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Homer1a-mGluR5 在抑郁症中作用的研究进展

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[摘 要] Homer1a是由中枢神经系统即刻早期基因(immediate early genes，IEG)编码的支架蛋白质，广泛的临床及基础研究表明Homer1a不仅与多种神经精神疾病的发病有关，也是多种抗抑郁治疗方案的关键蛋白质。抑郁症的发病与1型代谢型谷氨酸受体(metabotropic glutamate receptor，mGluR1/5)的表达和可用性降低，N-甲基-D-天冬氨酸受体(N-methyl-D-aspartate receptor，NMDAR)的功能障碍所致的突触可塑性失调相关。Homer1a对mGluR1/5的作用具有高度特异性。Homer1a过表达可通过增加突触后膜mGluR1/5的表达和可用性，调节突触后膜的离子型谷氨酸受体NMDAR和α-氨基-3-羟基-5-甲基-4-异噁唑丙酸受体(α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor，AMPAR)，调节突触可塑性，最终发挥抗抑郁作用。Homer1a在突触活动的调节中发挥中心作用，因此了解Homer1a发挥作用的机制能为研究靶向Homer1a蛋白的抗抑郁药物提供新思路。

[关键词] 抑郁症；Homer1a；1型代谢型谷氨酸受体；N-甲基-D-天冬氨酸受体；α-氨基-3-羟基-5-甲基-4-异噁唑丙酸受体

Research progress in homer1a-mGluR5 in depression

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Abstract Homer1a is a scaffold protein encoded by immediate early genes (IEG) in the central nervous system. Extensive clinical and basic studies have shown that Homer1a is not only involved in the pathogenesis of a variety of neuropsychiatric diseases, but also a key protein in a variety of antidepressant treatment regiments. The onset of depression is associated with the expression and availability of metabotropic glutamate receptor type 1 (mGluR1/5) and the dysfunction of N-methyl-D-aspartate receptor (NMDAR), which causes synaptic plasticity disorders. Homer1a is highly specific to mGluR1/5. The overexpression of Homer1a regulates the synaptic plasticity by increasing the expression and availability of mGluR1/5 in the postsynaptic membrane, and then regulating the ionic glutamate receptor NMDAR and α-amino-3-hydroxy 5-methyl-4-oxazolepropionic acid receptor (AMPAR) in the postsynaptic membrane, ultimately playing an antidepressant role. Because Homer1a plays a central role in the regulation of synaptic activity, understanding the mechanism about how Homer1a works

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provides new insights into researching antidepressant drugs that target homer1a proteins.

Keywords depression; Homer1a; metabotropic glutamate receptor type 1; N-methyl-D-aspartate receptor; α-amino-3-hydroxy 5-methyl-4-oxazolepropionic acid receptor

抑郁症是一种发作性的精神障碍性疾病，是全球范围第3大致残原因，其主要临床症状为心境持续低落、兴趣衰退、睡眠障碍以及认知功能损害，严重者甚至出现自杀倾向[1]。全球有5.0%的成年人患有抑郁症，约超3.5亿人。据统计，中国有超9 500万患者，占全国人口总数的4.2%[2]。如此高的发病率及其引起的严重后果亟需新的快速持久且不良反应小的抗抑郁药物。关于抑郁症的原因已有几种假说，然而没有一个单一的假设可以解释抑郁症的完整机制，或者为什么治疗反应显示出个体差异。临床前研究以及在人类中进行的遗传研究[3-4]结果表明：Homer1的构成亚型(Homer1b/c)和诱导亚型(Homer1a)在抑郁症的神经生物学中发挥作用。短剪接体Homer1a蛋白质作为可调节细胞内稳态及突触可塑性的蛋白质，与抑郁样行为相关，并且是不同抗抑郁药物治疗的共同作用机制[5]。Holz等[6]通过应用融合到蛋白质转导域(protein transduction domain，TAT)的Homer1a模拟Homer1a的表达增加，发现TAT融合肽可以特异性地调节代谢型谷氨酸受体5(metabotropic glutamate receptor 1，mGluR5)信号通路而发挥快速的抗抑郁作用。本综述旨在了解Homer1a/mGluR5在抑郁症中的作用以及Homer1a发挥抗抑郁作用的机制，为继续深入探究该蛋白质在抑郁症中调节细胞内稳态及突触可塑性的具体机制提供理论依据，有助于靶向Homer1a的快速、持久且不良反应更小的新抗抑郁药物的研发和应用。

