·AD 的基础和临床研究专题·

突触后骨架蛋白与阿尔茨海默病

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【摘要】 阿尔茨海默病(AD)是老年期最常见的慢性疾病之一，其患病率与年龄密切相关。突触作为神经元间信息传递的关键部位，与 AD 密切相关。突触结构与功能的丧失被认为是 AD 早期的标志。突触后密度蛋白-95、Shank 和 Homer 蛋白是突触后主要骨架蛋白，在维持突触结构与功能中起重要作用，现就突触后骨架蛋白与 AD 的研究进展进行系统阐述。

【关键词】 阿尔茨海默病； 突触后骨架蛋白； 突触后密度蛋白-95； Shank； Homer； 综述
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Postsynaptic scaffold proteins and Alzheimer disease *Wang Qian, Huo Mingxuan, Zhao Ruiqing, Feng Bo*

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【**Abstract**】 Alzheimer disease (AD) is one of the most common chronic diseases in the elderly. The prevalence of AD is closely related to age. Synaptic structure, as a key part of information transmission between neurons, is closely related to AD. The loss of synaptic structure and function is considered to be a sign of early AD. Postsynaptic density protein-95, shank and Homer proteins are the main postsynaptic scaffold proteins, which play an important role in maintaining synaptic structure and function. We systematically describe the research progress of postsynaptic scaffold proteins and AD.

【**Key words**】 Alzheimer disease; Postsynaptic scaffold proteins; Postsynaptic density protein-95; Shank; Homer; Review
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突触后致密区是整合和转导突触信号的结构基础，由多种突触后相关蛋白构成，在维持突触可塑性、调节神经元功能中具有重要作用。AD 发病与突触丢失有关，这种丢失在局部特异性突触后致密物质最为明显[1]。突触后致密物质的结构、数量和功能的改变可引起突触可塑性改变[2]，进而影响学习和记忆功能，诱发 AD。突触后密度蛋白-95(postsynaptic density protein-95，PSD-95)、Shank 和 Homer 蛋白是突触后致密区重要的骨架蛋白，通过聚集谷氨酸受体的不同亚基，调节谷氨酸受体的转位和信号传递，影响树突结构和功能以及突触可塑性，具有调节受体、稳定突触结构、整合与传递生物信息的作用[3]，与 AD 的发生和发展密切相关。研究表明，β-淀粉样蛋白(β-amyloid，Aβ)和 tau 蛋白能够损伤突触后致密区蛋白，诱发突触结构与功能障碍[4]，导致认知功能障碍。

一、PSD-95 蛋白家族

1. PSD-95 蛋白结构：PSD-95 是膜相关鸟苷酸激酶家族的成员，是兴奋性谷氨酸能神经元突触后致密区中含量最丰富的蛋白之一[5]。PSD-95 最早在大鼠的突触后致密区被发现，在人类基因组中由 DLG4 基因表达，因其分子量约为 95 kD，所以被命名为 PSD-95。PSD-95 包含了 3 个 PDZ 结构域及 1 个 SH3 和 1 个 GK 结构域[6]，绝大多数 PSD-95 介导的相互作用都归因于 3 个 PDZ 结构域[7]。PDZ 结构域是蛋白质-蛋白质识别模块，通过羧基末端的短序列与其他蛋白质相互作用[8]。

2. PSD-95 蛋白功能：PSD-95 参与突触后谷氨酸受体的募集和稳定，是谷氨酸能突触成熟的主要调节因子。N-甲基-D-天冬氨酸(N-methyl-D-aspartate，NMDA)受体是离子型谷氨酸受体的一种亚型，对突触可塑性和皮层发育以及学习记忆等功能至关重

