

S100A10在抑郁症发病中的作用及其机制研究进展

化瑞芳 张婧婧 丁彦 杨佩 刘荣勋 刘科锐 王辉*

(河南省免疫与靶向药物重点实验室, 河南省分子诊断与医学检验技术协同创新中心,
新乡医学院医学检验学院, 新乡 453003)

摘要 抑郁症是一种慢性的可反复发作的精神类疾病, 与大脑回路、神经网络、分子信号通路和神经递质等改变密切相关。S100A10蛋白是S100家族中的一员, 在中枢神经系统包括前额叶皮层、海马、杏仁核等多个情绪调节的关键脑区中广泛表达, 与五羟色胺受体、代谢型谷氨酸受体、脑源性神经营养因子等相互作用, 在抑郁症的发病机制研究中备受关注。基于课题组多年来的研究和最新进展, 该文就S100A10在抑郁症发病中的作用及其神经和分子机制进行综述, 以期S100A10在抑郁症发病中的进一步研究和临床疗效提供借鉴。

关键词 抑郁症; S100A10; 前额叶皮层; 海马; 杏仁核; 五羟色胺受体; 代谢性谷氨酸受体; 脑源性神经营养因子

Research Progress on the Role and Mechanism of S100A10 in the Pathogenesis of Depression

HUA Ruifang, ZHANG Jingjing, DING Yan, YANG Pei, LIU Rongxun, LIU Kerui, WANG Hui*

(Henan Key Laboratory of Immunology and Targeted Drugs, Henan Collaborative Innovation Center of Molecular Diagnosis and Laboratory Medicine, School of Laboratory Medicine, Xinxiang Medical University, Xinxiang 453003, China)

Abstract Depression is a chronic and recurrent psychiatric disorder associating with the alterations of brain circuitries, neuronal networks, molecular signaling pathways and neurotransmitters. S100A10, a member of S100 family, is widely expressed in the central nervous system, including prefrontal cortex, hippocampus, amygdala and other brain areas in emotion modulation. It interacts with serotonergic receptor, metabotropic glutamate receptor, brain-derived neurotrophic factor and so on. It has attracted much attention in the pathogenesis of depression. Based on the previous research and the recent insights, the focus of this review is to provide an update on the roles of S100A10 and its neural and molecular mechanism in the pathogenesis of depression, which provides new avenues for further research and clinical treatment.

Keywords depression; S100A10; prefrontal cortex; hippocampus; amygdala; serotonergic receptor; metabotropic glutamate receptor; brain-derived neurotrophic factor

抑郁症是一种慢性的可反复发作的精神类疾病, 给人类生活和社会带来严重负担。根据世界卫生组织组织数据推测, 到2030年抑郁症将会成为造成全

球精神类疾病负担的主要原因^[1]。S100A10蛋白是S100家族中的一员, 在中枢神经系统包括前额叶皮层(prefrontal cortex, PFC)、海马、杏仁核等多个情

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*通讯作者。Tel: 0373-3029977, E-mail: wanghui@xxmu.edu.cn

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*Corresponding author. Tel: +86-373-3029977, E-mail: wanghui@xxmu.edu.cn

绪调节的关键脑区中广泛表达, 并与五羟色胺系统、谷氨酸受体、脑源性神经营养因子等密切相关, 在抑郁症的发病机制研究中备受关注。我们之前研究发现, S100A10与慢性应激和炎症有紧密联系^[2]。在干扰素诱导的抑郁模型小鼠中, 我们发现其海马和大脑皮层中S100A10与五羟色胺受体(5-hydroxytryptamine receptor, 5HTR)表达均显著降低, 并与抑郁水平负相关^[3], 并通过抗抑郁药物研究证实S100A10参与调控细胞自噬从而发挥抗抑郁的作用^[4]。本文基于我们多年来对S100A10和抑郁症的研究, 结合国内外最新研究进展进行综述, 以期探究抑郁症发病的神经分子机制以及临床治疗靶点提供重要思路。

