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鸢尾素及其上下游抗抑郁的研究进展

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【摘要】 抑郁症是主要的致残原因之一,对人们带来不利影响。尽管抗抑郁药种类较多,但临床上抑郁症治疗效果依然欠佳。因此,目前仍需要探索新的抗抑郁机制。鸢尾素对神经系统的有益作用逐渐被阐明,研究发现鸢尾素具有抗抑郁的作用,其或将成为治疗抑郁症的新靶点。本研究旨在探讨鸢尾素及其上下游抗抑郁的作用机制,通过查阅现有的研究阐释鸢尾素与抑郁症之间的联系,提出 SIRT1/PGC-1α 可能介导 FNDC5/鸢尾素调控脑源性神经营养因子(BDNF)促进神经发生,改善抑郁症的潜在机制,为鸢尾素及其上下游抗抑郁的研究提供新思路。

【关键词】 抑郁症;鸢尾素;脑源性神经营养因子
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Progress in irisin and its upstream and downstream antidepressants

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【Abstract】 Depression is a major cause of disability and has adverse effects. Despite the many types of anti-depressants, clinical treatments of depression remain poor. Therefore, novel anti-depressant mechanisms need to be explored. The beneficial effects of irisin on the nervous system are gradually being elucidated, and studies have found that irisin has an anti-depressant effect, which may become a new treatment for depression. This study explored the mechanism of irisin and its upstream and downstream anti-depressants by reviewing the existing studies explaining the link between irisin and depression, and proposes that SIRT1/PGC-1α may mediate FNDC5/irisin to regulate BDNF to promote neurogenesis and improve depression, which provides a new idea to study irisin and its upstream and downstream anti-depressants.

【Keywords】 depression; irisin; BDNF
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抑郁症是重要的致残原因之一,给全球造成沉重的负担[1-2]。据世界卫生组织(World Health Organization,WHO)报道,2030 年抑郁症将成为全球第一大负担疾病。目前,全球约 3.4 亿人患有抑郁

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症,其中有 2/3 的人产生过自杀的念头[3]。抑郁症发病率逐年增高[4],但临床上仍不能充分治疗抑郁症[5]。目前主流的抗抑郁药物大多数是基于单胺类神经递质假说[6],例如早期的三环类抗抑郁药(tricyclic antidepressive agents, TCAs)、单胺氧化酶抑制剂(monoamine oxidase inhibitors, MAOIs)以及新型抗抑郁药选择性 5-羟色胺再摄取抑制剂(selective serotonin reuptake inhibitors, SSRIs)。新型抗抑郁药对患者副作用更小,但其疗效依然欠佳,只有 1/3 的患者在第一次治疗后抑郁症状得到缓解[7]。因此,探索新的抑郁症治疗方案非常迫切。随着研究的深入,鸢尾素在心理疾病中的作用逐渐被阐明。2016 年,Wang 等[8]研究发现鸢尾素与抑郁症相关,鸢尾素在慢性不可预测应激(chronic unpredictable stress, CUS)抑郁模型大鼠海马中的水平下降,外周注射鸢尾素后 CUS 模型大鼠抑郁样行为得到改善。随后,一系列新的研究进一步证实了鸢尾素和抑郁之间的相关性。然而,关于鸢尾素与抑郁及其可能的上下游相关研究仍未见系统报道。基于此,本研究旨在探讨鸢尾素及其上下游抗抑郁的作用机制。

1 鸢尾素与抑郁症

2012 年,发表在 *Nature* 上的一项研究首次报道了鸢尾素[5]。运动后,骨骼肌会分泌过氧化物酶体增殖物激活受体 γ 辅助活化因子 1(peroxisome proliierators-activated receptor γ coactivator 1α, PGC-1α),该蛋白调控的下游肌肉因子纤连蛋白Ⅲ型结构域蛋白 5(fibronectin type-Ⅲ domain-containing protein 5, FNDC5)可以在细胞膜上发生水解生成鸢尾素[9]。鸢尾素是 FNDC5 裂解的产物,在心脏、骨骼肌以及脊髓中高表达[10]。鸢尾素可以调节能量代谢[11-12],在脂肪组织中,鸢尾素可诱导白色脂肪组织褐变,并促进能量消耗[13]。鸢尾素在大脑中也有表达,如中脑和海马体[10],其可以减轻神经炎症、记忆缺陷,对记忆相关的大脑区域具有积极影响。FNDC5/鸢尾素的过表达与神经可塑性有关,因其可以调节神经元的增殖[14]。病理条件下鸢尾素发挥了较强的抗炎、抗凋亡、抗氧化作用[15]。鸢尾素在阿尔茨海默病(Alzheimer's disease, AD)中也起到有益作用,FNDC5/鸢尾素水平在 AD 模型小鼠海马体和脑脊液中降低,敲低大脑中 FNDC5/鸢尾素后会损害小鼠的新型物体识别记忆。外周递送 FNDC5/鸢尾素可以提高大脑中 FNDC5/鸢尾素水平,从而改善 AD 模型小鼠的突触可塑性和记忆力[16]。Guo 等[17]发现鸢尾素可以改善血脂参数,降低甘油三酯、总胆固醇和低密度脂蛋白胆固醇水平,并且可以增加能量消耗,从而改善代谢功能障碍。

