星形胶质细胞在阿尔茨海默病发病进程中的作用

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摘要 阿尔茨海默病(Alzheimer's disease, AD)是导致老年人记忆、思维和行为障碍的最常见神经退行性疾病。星形胶质细胞(astrocyte, AS)在AD发病进程中扮演重要角色。在AD病理情况下, AS具有神经保护和损伤双重功能。AS通过摄取、清除异常物质和释放神经营养因子起到神经保护的作用; 激活型AS产生和释放促炎细胞因子与毒性物质等直接或间接作用于其他脑细胞, 增强炎症级联反应和Aβ聚集沉积, 影响着AD的病理进程。该文总结在AD发病进程中AS对其他脑细胞的影响, 以期待为AS作为目标靶点预防和治疗AD提供新思路。

关键词 星形胶质细胞; 阿尔茨海默病; 炎症反应; 脑细胞

The Roles of Astrocytes in the Pathogenesis of Alzheimer's Disease

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Abstract AD (Alzheimer's disease) is the most common neurodegenerative disease that causes memory decline, cognitive dysfunction and behavior disorders in the aged people. Current evidences have shown that astrocytes play an important role in the development of AD. Under the pathological conditions of AD, astrocytes have both protective and damaging effects on the nervous system. On one hand, astrocytes serve as protectors of the nerves system by ingesting and expulsing the abnormal substances and by producing neurotrophic factors. While, on the other hand, astrocytes can directly or indirectly impact the other brain cells by releasing pro-inflammatory cytokines and toxic substances. In this process, the astrocytes enhance the inflammatory cascade reaction and Aβ accumulation, which exacerbates the pathological process of AD. This article summarizes the effects of astrocytes on other brain cells in AD, hoping to provide a new strategy that targets astrocytes in the prevention and treatment of AD.

Keywords astrocytes; Alzheimer's disease; inflammatory response; brain cells

阿尔茨海默病(Alzheimer's disease, AD)又称老年痴呆症, 是以进行性记忆减退和认知功能障碍为主要特征的神经退行性疾病[1], 主要病理特征包括脑细胞内神经纤维缠结(neurofibri-llarytangle, NFT)及

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细胞外β-淀粉样蛋白(amyloid-β, Aβ)聚集形成老年斑[2-3]。据世界阿尔茨海默病报告指出[4], 目前, 全世界范围内痴呆病人数约有5 000万, 其中约2/3的人患有AD。随着人口老龄化趋势加剧, 预计到2050年, 痴呆人病数约增至1.5亿, 其中AD人数也将相应增至1亿。预计每3秒就会新增1名AD病例, 每年将导致近100万新增病例。AD已成为继心脏病、癌症及中风之后老年人的第四杀手。2000－2017年, 中风、心脏病等死亡率下降, 而AD死亡率却增加了145%[5-6]。现阶段, 针对AD患者大多使用乙酰胆碱酯酶抑制剂(卡巴拉汀、加兰他敏和多奈哌齐)治疗, 而中度至重度患者使用*N*-甲基-*D*-天门冬氨酸受体拮抗剂(美金刚)药物治疗, 药物治疗虽可改善患者生活质量, 但无法阻止或逆转病理进程[7]。

长期以来, 认知功能障碍领域的研究主要集中在神经元畸变方面, 研究表明, 神经胶质细胞在大脑发育中也发挥重要的作用[8]。AD患者认知下降, 除了β-淀粉样蛋白沉积和Tau过度磷酸化引起神经元丢失外, 还受胶质细胞激活形成神经炎症的影响[9]。AD是在神经元(neuron)、星形胶质细胞(astrocyte, AS)、小胶质细胞(microglia, MG)、少突胶质细胞(oligodendrocyte, OL)、神经干细胞(neural stem cell, NSC)等多种脑细胞间复杂的相互作用下引起的病理性改变和认知功能障碍。AS作为中枢神经系统中一类神经胶质细胞, 赋予大脑复杂性和高级认知能力, 因而在中枢神经系统疾病形成中扮演重要的角色[10]。AS的形态变化、生理改变及炎症反应对AD发生发展的影响逐渐成为关注热点[11]。利用AS调控AD病理进程可能成为潜在的预防和治疗AD的重要研究方向。那么, 了解AS如何影响其他脑细胞进而操控AD病理进程非常关键, 本文就AS与其他类型脑细胞间的相互作用调控AD发生发展的的作用机制进行综述。