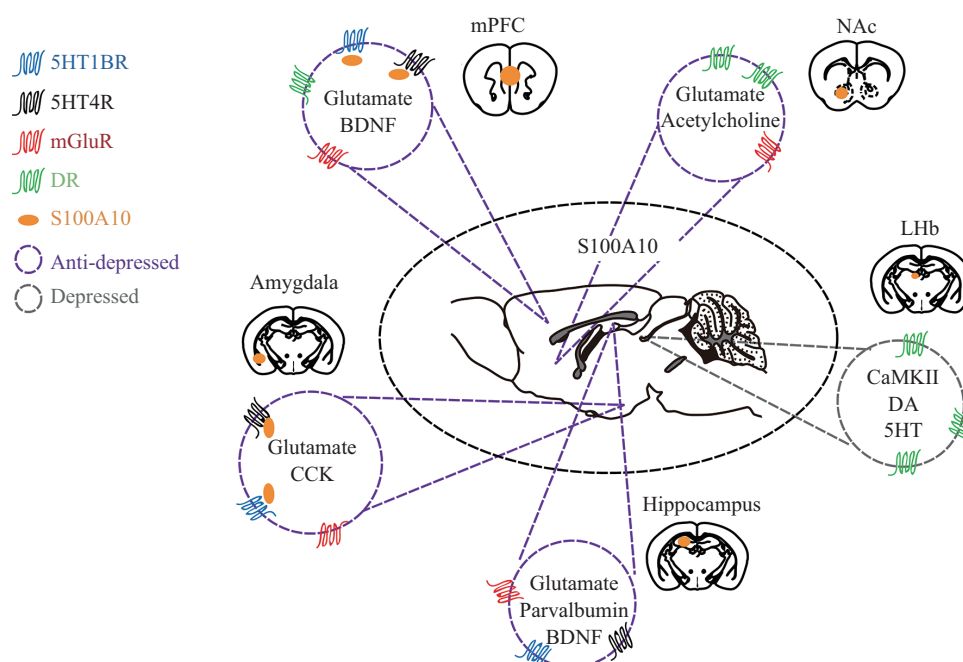
1 S100A10的表达与功能

S100蛋白是MOORE等^[5]首先在牛脑中发现的。S100蛋白家族是一组低分子量的钙结合蛋白, 具有高度的同源性序列和结构相似性, 且具有调控炎症、肿瘤发生发展、细胞分化和能量代谢等多种功能^[6]。S100A10又名p11、依钙蛋白I轻链(calpactin I light chain)和膜联蛋白II轻链(annexin II light chain), 是S100蛋白家族中的一员, 可与膜联蛋白A2(annexin

A2, AnxA2)结合。与其他家族蛋白不同, S100A10蛋白存在钙结合蛋白突变位点, 对钙离子不敏感^[7]。

在脊椎动物中, S100A10广泛表达在大脑、心脏、胃肠道、肾、肝、肺、脾脏、睾丸、表皮、主动脉以及胸腺等多种组织中, 通常存在于细胞内和细胞内表面质膜上, 与细胞膜受体、离子通道和酶相互作用^[7], 能够被炎症因子、细胞因子、生长因子、糖皮质激素、神经递质等调控^[8]。当S100A10表达异常时, 机体能够诱发多种疾病, 如肿瘤^[9]、心血管疾病^[10]和神经精神类疾病等^[11-12]。

在大脑中, S100A10主要在神经元中表达, 少数分布在胶质细胞中。在啮齿类动物的研究中发现, S100A10与多种类型的神经递质和蛋白分子共表达, 包括 γ 氨基酸、乙酰胆碱、谷氨酸、单胺类神经递质和小清蛋白等^[13]。S100a10基因敲除的小鼠表现出抑郁样行为, 并在情绪、学习认知等方面存在缺陷^[14]。如图1所示, 情绪调节的多个关键脑区如大脑皮层、杏仁核、海马、伏隔核(nucleus accumbens, NAc)和外侧缰核等^[15]中的S100A10参与了抑郁症的发生发展。不仅如此, S100A10还与神经系统中5-HTR、代谢性谷氨酸受体(metabotropic gluta-



DA: 多巴胺; CCK: 胆囊收缩素; DR: 多巴胺受体; mGluR: 代谢性谷氨酸受体; LHb: 外侧缰核。灰色虚线圆圈: 致抑郁作用; 紫色虚线圆圈: 抗抑郁作用。

DA: dopamine; CCK: Cholecystokinin; DR: dopamine receptor; mGluR: metabotropic glutamate receptor; LHb: lateral habenula. Grey dotted circle: depressive effect; purple dotted circle: antidepressant effect.

