotillins介导的信号转导和转运途径共同调节神经元形态和功能的多样性[35]。

突触发育异常容易导致神经发育疾病，因此，研究突触结构、突触间相关蛋白的互作与信号分子通路十分必要，而突触的成熟和维持离不开细胞膜中的脂筏结构[36]。Nakadate [27]发现，flotillin-1在兴奋性或抑制性神经元突触前末梢的动态变化决定了视皮层突触的形成和维持。Swanwick等[37-38]发现，flotillin-1/-2蛋白与N-甲基-D-天冬氨酸受体(NMDARs)的亚基(NR2A和NR2B)存在共定位和相互作用，神经元受到刺激后通过flotillins促进NMDARs内化。使用flotillin-1抗体标记体外培养两周的海马神经元谷氨酸能和GABA能突触后发现，flotillin-1与囊泡谷氨酸转运体1 (VGluT1)共定位，且flotillin-1定位于突触而不是突触外NR1；根据免疫组化和电生理实验，flotillin-1过表达增加了谷氨酸能突触的数量和微小兴奋性突触后电流(miniature excitatory postsynaptic current, mEPSC)的频率，但抑制性突触后电流(mIPSC)频率无差异，且振幅均不受影响[38]。Monje 等[39]发现，水迷宫训练后小鼠海马组织中flotillin-1的表达水平显著升高，表明flotillin-1与学习记忆存在联系。上述研究表明，flotillins表达上调可以促进神经元再生和生长，并且伴随着神经元的功能变化[30]。这说明在中枢神经系统中，flotillins不仅影响器官发育，而且对神经元突触传递以及学习和记忆功能具有重要影响。

3　Flotillins参与多种细胞信号过程

Flotillins以同源和/或异源四聚体的形式，通过

细胞表面蛋白(受体)内吞、分选与再循环以及与细胞骨架的相互作用，调节多种受体信号转导途径[40]。聚合体的结构和组分的动态变化依赖于肌动蛋白，破坏肌动蛋白可以增加flotillin-2微区的分子交换[41]；flotillins蛋白也可以反向调节细胞骨架蛋白的活性[40](图1A)。

3.1 Flotillins调节细胞黏附

Flotillins微区可以通过改变肌球蛋白IIa (myosin IIa)的磷酸化水平来加强与肌动蛋白的相互作用，促进蛋白质向质膜的运输[42]。Flotillins聚合体通过N-cadherin在细胞质膜微区富集，调节细胞黏附[43]。果蝇flotillin-2突变体没有明显缺失表型，但体内flotillin-1蛋白变得不稳定并被降解；而在果蝇中过表达flotillin-2会扰乱细胞间黏附分子及其配体SNS在细胞边缘的分布[24]。Flotillins微区与PrP蛋白聚合可以激活Src家族激酶，募集黏附分子，以及重组肌动蛋白细胞骨架。Flotillin-1/-2和cadherins在细胞连接处形成大分子复合物[25]，用shRNAs敲低间质和上皮细胞flotillin-1/-2的结果表明，flotillins表达降低会破坏细胞间连接的完整性和功能形成[44]。在七鳃鳗中，过表达L-flotillin-1可诱导参与细胞黏附反应的血管细胞黏附分子-1 (vascular cell adhesion molecule-1, VCAM-1)和细胞间黏附分子-1 (intercellular adhesion molecule-1, ICAM-1) mRNA水平上调[45]。Src激酶和flotillin-2可以形成复合体，flotillin-2磷酸化后从质膜转运到胞内体[46]。在上皮A431细胞中，flotillin-1/-2和PrP下调会减少C-cbl靶向的Src激酶活化和表皮生长因子受体(epidermal growth factor receptor, EGFR)磷酸化，并通过阻断EGFR内化而导致EGFR在膜上数量增加，最后引起细胞重叠和黏附连接异常[47] (图1B)。