1 AS的正常生理功能

AS作为中枢神经系统中分布最广泛、数量最多、体积最大的一类神经胶质细胞, 不仅仅具有支持、引导和分隔神经细胞的作用[10,12], 而且还具有许多更加复杂的调节功能, 参与神经递质的分泌和循环, 分泌神经营养因子和细胞因子, 促进邻近神经元树突发育和突触连接, 参与机体内免疫反应, 传递营养物质和传导电信号[13-14]。在正常生理状态下, AS处于静息状态, 一方面, 可释放神经营养因子如脑源性神经营养因子(brain-derived neurotrophic factor, BNDF)促进神经细胞的生存和生长, 起到神经保护作用。AS和神经元通过谷氨酰胺–谷氨酸循环(glutamine-glutamate cycle, GGC)相互作用, 支持神经元的代谢需求和神经递质传递[15]; 另一方面, AS也具有摄取和酶解细胞外间隙中Aβ和Tau蛋白的功能[16-17]。AS摄入Aβ斑块后, 通过内吞作用被特异性肽(kallikrein-related peptidase 7, KLK7)降解, 也有些Aβ斑块摄入后又被转运到邻近的AS, 通过转胞吞作用清除[18-19]。另外, 在中枢神经系统中AS可以释放抗氧化剂, 抑制氧化应激反应发生。AS通过分泌抗氧化剂去除兴奋性氨基酸, 激活抗氧化系统释放内源性还原物质如维生素C、谷胱甘肽(glutathione)等, 保护中枢神经系统免受氧化应激损伤[20]。AS的足突与神经元突触前后膜偶联, AS膜上有与神经元信号交流相关的电压门控通道和神经递质受体(如5-羟色胺、乙酰胆碱等受体), 接受神经元释放的神经递质, 诱导AS胞内Ca^{2+}浓度升高, 引起AS兴奋, 兴奋性信号可直接刺激突触后神经元, 使神经元发生兴奋性或抑制性反应[21]。AS的足突分别与血管内皮细胞和室管膜上皮细胞相关联, 形成血脑屏障, 共同维持脑组织内环境的稳态。AS的终足包裹神经微血管, 控制中枢神经的血流量和神经细胞的能量供应, 影响着中枢神经系统的正常功能[22]。AS在AD中参与病理进程, 包括摄取和降解Aβ和Tau毒性蛋白、产生神经炎症因子、形态和代谢异常、功能失常等。从分子水平探究, AS发挥神经损伤或是神经保护作用主要受AS自身基因表达水平的影响, 其表达异常将导致与AD病理特征相关的症状出现。例如, AS中的某些基因表达水平升高或降低, 导致AS降解Aβ和Tau的能力减弱, 或激活神经炎症反应, 或神经元大量丢失, 增加患AD的风险。本文整理了近3年内文献涉及AS相关的AD风险基因(表1)。AS功能障碍发生在神经退行性病变和明显的Tau蛋白神经病理特征(如神经纤维缠结的磷酸化、聚集和形成)之前[15]。因此, AS形态和功能异常可以作为神经退行性疾病的发生发展的指标之一。

2 AD发病进程中AS的特征变化

在AD病理条件下, AS形态主要表现为萎缩型和激活型2种。在AD形成的早期, 大量异常AS处于萎缩型, 形态表现为体积变小、表面积减少和原生质

表1 星形胶质细胞相关的AD风险基因

Table 1 Summary of astrocyte-associated AD risk genes

基因名称 Gene name	表达变化 Expression change	主要的AD特征 Major AD outcome	参考文献 Reference
NRF2	↑	Inflammatory and amyloid ↓	[23]
CB2	↓	Amyloid and neurons loss ↓	[24]
hCD300f	↑	Neurons loss and amyloid ↓	[25]
NDRG2	↓	Memory impairment ↓	[26]
LXR α/β	↓	Apoe secretion ↓	[27]
PPARA -α	↑	Amyloid and cognitive decline ↓	[28]
sEH	↓	Inflammatory and amyloid ↓	[29]
Sort1	↓	Amyloid ↑	[30]
GAD67	↓	Amyloid ↓	[31]
Apelin-13	↑	Neuroinflammation and cognitive deficit ↓	[32]
Il33	↓	Tau abnormality and neurons loss ↑	[33]
AQP4	↑	Cognitive impairment ↓	[34]
TREM2	↑	Microglia activation ↑	[35]
alpha-amylase	↓	Amyloid ↑	[36]
LRP1	↓	Amyloid ↑	[37]
Stat3	↓	Inflammatory and amyloid ↓	[38]

↑: 上调; ↓: 下调。

↑: up-regulated; ↓: downregulated.