图1 S100A10在抑郁症发病中的重要脑区和信号分子

Fig.1 S100A10 in brain regions and interacting signal molecules in the pathogenesis of depression

mate receptor, mGluR)和脑源性神经营养因子(brain-derived neurotrophic factor, BDNF)等多个信号分子相互作用,在抑郁症发病中发挥着举足轻重的作用。在人类研究中发现,重症抑郁症患者经过氯胺酮治疗后抑郁症状显著减轻,并且其外周血细胞毒性T细胞中*S100a10*表达水平升高^[16]。通过尸体解剖发现,抑郁症自杀者的前额叶皮层S100A10蛋白表达水平显著降低。有自杀想法的抑郁症患者的外周血单个核细胞中*S100a10*的水平明显低于对照组^[17]。由此推测,血液中S100A10的水平将有可能用于抑郁症患者病情发展和临床疗效的评估。因此,探析S100A10在抑郁症发病中的作用及其神经机制将在疾病诊疗中具有重要的现实意义。

2 S100A10、脑区和抑郁症

随着研究的深入, S100A10在抑郁症发病和诊疗中占据了重要地位。在中枢神经系统中, S100A10蛋白广泛存在于大脑皮层、伏隔核、海马、杏仁核、缰核、下丘脑和中缝核等多个脑区,与抑郁症密切相关。

2.1 前额叶皮层

PFC是大脑中重要思维和行为调控中枢。内侧前额叶皮层(medial prefrontal cortex, mPFC)是一个控制高级执行功能的脑区,是情绪性应激反应的重要脑区。临床神经影像学研究发现,重症抑郁症患者大脑皮层灰质体积减少,并与胶质细胞的减少有关^[18]。SEO等^[19]研究发现,在慢性束缚压力应激所致抑郁模型小鼠mPFC中S100A10阳性神经元数量和蛋白表达均减少。mPFC中的S100A10阳性神经元多数是兴奋性神经元,与多巴胺D2受体(dopamine D2 receptor, D2R)存在大量共定位。条件性敲除mPFC中D2R阳性神经元*S100a10*基因后,小鼠产生了抑郁样行为;而增加D2R神经元*S100a10*表达后能够缓解其抑郁样行为。不仅如此,压力应激所致小鼠mPFC脑区中离子型谷氨酸能受体的兴奋性突触后电流降低,也与S100A10的减少密切相关。研究还发现,抗抑郁药物治疗和电休克治疗后,啮齿类动物额叶皮层S100A10水平上调^[20]。以上结果表明, mPFC脑区中S100A10在抑郁症发病中具有关键作用。解析大脑皮层中S100A10的表达水平和活性状态,能够为抑郁症发病的分子机制研究提供重要理论借鉴。

2.2 伏隔核

伏隔核(NAc)是腹侧纹状体的重要组成部分,能够调控情绪、奖赏和动机性行为,参与了抑郁症等精神类疾病的病理过程。研究发现,对抑郁症患者伏隔核脑区进行深部脑刺激治疗具有较好的抗抑郁和抗焦虑的临床疗效^[21]。在啮齿类动物研究中发现,慢性社会应激能够改变伏隔核与mPFC、海马和杏仁核之间的兴奋性突触联系,从而导致抑郁样行为的产生^[22]。S100A10在伏隔核中高表达,并与胆碱能神经元存在大量共定位。病毒干扰降低NAc中S100A10蛋白表达水平或者特异性敲除胆碱能神经元中该基因,均能够导致抑郁表型。值得探究的是,敲除伏隔核脑区中*S100a10*并没有对选择性五羟色胺再摄取抑制剂(selective serotonin reuptake inhibition, SSRI)的抗抑郁作用产生影响^[23]。结合以上研究,发现伏隔核脑区在调节情绪障碍等精神类疾病中发挥重要作用,而S100A10极有可能参与其中。