3.2 Flotillins调节物质内吞

Flotillin-1和flotillin-2在细胞膜上募集相关分子形成的微区与窖蛋白(caveolin)形成的穴样内陷(caveolae)不同，flotillins蛋白激活网格蛋白(clathrin)非依赖的蛋白转运过程[48]，包括内吞和吞噬(phagocytosis)两个过程[49-50]。但在人肠上皮细胞中，siRNA敲低flotillin-1不仅会破坏脂筏介导的内吞作用，还会降低caveolin-1表达水平，此过程可以被溶酶体抑制剂MG262阻断[51]。Flotillin-1/-2通过结合不同蛋白内吞，参与复杂的细胞转运过程。在极化的HepG2肝细胞系中，动力蛋白dynamin和flotillin-2介导霍乱毒素B亚基(cholera toxin B subunit, CTB)和GPI锚定蛋白的基底侧内化[52]；蛋白激酶C (PKC)诱发兴奋性氨基酸转运体2 (excitatory amino acid transporter 2, EAAT2)和多巴胺转运体(dopamine transporter, DAT)内吞，这个过程需要flotillin-1中保守的丝氨酸残基参与[53]。Flotillin-1也介导了动力蛋白非依赖的内吞过程，通过转运轴突导向因子semaphorin 3A和它的受体，调节皮层神经元LIM激酶活性、细胞骨架动态变化以及细胞黏附能力[54]。敲除flotillin-1，并抑制动力蛋白，减少了CD59和CTB的内化[49]。Flotillin-1/-2介导内吞作用的前提是flotillin-1中的Tyr160和flotillin-2中的Tyr163被磷酸化，该过程由Src家族Fyn蛋白激酶介导；当这两个残基突变为苯丙氨酸后，则会抑制内吞作用[55]。除此以外，flotillin-1/-2蛋白从质膜转运到胞内小体也需要Fyn蛋白激酶诱导[55-56](图1B)。

3.3 Flotillins参与蛋白分选与再循环

在T细胞中，flotillin-1/-2蛋白所在微区称为“CAP”结构，该帽子结构对flotillin-1/-2发挥正常功能至关重要[57]。在flotillin-2缺失突变体中，T细胞激活可干扰CAP组装，减弱脂筏极化和微区的形成，造成鸟苷酸交换因子Vav定位错误和细胞骨架重组能力受损[58]。当受到刺激或抗原交联时，PrP激活可以通过MAPK促进ERK1/2磷酸化和Ca^{2+}释放，flotillin-1/-2蛋白被转运到CAP结构中，在Src酪氨酸激酶作用下磷酸化[40]，依赖Vav1和Rho GTPases的肌动蛋白骨架重组[59]，从而招募相应的T细胞抗原受体[60] (图1A)。Flotillins蛋白除了分布在质膜上，也有部分分布在膜蛋白运输相关的囊泡转运体上[61]。在含有Rab5和Rab11的胞内体中，flotillins可以促进T细胞受体在膜间的转运循环[62]。下调HeLa细胞中flotillins蛋白的表达量，减少了Rab11a与管状回收囊泡的结合，减弱了转铁蛋白-转铁蛋白受体(transferrin receptor, TfR)复合物向质膜的循环利用，而过表达Rab11a可以逆转此过程[63] (图1C)。在神经元中，flotillin-2和Rab11a共同转运PSD-95、GluA1、GluN1以及N-cadherin[64]，促进树突棘突触形成，以及长时程增强(long-term potentiation, LTP)相关的AMPA受体(GluA1)转运上膜[61]。敲除或敲低神经元中flotillins蛋白的表达，将导致神经元突触减少、物质运输障碍，以及突触蛋白表达量变化等现象，说明flotillins对神经元的生理功能和生长过程至关重要。另外，flotillin-2缺失突变体在Hela、Jurkat和PC12细胞的高尔基体中累积，说明flotillins的转运是高尔基体依赖的[65]。

综合以上的研究发现，flotillins能够发挥信号

转导中心的作用与蛋白本身独特的结构、定位以及与微区相关信号分子的相互作用密切相关。Flotillins合适的表达量、多聚体形成并动态分布到恰当的位置、精准的氨基酸残基修饰、信号交联激活等任意环节出现差错，对细胞、组织、器官，乃至生命体的发生和功能都有重要影响。