1 Homer1a 及其相关蛋白质的结构

突触后密度(postsynaptic density，PSD)是一个增厚的谷氨酸突触，是包含复杂的受体、支架蛋白和适配器蛋白的多模式枢纽[7]，在组成和调节方面均是动态的。突触后密度蛋白主要是通过谷氨酸受体与突触前神经元和各种神经递质系统的突触信号来调节信号转导的。Homer1是中枢神经系统中由即早基因(immediate early gene，IEG)编码、转录和翻译的一种在大脑中广泛表达、在突触后密度中富集的支架蛋白，其功能包括调节mGluR1的转运、调节钙信号、调节长时程电位(long-term potentiation，LTP)、调控树突棘生长的组织以及稳态和稳态可塑性。Homer家族主要有两个结构特征：N端为高度保守同源序列的激活/血管舒张剂刺激磷蛋白同源性1[enabled/vasodilator-stimulated phosphoprotein (Ena/VASP) homology 1，EVH1]结构域；C端为卷曲的螺旋(coil-coil，CC)结构[8]。EVH1结构域的存在使这些异构体能够与几种确定的富含脯氨酸的受体结合，包括mGluR1/5[9]、Shank家族[9]、1-4-5肌醇三磷酸受体[10]、几种肌动蛋白质结合蛋白[11]等，发挥调节信号传输的功能。Homer1a是由186个氨基酸构成的仅有N端EVH1结构域的短剪接体，不能形成寡聚体复合物介导信号转导，是在多种生理、病理活动下诱导的直接早期基因的产物。Homer1b/c具有C末端CC结构域，两两之间通过亮氨酸拉链型的特定基序反向平行结合，形成四聚体结构，该结构可与许多不同的效应蛋白结合，保证突触后膜的高速传递[9]。

Shank蛋白是Homer的支架蛋白，通过PDZ(PSD-95/Discs large/zona occludus-1)结构域和长脯氨酸丰富序列在Homer1b/c组织构成的复合体中发挥重要作用[12]。Shank通过其PDZ结构域与鸟苷酸激酶相关蛋白(guanylate kinase associated proteins，GKAP)的C端结构域发生物理结合，通过其富含脯氨酸的结构域与长形式Homer1b/c EVH1(Ena/Vasp同源)的N端结构域发生物理结合；另外Homer1b/c可以通过其多聚化与mGluR连接，形成PSD95-GKAP-Shank-Homer1b、c复合物[13-15]，由此在亲离子型NMDA和mGluR1/5之间形成一个物理分子桥，称为谷氨酸受体。Stillman等[16]的研究发现Homer1蛋白与Shank蛋白、1型mGluR在皮质中的相互作用具有惊人的特异性，形成了一个高度特异和严格调控的活性依赖的支架系统。支架复合体的动力学在受体功能和突触传递的控制中发挥主导作用。这些受体相关的支架蛋白可以调节受体的表达和活性，从而调节相关信号通路[17]。Homer蛋白通过与Shank蛋白合作调节mGluR，形成了一个协调谷氨酸受体活动和突触可塑性事件的支架，而Homer1a在突触活动的调节中发挥了中心作用[18-19]。