2.3 海马

海马属于边缘系统的重要组成部分,在调节情绪、学习记忆和认知中占据战略地位。海马脑区神经元能够表达高水平的糖皮质激素受体和谷氨酸,进而调节下丘脑-垂体-肾上腺轴(hypothalamus-pituitary adrenal axis, HPA轴),表现出应激易感性^[24]。在人类影像学研究中发现,抑郁症患者经临床治疗后海马脑区体积显著增加^[25]。慢性不可预知应激进行抑郁症造模后,大鼠海马脑区S100A10表达显著降低。与此同时,敲除海马脑区该基因能够使小鼠产生抑郁状态,而过表达该基因则能够使行为改变被逆转^[26]。在干扰素引起的抑郁症小鼠模型中,海马脑区*S100a10* mRNA和S100A10蛋白表达均显著降低,并与抑郁程度有相关性^[27]。在海马亚区齿状回中S100A10与小清蛋白(parvalbumin, PV)共表达。当PV阳性神经元*S100a10*基因缺失时,海马脑区神经元高频放电能力减弱,突触可塑性发生改变,从而使小鼠表现出焦虑样表型^[28]。鉴于海马脑区神经元中S100A10与五羟色胺能(5-hydroxytryptamine, 5HT)系统相互作用,在给予*S100a10*基因敲除小鼠的海马脑区定位注射5HT_{1B}受体激动剂后,能够显著增强谷氨酸神经递质的信息传递能力,进而强化小鼠的情绪记忆,确立S100A10与五羟色胺受体在调控情绪障碍中的地位^[29]。由此可见,海马脑区S100A10在抑郁症发病中发挥着重要作用。

2.4 杏仁核

杏仁核是一个备受瞩目的多功能脑区,能够调节机体内脏活动和情绪相关行为,对压力、应激和情绪刺激有较强的响应,还参与调节机体摄食行为、垂体激素的分泌和神经内分泌系统功能。在人类研究中发现,抑郁症患者的基底外侧杏仁核(basolateral amygdala, BLA)脑区表现出形态学异常和功能障碍,经过抗抑郁治疗后被逆转^[30]。前额叶皮层到杏仁核的神经环路与慢性应激所导致的焦虑障碍密切相关^[31]。通过功能性核磁共振发现,在恐惧行为中杏仁核脑区与内侧前额叶皮质脑区间的联系和体积变化发生改变^[32]。啮齿类动物研究中发现,杏仁核脑区中胆囊收缩素(cholecystokinin, CCK)阳性神经元能够通过NAc介导负性强化效应^[33]。通过解剖学研究证实了小鼠杏仁核脑区中高表达S100A10^[13],且与五羟色胺能系统紧密相连。五羟色胺的水平能够显著影响杏仁核脑区中五羟色胺受体表达^[34]。以上研究表明,杏仁核脑区与前额叶皮层和海马脑区之间存在突触联系,参与调节抑郁状态,但是目前关于杏仁核不同脑区中S100A10与抑郁症的直接证据尚待进一步研究。

2.5 外侧缰核

缰核是一个调节奖赏和情感状态的关键脑区,位于后背侧丘脑核团的外侧,分为内侧缰核(medial habenula, MHb)和外侧缰核(lateral habenula, LHb)。近年来LHb备受关注,因其在动机、运动和认知功能中发挥重要负性调节作用,并且能够同时控制多巴胺能系统和五羟色胺能系统,是为数不多的脑区之一^[35]。LHb脑区主要是谷氨酸能神经元,能够表达2型或3型囊泡谷氨酸转运体,少量是抑制性神经元,表达谷氨酸脱羧酶2或 γ 氨基丁酸转运体,构成局部抑制性神经环路。通过功能磁共振成像技术研究发现,重症抑郁症患者在氯胺酮治疗后的抗抑郁的效应与缰核和大脑结构连接改变有关^[36]。在猕猴的研究中发现,LHb脑区神经元编码了负性动机评估^[37]。在脂多糖诱导的抑郁症大鼠模型中,LHb星形胶质细胞中钾通道(Kir4.1)表达上调,并且能够调节周围神经元的成簇样放电和抑郁样行为^[38]。氯胺酮局部阻断大鼠LHb脑区中N-甲基-D-天冬氨酸受体(N-methyl-D-aspartate receptor, NMDAR)能够达到快速抗抑郁的作用^[39-40]。在小鼠研究中发现,在慢性压力应激作用下LHb脑区S100A10表达增多,且