临床研究发现,抑郁症患者血清鸢尾素水平低于非抑郁症患者[18],老年抑郁症患者脑脊液中的鸢尾素水平低于非抑郁患者[19],患者大脑中鸢尾素水平与轻度抑郁呈负相关[20]。有临床研究报道,在人类受试者中中枢鸢尾素和血清鸢尾素之间呈正相关,这表明在中枢中发现的鸢尾素可能来源于外周[21]。多发性硬化症患者血液中鸢尾素水平在运动疗法后提高,可以起到抗抑郁、缓解疲劳的作用[22]。临床研究结果提示鸢尾素可能参与抑郁症的治疗。在动物研究中,CUS 抑郁模型大鼠海马中 FNDC5/鸢尾素蛋白含量降低[23]。在啮齿动物中,通常使用以下几种行为学检测其抑郁样行为,如强迫游泳测试、旷场测试、糖水偏爱测试、悬尾试验等[24]。运动可缩短抑郁模型小鼠在悬尾试验和强迫游泳试验中的不动时间[25],并提高小鼠海马中 FNDC5/鸢尾素的表达,从而改善小鼠抑郁样行为。同样的,鸢尾素在体内过表达也有抗抑郁的效果,外周注射鸢尾素[8,26-27]和中枢注射鸢尾素[28]都可以缓解小鼠的抑郁样行为,从而起到抗抑郁的作用。最近一项研究表明,短期皮下注射鸢尾素可以缩短年轻小鼠悬尾试验和强迫游泳试验的不动时间,发挥抗抑郁效应[29]。综上所述,初步推断鸢尾素可能来源于外周,通过血脑屏障作用于海马,从而减轻抑郁模型动物的抑郁样行为。

2 鸢尾素上下游在抑郁症中的作用机制

2.1 SIRT1 在抑郁症中的治疗作用

沉默信息调节器 1(NAD-dependent deacetylase sirtuin-1, SIRT1)是消耗 NAD 的脱乙酰酶,参与基因沉默[30]、脂肪和葡萄糖代谢、细胞氧化应激和衰老[31]。研究表明,SIRT1 水平的变化会改变突触可塑性和学习能力[32]。牛津大学、弗吉尼亚联邦大学、华大基因和中国五十多家医院组成的国际联盟(CONVERGE)通过与中国 58 家医院的合作招募了 11 670 名汉族女性,对 4509 例患有严重抑郁症亚型忧郁症的病例进行分析,发现 SIRT1 位点的遗传信号增加[33]。日本的一项病例对照研究表明,SIRT1

基因中的 rs10997875 可能在日本人群抑郁症的病理生理学中发挥作用[34]。此外,该研究表明,抑郁症患者外周血中的 SIRT1 表达明显低于健康受试者。同样,与健康受试者相比,抑郁症患者血液中 SIRT1 表达明显降低[35]。基于上述研究,SIRT1 在抑郁症中起着重要作用。最近的抑郁症动物研究还发现,SIRT1 信号失调在小鼠抑郁样行为中起着关键作用。慢性压力抑郁模型降低了小鼠海马齿状回中的 SIRT1 活性,海马中 SIRT1 被抑制会导致抑郁样行为加重。当 SIRT1 被激活时,可以阻断慢性应激诱导的抑郁相关表型和异常树突结构的发展[36]。白藜芦醇是一种 SIRT1 激动剂,腹腔注射白藜芦醇可以改善大鼠的抑郁样行为[37-38]。在最近一项研究中,SIRT1 被白藜芦醇激活并通过增强海马神经发生来逆转脂多糖(lipopolysaccharide,LPS)诱导的抑郁样行为[39-40]。这些证据表明 SIRT1 激活后可以通过促进海马神经发生来改善抑郁症样行为。