2 Homer1a-mGluR1/5 参与抑郁症的发病与治疗

当前研究较多的一些抗抑郁通路有ERK1/2/NF-κB[20]、cAMP-PKA-CREB[21]、IL-6/IDO[21-22]、BDNF-TrkB[23]以及下调犬尿素(KYN)[22,24]。越来越多的研究发现Homer1a参与抑郁症的病理、生理与治疗。Buonaguro等[25]发现围产期应激后大鼠除杏仁核外的脑区域的Homer1a表达均下降；Serchov等[26]使用内侧前额叶皮层(medial prefrontal cortex，mPFC)的siRNA敲除Homer1a，显著增加了WT小鼠的抑郁样行为，并阻止氯胺酮、慢性丙咪嗪和睡眠剥夺(sleep deprivation，SD)的抗抑郁作用；Sun等[3]通过对慢性行为绝望小鼠抑郁模型(chronic despair mouse model，CDM)位于Homer1启动子区域的7个CpG位点甲基化的定量分析表明：CDM小鼠皮层DNA甲基化显著增加，而慢性丙咪嗪和氯胺酮等抗抑郁药物治疗降低了DNA甲基化水平证明了应激诱导的抑郁样行为和抗抑郁药物治疗与Homer1a启动子的表观遗传改变有关，均证实了Homer1a诱导是调节抗抑郁药物效果的关键联合机制，该结果与Rietschel等[4]发现的人类Homer1基因变异是重度抑郁症的病因这一结论相同。

mGluR对谷氨酸能神经传递的调节能力在抑郁症中作用引起重视。边缘系统的谷氨酸组分失调是情绪障碍的一个标志性特征[27]。考虑到谷氨酸在大脑中的重要性，靶向mGluR1/5受体调节谷氨酸神经传递的研究是发展精神疾病治疗的新策略。研究[28]已证实mGluR1/5作为突触后G蛋白偶联受体调节多种形式的突触可塑性，参与抑郁症的病理与治疗。Deschwanden等[29]在人类重度抑郁症患者的mPFC中发现mGluR5的表达和可用性降低，且mGluR5普遍缺失的小鼠表现出明显的应激诱导的抑郁样行为[30]，表明抑郁症中1型mGlu受体可用性低。而长期服用抗抑郁药物后的啮齿动物和人类大脑中mGlu5可用性增加[31]。Holz等[6]通过有条件地抑制钙调蛋白依赖激酶IIα(calmodulin-dependent protein kinase IIα，CaMKIIα)细胞中的mGluR5，发现mGluR5对于SD的抗抑郁作用也是必需的。此外，伏隔核中靶向mGlu5受体激活的阳性别构调节剂3-氰基-N-(1,3-二苯基-1H-吡唑-5-基)苯甲酰胺[3-cyano-N-(1,3-diphenyl-1H-pyrazol-5-yl)benzamide，CDPPB]促进了对慢性应激的恢复[30]，由此可见1型mGlu受体也参与抑郁症的发病和治疗。

Homer1a作为1型mGluR活性的关键调控因子，Homer-mGluR功能障碍可能是一些精神与神经疾病的共同病因。例如，一些通过对CDM小鼠的研究发现此类小鼠皮层中Homer1a mRNA表达减少[32]，mGluR5可用性和表达[6]、哺乳动物雷帕霉素靶蛋白(mammalian target of rapamycin，mTOR)磷酸化降低[33]；在使用SD、丙咪嗪和氯胺酮等抗抑郁药物治疗后mPFC中Homer1a特异性表达增加，mGluR5可用性和表达、mTOR磷酸化增加[6,32,34]。