4　Flotillins参与多种疾病的发生

Flotillins与各类肿瘤和神经退行性疾病发生相关。Zhong等[66]在抑郁症患者身上使用GWAS筛选发现，*Flotillin-1*是产生抑郁症的高风险基因。Reisinger等[67]在研究flotillin-1蛋白与抑郁的关系时发现，flotillin-1蛋白与5-羟色胺转运体相互作用，参与调节皮质酮(corticosterone)长期注射后的5-羟色胺能神经递质释放和抑郁状行为改变。对多种肿瘤以及神经退行性疾病病例分析发现，flotillins在各类组织均存在异常表达。例如，在帕金森病(Parkinson's disease, PD)患者的黑质/ 被盖腹侧区，*flotillin-1*基因表达水平显著升高[68]，说明flotillins的表达水平与PD的发生发展密切相关[69]。深入研究flotillins的机制有助于寻找检测神经发育障碍、情感与认知以及神经退行性疾病相关的靶点，筛选高效快捷的疾病早期诊断因子。

4.1　Flotillins与肿瘤

在很多的肿瘤组织中，均可检测到flotillins蛋白表达上调。如在口腔鳞癌细胞系、食管鳞癌细胞系和患者样本中检测到flotillin-1蛋白和mRNA表达上调[70]。Flotillin-1与卵巢肿瘤[71]、结直肠癌[72]相关；flotillin-2与乳腺癌[73]、鼻咽癌[74]、小细胞肺癌[75]等也具有相关性，降低其表达可以抑制肿瘤的生长和转移。在宫颈癌细胞系和癌组织中，flotillin-1蛋白和mRNA表达均显著增加，其表达量与盆腔淋巴结转移显著相关[76]。因此，flotillins在肿瘤发生、发展及侵袭过程中具有重要作用，flotillins蛋白和mRNA的水平可以作为肿瘤检测、早期诊断和治疗的指标之一。

更多的机制研究表明，flotillin-1激活肿瘤坏死因子-α受体(TNFR)信号，促进IκBα磷酸化，p65和p50易位入核激活NF-κB信号通路[70]，调节胞内反应，从而促进癌细胞的迁移和分裂。使用EGFR抑制剂AG1478可以阻断flotillin-1诱导的NF-κB信号通路[77] (图1B)。Flotillin-1通过Wnt/β-catenin和NF-κB信号通路调控上皮间质转化(epithelial-mesenchymal transition, EMT)，从而影响宫颈癌细胞的运动和侵袭[76]。因此，进一步揭示flotillins的生物学功能将会发现更多的潜在药物作用靶点。

4.2　Flotillins与阿尔茨海默病

阿尔茨海默病(Alzheimer's disease, AD)是一类以记忆障碍以及人格行为发生改变的神经系统退行性疾病，其发生机制不明，而且早期诊断困难，主要病理特征是含有大量细胞外不溶的淀粉样斑块和细胞内神经纤维缠结。具有神经毒性的淀粉样斑块主要由淀粉样前体蛋白(amyloid precursor protein, APP)水解而来的淀粉样蛋白β (amyloid β-protein, Aβ)组成。目前可以通过分析大脑皮层Aβ沉积导致的老年斑、神经元数目减少和脑脊液中磷酸化tau含量进行AD诊断[78-79]，但是脑脊液的抽取有创伤，且需要特殊技术和设备，普通患者不易接受。正电子发射断层成像(Pittsburgh compound B and positron emission tomography, PiB-PET)结合匹兹堡复合物成像可以检测淀粉样病变，但该检测方法有创伤且费用昂贵。因此，临床需要寻找侵入性较小且易于检测的血液标志物。