2.2 PGC-1α 在抑郁症中的作用

PGC-1α 对中枢神经系统具有许多有益作用,包括线粒体生物发生、抗氧化和抗炎症[41]。临床研究发现,抑郁患者血清中 PGC-1α 水平降低[42],经过 12 周运动训练后骨骼肌中 PGC-1α 的基因表达增加,患者的抑郁情绪得到改善[43]。此外,越来越多的证据表明 PGC-1α 在抑郁症中具有潜在治疗作用,国外有研究发现全身性 PGC-1α 缺陷小鼠与野生小鼠相比在悬尾试验中不动时间更长,表现出显著的抑郁样行为[44]。邓宇辉等[45]发现海马注射 PGC-1α 沉默病毒敲低 PGC-1α 后,小鼠糖水偏爱率降低,强迫游泳试验中小鼠不动时间增加,因此敲低海马中 PGC-1α 会诱导小鼠出现抑郁样行为;而海马注射 PGC-1α 过表达病毒后,小鼠在强迫游泳试验中不动时间减少,因此激活海马中 PGC-1α 会改善小鼠的抑郁样行为,起到抗抑郁的作用。慢性轻度应激(chronic mild stress,CMS)模型小鼠经过运动训练后骨骼肌中的 PGC-1α 基因表达量增加,减少了 CMS 小鼠在强迫游泳试验中的不动时间,增加了 CMS 小鼠的糖水偏爱率[46],因此骨骼肌中的 PGC-1α 被激活也会改善 CMS 小鼠抑郁样行为。这些证据表明 PGC-1α 水平降低可以诱导抑郁的发生,而 PGC-1α 水平的升高可以起到抗抑郁的作用。

2.3 BDNF 对抑郁症的影响

抑郁症的神经营养假说认为,神经营养缺失会导致神经元萎缩、减少神经新生和破坏胶质细胞[47],而抗抑郁药物会减弱或逆转这些病理生理过程。其中,最广为接受的假说涉及脑源性神经营养因子(brain-derived neurotrophic factor,BDNF),部分抗抑郁药物与激活 BDNF 系统相关[48-49]。BDNF 是一种具有神经营养作用的蛋白质,在神经系统中广泛表达。患者突触可塑性损伤与抑郁症的发生有着紧密的联系[50],抑郁患者在特定区域 BDNF 的水平和功能方面也会发生改变。例如,有研究者在抑郁患者海马和内侧前额叶皮层中观察到 BDNF 水平下调[51]。研究发现,益生菌可以显著增加抑郁症患者血清中 BDNF 的水平,进而改善患者的抑郁情绪[52]。在动物研究中,限制神经发生会导致类似抑郁的症状[53],CMS 抑郁模型小鼠海马中 BDNF 水平较空白对照组降低[54]。BDNF 的异常也会导致抑郁回路中星形胶质细胞和小胶质细胞的功能障碍[55]。有证据表明,BDNF 水平的升高有助于提高突触可塑性、促进对神经元损伤的修复,从而缓解抑郁[56-57]。在 CMS 小鼠体内注射 BDNF 病毒会增强海马 BDNF 的水平,降低 CMS 小鼠在强迫游泳试验中的不动时间,进而改善 CMS 小鼠的抑郁样行为[58]。这些证据表明抑郁的发生会导致体内 BDNF 水平降低,相反,BDNF 水平升高会促进神经发生改善抑郁症状。