要[9-10]。PSD-95是NMDA受体发育的调节因子，影响神经发育过程中树突棘的大小和密度[11]，对突触的正常成熟至关重要。此外，PSD-95能够通过α-氨基-3-羟基-5-甲基-4-异恶唑丙酸（α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate，AMPA）受体调节突触可塑性。研究表明，PSD-95基因敲除小鼠海马区AMPA受体介导的突触后电流显著降低[12]，这表明PSD-95的下调会导致突触抑制，甚至导致“沉默突触”的形成[13]。然而，PSD-95过度表达则会上调AMPA受体，增加树突棘的数量和密度，从而诱导突触发生[11]。这些结果表明，PSD-95通过AMPA受体调节突触可塑性过程。PSD-95通过与NMDA和AMPA受体的相互作用参与谷氨酸能突触可塑性的调节。PSD-95失衡将影响NMDA受体的稳定性和动力学，调节AMPA受体的组成和功能，从而影响谷氨酸能突触传递。PSD-95不仅在谷氨酸能兴奋性突触的结构与功能中发挥重要作用，而且在GABA抑制性突触中也发挥重要作用。研究发现PSD-95缺乏导致GABA抑制性突触传递增加[14]。PSD-95参与调节海马神经元树突正确分支[15]，对树突形态形成至关重要。PSD-95是诱导翻译后修饰的几个信号通路的靶点，包括棕榈酰化、磷酸化、亚硝化和去乙酰化。这些修饰决定了PSD-95所在突触的稳定性和功能，从而调节神经系统中单个突触的功能[16]。综上所述，PSD-95参与突触传递、突触可塑性和树突棘形态形成等重要过程。

3. PSD-95蛋白与AD：研究表明PSD-95在AD小鼠模型的脑组织[17]、暴露于Aβ的神经组织[18]以及AD患者的脑组织[19]中均减少，证实Aβ的沉积可下调PSD-95在突触的表达水平。研究发现tau蛋白蓄积也能诱导海马兴奋性突触中PSD-95减少[20]。PSD-95表达失调可能是Aβ与tau蛋白引起的一系列事件的重要中间步骤。PSD-95进行性减少标志着突触后功能退化，而突触后功能退化是AD长期认知功能缺陷的基础[21]。PSD-95表达的减少导致含有NR2B亚基的NMDA受体在突触后膜表达急剧增加[22]，引起突触后膜钙离子内流增加[23-24]，突触过度兴奋，导致神经细胞损伤。此外，PSD-95减少能够导致突触后膜AMPA受体表达减少[25]，从而减弱谷氨酸能突触传递，导致长时程增强受损、长时程抑制增强，引起认知功能下降。实验通过表观遗传编辑增加老年或AD模型小鼠的PSD-95表达可增强认知功能[26]。另一项研究证实PSD-95能够保护突触不受Aβ的影响[27]，且PSD-95的过度表达能够促进突触传递[28-29]，说明PSD-95高水平表达将对AD具有保护作用。此项研究还表明维持PSD-95的棕榈酰化对于保护突触免受Aβ的伤害是必不可少的，由此可以推测增加PSD-95棕榈酰化的药物可以增强这种保护，并可能对AD治疗有效。因此，选择性阻断PSD-95去棕榈酰化可能是未来开发AD治疗方法的一个可行的选择。

二、Shank蛋白家族

1. Shank蛋白结构：Shank蛋白是谷氨酸能神经元突触后致密区中的主骨架蛋白[30]。Shank蛋白家族由3个基因SHANK1、SHANK2和SHANK3编码。Shank蛋白在中枢神经系统中广泛表达，其中Shank1几乎只在脑组织中表达，尤其在大脑皮层和海马组织中高度表达[31]。Shank蛋白是一种多结构域蛋白，包含5个结构域：ANK、SH3、PDZ、PRO和SAM结构域[32]，能将神经递质受体和其他膜蛋白与信号蛋白和肌动蛋白细胞骨架连接起来，是突触后蛋白网络的核心部分。