Chen等[80]在人脑cDNA文库中使用酵母双杂交系统筛选出flotillin-1与AICD (APP intracellular domain)直接相互作用，推测flotillin-1诱导APP募集到脂筏上，影响APP的定位和加工，导致Aβ含量改变，进而造成AD的发生。在*flotillin-1*敲除和*flotillin-1/-2*双敲除的小鼠大脑中，Aβ水平均显著降低[81]。正常人脑中的胆固醇浓度远低于AD患者，人神经母细胞瘤细胞中的胆固醇含量升高可以同时上调flotillin-2和Aβ的表达，导致胆固醇稳态失衡，从而诱导细胞凋亡[82]。这些研究结果表明，flotillins介导了Aβ的聚集和转运，从而影响Aβ的含量和定位，和AD的病理发展密切相关[83-85]。Abdullah等[78]通过蛋白质印迹分析AD、血管性痴呆(vascular dementia, VaD)和非AD尸检病例的脑室液和血清，发现AD患者的脑脊液和血清flotillins蛋白水平明显降低；使用PiB-PET法检测轻度认知功能障碍(mild cognitive impairment, MCI)患者脑脊液和血清，结果表明，AD患者脑脊液和血清中的flotillin水平显著降低，可能原因是大脑中的Aβ沉积减少了脂筏蛋白的分泌，但具体机制尚不清楚。因此，血清flotillins蛋白水平与Aβ沉积呈负相关，意味着血液中flotillins蛋白含量具有成为预测脑中Aβ含量并进行AD早期诊断标志物的潜力[86]。但后期临床仍需按照患者年龄匹配、发病阶段等进行批量比较研究[79]，深入探讨flotillins在临床诊断和治疗中的实际应用。

5 讨论

Flotillins功能具有多样性，其微区相当于一个信号中心，参与多种细胞生命活动，包括调节细胞黏附、物质内吞、蛋白质分选与再循环、促进细胞迁移等，表明flotillins对细胞生命活动的重要性，也从侧面解释了为什么flotillins在生命体中分布如此广泛。Flotillins家族中的flotillin-1和 flotillin-2两种蛋白既有共性，又有差异性，并相互依赖[6,33,87]，一种缺失可能会导致另一种蛋白水平的降低[50]。在Flotillin-1被敲除后，HeLa细胞仍然大量表达flotillin-2，而当flotillin-2敲除后，flotillin-1蛋白不稳定或降解，导致许多细胞系中两种蛋白的表达都显著降低[87]。因此，改变其中一种蛋白的表达水平，必须要同时考虑另一种蛋白表达变化带来的影响。

Flotillins与中枢神经系统功能关系特别密切，其表达量的改变能导致神经元功能和形态的异常，甚至导致发育缺陷。已有研究指出，部分降低或增加抑制性和兴奋性突触输入会干扰脊椎动物视觉系统信息处理和视觉诱导的行为改变，以及神经环路可塑性变化[88-89]。Flotillin-1过表达增加了谷氨酸能突触的数量，但对抑制性突触没有影响，意味着生物体大脑中兴奋-抑制突触输入平衡可能发生变化[38]。除此以外，改变flotillins的表达量在不同的模式动物中可能存在不同的效应。在鱼类中，过表达flotillins能够使受损的视网膜神经节细胞轴突再生，恢复个体视觉；而在哺乳动物中，过表达却无法恢复视觉[32]。因此，在检测指标的设定中，不仅要关注flotillins表达量对神经元和神经环路的影响，也要考虑实验动物种类和行为指标的差异。

在与肿瘤相关性研究方面，flotillins具有成为肿瘤诊断和预后评估指标的潜力[90]。在大多数肿瘤中，flotillins表达情况与肿瘤分期相关，与各类信号分子相互作用调控肿瘤细胞的增殖和迁移。NF-κB信号转导途径与flotillins密切相关。通过上调PI3K/AKT3激活NF-κB信号转导途径，下调细胞周期相关的负调控因子p21，从而促进肿瘤细胞的迁徙和增殖[74,77]。但也有研究指出，flotillins蛋白或mRNA表达升高不是所有肿瘤的特征[91]。因此，明确的结论还需要扩大样本数量，比较不同实验条件造成的差异，提高flotillins在人体肿瘤临床治疗的实用性[92]。

Flotillins蛋白发现已有20余年，但是仍有许多机制不清楚。近些年研究发现，*flotillins*基因参与调控其他基因，如干扰素相关蛋白的基因[93]、ETM转换蛋白的基因[8]等。但值得注意的是，在改变flotillins蛋白的表达时，可能会导致细胞中生长相关基因的异常和细胞信号通路的代偿性变化[87]，因此需要综合分析flotillins改变所引起的生物学效应。

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