3 Homer1a-mGluR1/5 的抗抑郁症机制

现有研究[33,35]表明睡眠剥夺、氯胺酮、电休克等一些抗抑郁方案治疗后均会诱导Homer1a表达增加。表达增多的Homer1a促进膜表面钙通道的转运，通过增加瞬时受体电位阳离子通道蛋白(transient receptor potential cation channel，TRPC)和L-型电压依赖钙通道(L-type voltage-dependent calcium channel，L-VDCC)活性[36]，增加胞内Ca^{2+}浓度，从而将钙信号从细胞内储存转移到膜表面[36]。另外过表达的Homer1a与Homer1b/c的多聚体形式竞争，分离破坏Homer1b/c的多聚复合物，将mGluR1/5从mGluR1/5-Homer1b/c-Shank-GKAP-PSD95-离子型谷氨酸受体复合物中释放出来，并且Homer1a可以与内质网mGluR1/5的结合导致其转移到突触后空间[37]。突触后膜增加的mGluR1/5，激活G蛋白介导的磷脂酶C(phospholipase C，PLC)，水解磷酸肌醇(phosphoinositide，PI)，进而激活三磷酸肌醇(inositol triphosphate，IP3)和蛋白激酶C(protein kinase C，PKC)，促进内质网Ca^{2+}释放到细胞内；空间活跃的PKC和释放的Ca^{2+}，增加mTOR通路的活性，增加突触后膜α-氨基-3-羟基-5-甲基-4-异噁唑丙酸受体(α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor，AMPAR)的翻译和突触表达并保证其在突触后膜上的稳定性，进而调节突触可塑性[36,38]。

慢性应激降低了AMPAR水平和AMPAR诱导的Ca^{2+}反应，而氯胺酮和SD可逆转这种效果。Holz等[6]通过TAT-H1A处理模拟Homer1a过表达，从而将mGluR5信号从Ca^{2+}转移到Akt-mTOR，导致AMPAR合成和转位到质膜；进一步通过使用AMPAR阻断剂后则阻止了TAT-H1A和SD诱导的抗抑郁作用，表明AMPAR在Homer1a抗抑郁作用中的转运和信号转导是必不可少的。此外，

Homer1a过表达可以增加AMPAR介导的兴奋性突触后电流(excitatory postsynaptic currents，EPSCs)的振幅，降低EPSC间的间隔，从而增加了AMPAR的功能和聚集[39]。由此可见Homer1a是快速抗抑郁作用的关键介质，可被Homer1a过表达、mGluR5配体或其他增强Akt-mTOR通路信号的配体靶向[40]。

另一方面，Reshetnikov等[9]以及Bockaert等[36]发现表达增加的Homer1a可以通过mGluR1/5 G蛋白的β亚基与C端的结合直接抑制NMDA受体的NR1亚基的信号转导。NMDAR同mGlu5R一样在突触可塑性的诱导、支架的精细调控中发挥着巨大的作用，并且谷氨酸受体间的相互作用在可塑性突触微调中至为重要[41]。越来越多的证据表明NMDAR的功能障碍也参与抑郁症的发病和治疗。Berman等[42]首次报道了亚麻醉剂量的单次氯胺酮注射有显著的抗抑郁作用，在后续的临床前和临床研究[43-44]中也证实了其余NMDAR拮抗剂如右美沙芬/安非他酮等药物也具有相同的效果。该类药物的抗抑郁作用可通过抑制NMDAR过度激活导致的过量Ca^{2+}流入神经细胞，从而减轻神经细胞坏死、凋亡和树突状损伤[45]；另外一种可能的机制即是通过诱导Homer1a过表达，增加突触后膜mGluR1/5的表达及可用性，形成活动依赖性的重排复合物Homer1a-mGluR1/5[46-47]，直接抑制NMDAR，尚需进一步的实验验证。由此可见Homer1a的表达增加对于诱导mGlu5R-NMDAR相互作用和阻断NMDAR活性也是必要的。

4 结语

Homer1在中枢神经系统广泛表达，作为调节内稳态及突触可塑性的重要支架蛋白，已有研究证实活动诱导的Homer1a表达具有神经保护作用，且在抑郁症的发病和治疗中均有涉及，虽然目前尚不清楚所有这些治疗趋同于内稳态升级的机制，但Homer1a可能是核心，因为几乎所有的抗抑郁治疗都会上调Homer1a的表达[35]，并最终通过上调mPFC谷氨酸突触的AMPAR表达，增加整个神经网络活动的同时保持突触的相对强度[27,36]，进而发挥抗抑郁作用。因此，继续深入探究该蛋白在细胞内稳态及突触可塑性中的作用机制，为研究快速持久且不良反应更小的抗抑郁药物提供理论依据，对该疾病患者具有重要意义。

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