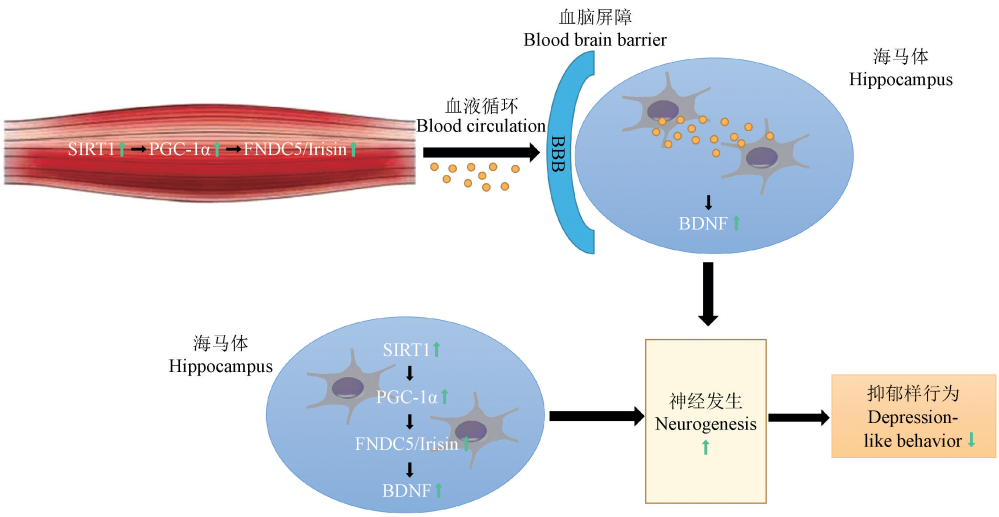
2.4 FNDC5/鸢尾素上调 BDNF 水平促进神经发生改善抑郁

近年来,越来越多的研究证明 FNDC5/鸢尾素可以上调大脑中 BDNF 的水平,而大脑中的 BDNF 水平变化与抑郁症密切相关。FNDC5 过表达可增加神经元前体标志物和成熟神经元标志物,促进神经分化[59]。并且,FNDC5 在初级皮层神经元中的过表达可增加 BDNF 的表达,而 FNDC5 敲低则可降低 BDNF 的表达[60]。在小鼠体内,外周递送腺病毒载体 FNDC5 也可以增加海马中 BDNF 的表达,起到神经保护的作用[60]。有研究发现,系统注射鸢尾素可显著诱导小鼠脑中 BDNF[61-62]以及胰岛素样生长因子(insulin-like growth factors-1,IGF-1)的基因表达,起到抗抑郁的作用[27]。糖尿病模型大鼠在注射鸢尾素-shRNA 敲低鸢尾素后,大鼠血清 BDNF 水平显著降低,海马 BDNF 蛋白含量也显著降低[63]。体外实验证明,原代大鼠海马神经元在转染鸢尾素过表达病毒后,BDNF 水平显著增高[64]。临床研究发现,患者体内鸢尾素水平与 BDNF 水平呈正相

关[65-66]。这些证据表明 BDNF 水平受鸢尾素的调控。AD 模型小鼠海马中 FNDC5/BDNF 途径也可被运动激活，经过运动训练后，AD 模型小鼠海马当中 FNDC5/BDNF 基因表达量以及蛋白含量增加，进而对 AD 模型小鼠起到神经保护的作用[67]。最近一项研究发现，肌酸慢性给药通过调节 FNDC5/BDNF 介导的小鼠海马信号通路产生抗抑郁样作用[68]。综上所述，FNDC5/鸢尾素过表达可能使大脑中 BDNF 表达增加，促进神经发生，起到抗抑郁的作用。

3　SIRT1/PGC-1α 介导 FNDC5/鸢尾素调控 BDNF 促进神经发生改善抑郁症

SIRT1 被白藜芦醇激活可减少海马中的神经变性，防止学习障碍，并降低 PGC-1α 的乙酰化，促进线粒体生物发生，从而起到神经保护的作用[69]。此外，SIRT1 特异性激动剂（SRT1720）增加了帕金森病（Parkinson's disease，PD）模型中的 PGC-1α 水平，促进线粒体生物发生[70]。SIRT1 抑制剂 EX527 的应用不仅可降低 PGC-1α 的活性，而且进一步加重线粒体功能障碍[71]。可见，PGC-1α 受 SIRT1 调控，激活 SIRT1 可增加 PGC-1α 水平，而敲低 SIRT1 则降低 PGC-1α 的水平。FNDC5 也受到 SIRT1 的调控，在 SIRT1 敲低后 FNDC5 基因表达量降低[72]。敲低海马神经元 PGC-1α 后，蛋白印迹显示 FNDC5/BDNF 含量降低[73]。PGC-1α 可在体外和体内调节神经元 FNDC5/鸢尾素的基因表达，FNDC5/鸢尾素可正向调节 BDNF 的表达[60]。FNDC5/鸢尾素的外周过表达可挽救 AD 模型小鼠记忆障碍促进神经发生，而阻断外周或脑 FNDC5/鸢尾素可减弱体育锻炼对 AD 模型小鼠的突触可塑性和记忆的神经保护作用[16]。此外，有研究发现 SIRT1 激动剂白藜芦醇可以使高脂肪饮食（high-fat diet，HFD）所诱导的肥胖模型老年小鼠海马当中的 SIRT1/PGC-1α/FNDC5/BDNF 蛋白表达增加，从而减轻小鼠记忆丧失起到神经保护的作用[74]。体育锻炼可以预防、减弱并可能逆转抑郁症引起的生化和行为的负面变化[75]。运动后，CUS 大鼠海马 PGC-1α/FNDC5/BDNF 蛋白含量增加，强迫游泳试验不动时间减少，大鼠抑郁样行为得到改善[23]。Apelin-13 是一种新型神经肽，其受体可以改善大鼠的认知障碍和抑郁样行为[76]，apelin-13 通过 PGC-1α/FNDC5/BDNF 途径改善慢性不可预测轻度应激（chronic unpredictable mild stress，CUMS）小鼠的抑郁样行为。近年有研究发现，CUMS 抑郁模型小鼠海马 *miR*-138 基因表达升高，而小鼠海马注射 miR-138 过表达病毒后海马中 SIRT1/PGC-1α/FNDC5/BDNF 基因相对表达量和蛋白含量均降低，诱导小鼠发生抑郁样行为[77]。综上所述，SIRT1/PGC-1α 可能介导 FNDC5/鸢尾素调控 BDNF 促进神经发生改善抑郁症。鸢尾素及其上下游抗抑郁可能形成的作用机制见图 1，鸢尾素及其上下游靶点和途径见表 1。