2. Shank蛋白功能：Shank蛋白在突触后形成功能蛋白平台，在整合多种突触后膜蛋白包括NMDA受体复合体、AMPA受体复合体和代谢型谷氨酸受体复合体中发挥重要作用[33]。Shank蛋白家族被认为是兴奋性突触结构的主要调节者[34]。研究发现Shank1在培养的兴奋性海马神经元中过度表达时，会促进树突棘的增大，特别是树突棘头部的增大[35]，而在Shank1基因敲除小鼠中发现突触后致密区组成改变，树突棘和突触变小，突触后致密区变小、变薄，导致突触传递效能减弱[36]。另一项研究在Shank3基因敲除小鼠模型中发现代谢型谷氨酸受体5-Homer蛋白骨架和代谢型谷氨酸受体介导的信号转导通路都被选择性地改变，导致突触功能障碍[37]。这些结果表明，Shank蛋白家族在调节兴奋性树突棘形态和功能方面起重要作用。此外，Shank蛋白还被证实能够影响抑制性突触传递[38-39]。Shank蛋白能够调节离子型[34]和代谢型谷氨酸受体的功能[40]，促进突触形态的自发重塑，并在突触后募集和稳定皮层肌动蛋白，使肌动蛋白细胞骨架能够动态调节突触的形态和功能[41]，对突触可塑性和信息传递起关键作用[42]。除了在突触后发挥作用外，Shank蛋白还参与调节轴突终末端NMDA受体水平[43]，其突触前功能是维持脑内突触正常结构与功能的重要组成部分[44]，但具体机制需要进一步研究阐明。此外，Shank蛋白还通过调节L型钙通道[45-46]、参与轴突生长[43]等影响脑内信息传递过程。

3. Shank蛋白与AD：Shank蛋白通过鸟苷酸激酶相关蛋白与PSD-95结合[47]，PSD-95可直接与NMDA受体相连接。Shank蛋白能够通过谷氨酸受体相关蛋白与AMPA受体间接连接。Homer蛋白通过其EVH1结构域分别与代谢型谷氨酸受体和Shank蛋白相结合[48]。Shank蛋白作为突触后主骨架蛋白，通过蛋白质–蛋白质互相作用，在突触后致密区形成蛋白复合物，使突触后致密区离子型和代谢型谷氨酸受体系统之间紧密联系，在突触发育、突触后膜受体锚定和信息传递过程中发挥关键作用。研究指出Shank蛋白和AD病理生理之间可能存在联系，但具体机制尚不清楚。用Aβ处理大鼠额叶皮质神经元能够导致Shank1和Shank3的突触水平降低，在APP转基因小鼠的大脑中也观察到Shank1和Shank3蛋白的类似减少[49]，同时在AD患者额叶皮质中也发现Shank1蛋白水平的降低[50]。Shank蛋白水平降低能够导致突触后其他骨架蛋白丢失，从而影响突触后致密区的整体稳定性，引起突触功能障碍和丢失[51]，进而导致谷氨酸能突触传递减少[52-53]、长时程增强受损[54]，最终引起认知功能障碍。由此可以认为Shank蛋白家族为AD药物开发提供了一个新靶点。直接干扰Shank蛋白水平或Shank蛋白功能的调节可以作为药物开发潜在靶点。Shank3的组织特异性表达受到DNA甲基化的调控[55]，这也可能是未来治疗的潜在靶点。

三、Homer蛋白家族

1. Homer蛋白结构：Homer蛋白家族由3个基因Homer1、Homer2和Homer3编码，其中Homer1蛋白最早被发现。Homer蛋白主要在神经系统中表达，在视网膜、心肌、骨骼肌等组织中也有低水平表达[56]。每个Homer基因都表达长型和短型Homer蛋白，长型有Homer1b/c、Homer2a/b、Homer3a/b，短型的有Homer1a、Homer2c/d、Homer3c/d。短型Homer蛋白缺乏含有卷曲螺旋结构和亮氨酸拉链基序的自组装结构域[57]。Homer蛋白的氨基末端均含有1个高度保守的EVH1结构域，可以与代谢型谷氨酸受体[58]、Shank蛋白[59]、三磷酸肌醇受体[60]、瞬时受体电位通道[61]等相结合，从而发挥相应效能。