该类神经元活性增强,是抑郁症负性信号编码的重要分子。LHb脑区中S100A10神经元绝大多数是兴奋性神经元,与D2R大量共定位。在LHb脑区D2R阳性神经元中过表达S100a10能诱导小鼠产生抑郁样行为,而局部敲低S100a10则能够改善应激所致的抑郁样行为^[15]。结合以上研究可知,LHb脑区在多种精神类疾病的病理过程中发挥重要作用,尤其是抑郁症,而S100A10极可能参与其中。

3 S100A10、信号分子与抑郁症

近来研究发现,G蛋白偶联受体(G protein coupled receptors, GPCRs)和脑源性神经营养因子(brain derived neurotrophic factor, BDNF)等重要信号通路和分子在抑郁症发病中发挥着关键作用,而S100A10与这些重要信号分子能够相互作用参与功能调控。

3.1 五羟色胺受体

GPCRs参与了抑郁症发病的病理过程,并在抗抑郁药物的靶点研究中备受关注^[41]。五羟色胺能系统,特别是5HT受体功能改变在抑郁症发病和抗抑郁治疗中具有重要作用。在啮齿类动物的研究中发现,大脑皮层、海马和伏隔核中S100A10与5HT_{1B}受体和5HT₄受体相互作用,参与抑郁样行为的调控^[42]。在细胞水平上发现,S100A10能够增强5HT_{1B}受体和5HT₄受体的表达和调控作用^[14,43]。多种抗抑郁治疗,如药物治疗和电休克治疗等,都能够上调啮齿类动物的大脑额叶皮层和海马脑区的S100A10的水平,而S100a10基因敲除的小鼠对各种抗抑郁样药物的反应效能均降低^[20]。研究发现,S100A10敲除小鼠表现出抑郁表型,并发现大脑苍白球中5HT_{1B}受体结合位点减少,与激动剂和拮抗剂的结合能力减弱,进而减少五羟色胺的生成量。五羟色胺通过5HT_{1B}受体降低了大脑皮层中谷氨酸的释放,并且抑制了皮层纹状体之间兴奋性突触的传递^[14]。该研究说明了S100A10引发5HT_{1B}受体的失调可能是引起抑郁症的重要分子机制。在小鼠大脑伏隔核中过表达S100A10后,5HT_{1B}受体表达量也增加,发挥抗抑郁作用^[44]。海马中表达S100A10的神经元能够调节5HT_{1B}受体的活性,参与情绪性记忆^[29]。酪蛋白激酶2(casein kinase 2, CK2)是5HT₄受体重要调节因子。Ck2 α 基因敲除的小鼠表现出抗抑郁样表型,其mPFC脑区中5HT₄受体的表达显著增加^[45]。氟西汀进行抗抑郁治疗能够增加S100A10神经元中