注：↑代表激活或升高，↓代表抑制或减弱，●代表鸢尾素。

图 1　鸢尾素及其上下游抗抑郁作用机制

Note. ↑ represents an activation or an elevation, ↓ represents either inhibition or weakening, ● represents irisin.

Figure 1　Mechanism of action of irisin and its upstream and downstream antidepressants

表 1 鸢尾素及其上下游靶点和途径

Table 1 List of irisin and its upstream and downstream targets and pathways

研究者 Investigator	动物模型 Animal model	干预措施 Intervention study	调控途径 Regulatory pathway	作用部位 Site of action	作用靶点 Action target	作用 Effects
Wrann, et al [60]	野生小鼠 Wild mouse	尾静脉注射腺病毒 FNDC5 Tail vein injection of adenovirus FNDC5	FNDC5/ Irisin ↑	海马 Hippocampus	BDNF ↑	神经保护 ↑ Neuroprotection ↑
	体外实验 Experiment *in vitro*	转染腺病毒 PGC-1α Transfection of adenovirus PGC-1α	PGC-1α/ FNDC5 ↑	海马神经元 Hippocampal neurons	BDNF ↑	
Kim, et al [62]	野生小鼠 Wild mouse	腹腔注射鸢尾素 Intraperitoneal injection of irisin	Irisin ↑	海马 Hippocampus	BDNF ↑	神经保护 ↑ Neuroprotection ↑
Huang, et al [63]	糖尿病模型大鼠 Diabetes model rats	海马注射鸢尾素-shRNA Hippocampal injection of irisin-shRNA	Irisin ↓	海马 Hippocampus	BDNF ↓	认知功能 ↓ Cognitive function ↓
Lourenco, et al [64]	体外实验 Experiment *in vitro*	转染鸢尾素病毒 Transfection of iris virus	Irisin ↑	海马神经元 Hippocampal neurons	BDNF ↑	
Belviranlı, et al [67]	AD 模型小鼠 AD model mice	运动训练 Exercise	FNDC5 ↑	海马 Hippocampus	BDNF ↑	神经保护 ↑ Neuroprotection ↑
Cunha, et al [68]	抑郁模型小鼠 Depression model mice	口服肌酸 Oral creatine	FNDC5 ↑	海马 Hippocampus	BDNF ↑	抑郁样行为 ↓ Depression-like behavior ↓
Kim, et al [69]	AD 模型小鼠 AD model mice	侧脑室注射白藜芦醇 Lateral ventricular injection of resveratrol	SIRT1 ↑	海马 Hippocampus	PGC-1α ↑	神经保护 ↑ Neuroprotection ↑
Ye, et al [71]	体外实验 Experiment *in vitro*	EX527	SIRT1 ↓	HK-527 细胞 HK-527 cells	PGC-1α ↓	线粒体功能 ↓ Mitochondrial function ↓
El Hayek, et al [72]	野生小鼠 Wild mouse	腹腔注射乳酸 Intraperitoneal injection of lactic acid	SIRT1/ PGC-1α/ FNDC5 ↑	海马 Hippocampus	BDNF ↑	学习和记忆能力 ↑ Learning and memory capacity ↑
Hu, et al [73]	抑郁模型大鼠 Depression model rats	侧脑室注射 apelin-13 Lateral ventricular injection of apelin-13	PGC-1α/ FNDC5 ↑	海马 Hippocampus	BDNF ↑	抑郁样行为 ↓ Depression-like behavior ↓
Zhao, et al [74]	肥胖模型老年小鼠 Obesity model of older mice	腹腔注射白藜芦醇 Intraperitoneal injection of resveratrol	SIRT1/ PGC-1α/ FNDC5 ↑	海马 Hippocampus	BDNF ↑	神经保护 ↑ Neuroprotection ↑
Babaei, et al [23]	抑郁模型大鼠 Depression model rats	运动 Exercise	PGC-1α/ FNDC5 ↑	海马 Hippocampus	BDNF ↑	抑郁样行为 ↓ Depression-like behavior ↓
Li, et al [77]	抑郁模型小鼠 Depression model mice	海马注射 miR-138 病毒 Hippocampal injection of miR-138 virus	SIRT1/ PGC-1α/ FNDC5 ↓	海马 Hippocampus	BDNF ↓	抑郁样行为 ↑ Depression-like behavior ↑