2. Homer蛋白功能：Homer蛋白作为突触后致密区主要骨架蛋白之一，将质膜上的受体与细胞内信号复合体和细胞骨架蛋白联系起来，还和细胞信号转导的多种胞浆蛋白结合。研究表明Homer1在海马CA1区锥体神经元AMPA受体的定位中起着重要作用，且Homer1的缺失增加了Schaffer侧支突触上AMPA受体介导的突触后电流，Homer1的过表达则导致CA1锥体神经元的AMPA/NMDA受体介导的突触后电流减少，提示Homer1是一种离子型谷氨酸受体调节剂[62]。Homer蛋白还可以调节代谢型谷氨酸受体活性[63]，从而调节突触功能。在体外培养的海马神经元中，通过与Shank1B共表达，外源表达的Homer1b的突触靶向性增加，导致树突棘头部增大和突触后电流增加[35]，提示Shank与长型Homer蛋白之间的相互作用对于维持树突棘结构和突触功能是重要的。研究发现Homer1a降低了培养的海马神经元中树突棘的密度和大小。Homer1a下调PSD-95蛋白的表达、NMDA受体和AMPA受体的突触数量，意味着Homer1a对突触发育有负性调节作用。此外，Homer1a在负反馈环中以活动依赖的方式调节突触的结构和功能[64]。Homer蛋白还能够调节钙稳态[65]和神经元分化[66]，并引导轴突按照正确路径进行信息传递[67]，在大脑的信息传递中起关键作用。

3. Homer蛋白与AD：研究证明Aβ可以破坏Homer蛋白，并诱导突触后致密区的超微结构变化[68]。实验中用Aβ处理额叶皮质神经元后，突触后致密区在1 h内迅速变薄，Homer1b/c蛋白水平降低[49]。Homer蛋白水平降低可能与Aβ和tau蛋白导致谷氨酸稳态失衡有关[69]，使谷氨酸在突触处异常释放，导致NMDA受体过度激活，引起NMDA受体依赖性钙内流增加，导致突触后结构与功能改变[70]。Homer蛋白水平降低能够引起突触后膜代谢型谷氨酸受体表达下调，进而损害代谢型谷氨酸受体依赖性长时程增强[71]，导致学习和记忆功能受损。高血压病和衰老作为AD的危险因素，均被证实与Homer1蛋白水平降低有关[72]。此外，Homer1a还可以通过破坏Homer-Shank蛋白复合体来抑制NMDA受体介导的突触传递[73]，导致突触功能障碍。以上证据表明，Homer蛋白与AD的发生发展密切相关。Aβ能够抑制钙激活钾通道，导致神经元过度兴奋和谷氨酸释放过多，从而导致兴奋性神经元损伤[74]。研究发现Homer1a能够解除Aβ诱导的钙激活钾通道抑制，提示Homer1a对早期AD具有治疗潜力[75]。研究表明，Homer2和Homer3与淀粉样前体蛋白相互作用能够减少Aβ的产生[76-77]，为AD提供新的治疗依据。

四、小结

AD是一种以进行性认知功能障碍为特征的神经退行性疾病。AD病理变化有淀粉样斑块、神经

原纤维缠结和突触丢失等，其中突触丢失与功能损害程度相关性最强。PSD-95、Shank、Homer蛋白是突触后致密区主要骨架蛋白，3种蛋白均参与了受体转运、钙稳态、长时程增强和记忆形成等过程，对突触可塑性和神经生物信息传递有重要意义。突触后骨架蛋白及其信号通路是突触功能障碍导致AD的关键靶点，为AD的治疗提供了新的思路。

利益冲突 文章所有作者共同认可文章无相关利益冲突

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