5HT₄受体的表达量^[46]。综上所述, S100A10与五羟色胺受体是抑郁症发病机制研究和临床治疗中的重要作用靶点。

3.2 代谢性谷氨酸受体

谷氨酸能神经传递可以被离子型谷氨酸能和代谢型谷氨酸能受体(metabotropic glutamate receptors, mGluRs)调节。氯胺酮是一种变构的*N*-甲基-*D*-天冬氨酸(*N*-methyl-*D*-aspartate, NMDA)受体拮抗剂, 被批准可用于治疗对单胺类抗抑郁药耐药的抑郁症^[47]。动物研究也证实, 代谢性谷氨酸能受体将成为新型抗抑郁药物的重要靶点^[48]。其中, mGluR5可能是治疗压力相关精神障碍的极有希望的作用靶点。mGluR5能够调节NMDA受体的功能, 可能与氯胺酮的抗抑郁作用发挥协同作用^[49]。人类mGluR5主要表达在海马、壳核、尾状核、大脑皮层和丘脑中。在临床研究中, 利用正电子发射计算机断层成像发现, 创伤后应激障碍患者多个脑区mGluR5的代谢增强, 主要体现在额叶和边缘系统等脑区, 同时在创伤性应激障碍且有自杀想法的患者的上述脑区中的mGluR5表现出更高的代谢活性^[50]。细胞水平上, mGluR5与S100A10在细胞膜上共表达并相互作用。在细胞中过表达*S100a10*能够增加mGluR5的水平。动物研究中, 条件性敲除谷氨酸能神经元中的*Mglur5*后, 小鼠表现出抑郁样行为, 而在抑制性神经元中敲除该基因后, 小鼠却表现出抗抑郁行为学表型。同样, 条件性敲除兴奋性神经元中的*S100a10*后, 小鼠对慢性压力应激表现出易感性, 然而敲除抑制性神经元中的*S100a10*后表现出抗抑郁样表型。当使用mGluR5拮抗剂后, 野生型小鼠表现为抗抑郁样效应, 而在*S100a10*敲除的小鼠中无抗抑郁样作用, 从而说明S100A10在mGluR5调控抑郁样行为中是必要的^[51]。慢性不可预知的轻度应激抑郁动物模型和慢病毒敲除海马脑区*S100a10*的动物实验中还发现, 在氯胺酮发挥的持续抗抑郁效应中, S100A10可能发挥关键作用^[26]。最新研究发现, 抗抑郁药物治疗具有延迟行为效应, 体现在*S100a10*基因上调以及海马中间神经元中神经降压素的抑制, 而这一结果与谷氨酸受体的改变密切相关^[52]。综上所述, 代谢性谷氨酸受体是抑郁症治疗和药物研发的潜在靶点, 而深入解析S100A10的作用机制将会有助于后续研究。

3.3 脑源性神经营养因子

脑源性神经营养因子(BDNF)在神经系统中高

表达, 能够促进神经细胞生长存活, 调控突触可塑性及神经发生。人类临床研究发现, 抑郁症患者经过抗抑郁治疗后, 血清中BDNF水平与临床疗效呈正相关^[53]。条件性敲除*Bdnf*基因的小鼠表现出抑郁样表型^[54]。临床队列分析得知, BDNF在脑卒中抑郁患者中的作用与细胞内信号转导通路S100A10/tPA/BDNF通路基因变异相关^[53]。慢性应激处理后, 大鼠的海马脑区BDNF和S100A10水平降低, 在给与抗炎和抗抑郁药治疗后可上调其水平^[55]。研究还发现, *Bdnf*基因敲除小鼠的大脑皮层和纹状体中*S100a10* mRNA和S100A10蛋白水平均降低。海马脑区BDNF-S100A10表达水平与抗抑郁药物作用密切相关^[56]。妊娠应激对于小鼠妊娠期和产后海马BDNF和S100A10产生负性调节^[57]。以上强有力的证据表明, BDNF在抑郁症的调控中需要S100A10的参与。

4 展望

本综述总结了S100A10在抑郁症发病的重要脑区和神经信号分子, 阐述了其与五羟色胺受体、代谢型谷氨酸受体和BDNF等信号分子的相互作用, 以及其不同脑区的重要调控作用, 为后续抑郁症发病机制解析提供新的思路, 也为临床上抗抑郁药物新靶点的发掘提供理论依据。

鉴于研究中不同脑区S100A10在抑郁症发病中的作用存在差异性, 且中枢神经系统神经网络的错综复杂对抑郁症发病的分子机制和药物靶点提出更高的要求, 因此后续研究还需要进一步明确S100A10参与抑郁症调控中的关键脑区和信号通路分子, 并阐明其作用机制。在未来几年中, 以S100A10为靶点的基础研究和临床应用研究将有助于抑郁症的诊疗和药物研发, 为精神类疾病的机制研究提供重要思路。

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