注:↑代表激活或升高,↓代表抑制或减弱。

Note. ↑ represents an activation or an elevation, ↓ represents either inhibition or weakening.

4 小结与讨论

抑郁症患者人数逐年增长,现有的单胺类抗抑郁药仍不能有效治疗抑郁症,迫切需要探索新的抗抑郁治疗方法。鸢尾素在抑郁症中有潜在的治疗作用,或将成为抑郁症的治疗靶点。本文综述了鸢尾素对抑郁症的影响,提出鸢尾素可能来源于外周,通过血脑屏障作用于海马,从而减轻抑郁模型

动物的抑郁样行为。本文探讨了鸢尾素及其上下游可能的抗抑郁效应机制,初步推断 SIRT1/PGC-1α 可能介导 FNDC5/鸢尾素调控 BDNF,促进神经发生,改善抑郁症,为抑郁症治疗提供了新思路。近些年,关于鸢尾素与抑郁症的发病机制有了新的探索,有研究显示炎症也可能是抑郁症的诱发原因之一[78]。部分抑郁患者表现出更高的循环促炎细胞因子水平,包括白细胞介素 6(interleukin 6, IL-6)、肿瘤坏死因子 α (tumor necrosis factor-α, TNF-α)、白细胞介素 1β(interleukin 1β, IL-1β)[79]。近期有研究报道了鸢尾素与炎症有着密切相关性,外周注射鸢尾素可以抑制脑组织中 TNF-α 和 IL-6 的 mRNA 表达[80]。无论体外或者在体内,鸢尾素均可下调 IL-1β 的表达[81-83]。在缺乏鸢尾素的小鼠中,IL-6 和 TNF-α 的水平也有所增加[84]。可见,鸢尾素可以下调促炎细胞因子 IL-1β、TNF-α 和 IL-6 的水平,起到抗炎的作用,进而改善炎症引发的抑郁症。敲低 SIRT1 会引起 LPS 诱导的 IL-1β 分泌增加[85],而 SIRT1 的过表达会抑制 IL-1β 诱导的细胞凋亡起到抗炎的作用[86]。SIRT1 激动剂 SRT1720 可以降低 TNF-α 的水平[87],SIRT1 抑制剂 EX527 会使 TNF-α 的水平增高[88]。同时,SIRT1 激动剂 SRT1720 可以抑制卵清蛋白(ovalbumin, OVA)诱导的哮喘小鼠模型中 IL-6 的产生[89],而 SIRT1 抑制剂 EX527 消除了这种作用[90]。同样的,PGC-1α 与炎症因子也具有相关性,PGC-1α 的水平与促炎细胞因子 IL-1β[91]、TNF-α[92]和 IL-6[93]呈负相关。综上所述,鸢尾素及其上下游可能通过 BDNF 促进神经发生改善抑郁,也可能通过抗炎作用改善抑郁症状。然而,鸢尾素及其上下游与炎症如何影响抑郁的问题依然有待于进一步探讨。总之,鸢尾素在抑郁症中的影响受到越来越多的关注,本研究将为鸢尾素抗抑郁的机制研究提供新的思路,也可能为抑郁症的临床治疗和药物研发提供潜在靶标。

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