突起减少, 基本生理功能接近于完全丧失[39-40], 且AS萎缩早于Aβ斑块出现[41]。在AD进展中, AS由静息态转变成激活态, 此时AS称为激活型AS[42]。激活型AS主要表现为细胞增殖和分化速度快、胞体肥大肿胀、突起增多延长、胶质纤维酸性蛋白(glial fibrous acidic protein, GFAP)表达升高[43], 并且激活型AS多聚集于受损区域边缘[44]。激活型AS存在A1和A2 2种类型。A1型AS分泌产生大量的炎症因子和神经毒素, 对邻近的脑细胞产生高度毒性作用; 同静息型AS相比, A1型AS的提供神经营养因子和吞噬能力相对下降[45-46]。在AD患者皮层和海马组织内观察到大量的A1型AS优先聚集在病灶区且含量显著增高, 说明A1型AS驱动这些疾病中的神经变性[47]。然而, 缺氧诱导产生的A2型AS分泌神经营养物质, 支持神经元生长[45]。AS出现形态和生理变化调节AD进展[48]。

AS与Aβ之间存在双向的相互作用。Aβ主要由神经元产生, 并被淋巴细胞、吞噬细胞等免疫细胞清除, 维持Aβ在脑组织中的正常水平[49]。在AD病理状态下, Aβ不仅是由神经元产生, 也可以由激活型AS分泌产生。激活型AS产生Aβ氧化应激机制如下: AS细胞内钙离子含量升高时会刺激还原型辅酶II NADPH发生氧化反应, 产生活性氧(reactive oxygen species, ROS), ROS激活脂蛋白脂酶(lipoprotein lipase, LPL)和ADP核糖聚合酶(poly ADP-ribose polymerase, PARP), 并且消耗细胞内谷胱甘肽, 诱导AS和神经元发生氧化应激反应, 最终导致Aβ产生[1]。激活型AS产生Aβ比神经元所产生的更具有破坏性[50]。反过来, AS在持续的高浓度Aβ毒性蛋白暴露状态下被激活, 导致激活型AS增生[51-52]。激活型AS释放一些炎症因子, 如肿瘤坏死因子-α(tumor necrosis factor-α, TNF-α)、肿瘤坏死因子-γ(tumor necrosis factor-γ, TNF-γ)、白介素-1β(interleukin-1β, IL-1β)等, 不断刺激AS使其处于激活状态, 被过度激活的AS, 又发生一系列氧化应激反应。如此循环反复, AS没有达到清除作用, 反而加剧了Aβ产生, 造成Aβ斑块过度沉淀积聚, 恶化中枢神经系统疾病, 导致患者的记忆和认知发生“二次伤害”[53]。

综上, 在AD病理状态下AS的形态变化主要由脑组织中的Aβ或炎症因子的刺激导致, 也可通过自身释放的有毒物质引起。当AS发生形态或生理功能变化时, 说明脑组织的微环境已经发生变化。因而, AS异常可以作为判断AD脑部微环境发生变化的指标之一。

3 AD发病进程中AS对NSC的影响

NSC是一类具有自我更新和增殖能力, 能分化

为神经元、AS、MG和OL潜能的细胞群。NSC具有的多向分化潜能可改善中枢系统疾病的局部炎症, 抑制炎症引起的微环境恶化, 促进损伤修复, 加速神经结构的重构。AS对NSC的存活、增殖、分化和迁移产生影响。在正常状态下, 一方面, AS促进NSC生存和增殖。AS通过分泌多种神经营养因子, 为NSC存活提供必需的蛋白质和多肽分子, 对NSC生长、发育、存活维持起营养作用。而且, AS促进NSC分化。AS分泌EGF(epidermal growth factor)、FGF(fibroblast growth factor)、IGF(insulin like growth factor)等生长因子诱导NSC分化成为神经元, 分泌EGF、睫状神经营养因子(ciliary neurotrophic factor, CNTF)等诱导NSC分化成为胶质细胞[54]。另一方面, AS提供NSC迁移引导的支架, 发育中的NSC沿着AS辐射状突起方向迁移到它们的定居部位[55]。因此, NSC增殖、分化和迁移效率取决于AS的状态。在AD病理状态下, 激活型AS出现形态和生理的变化, 影响NSC的再生和迁移。研究发现, 中枢神经病灶区附近的AS会形成结痂状组织即胶质瘢痕, 胶质瘢痕会阻碍NSC再生和迁移[56]。激活型AS释放炎症因子, 影响脑组织内NSC的存活和分化[57]。激活型AS释放Aβ和Tau毒性蛋白, 威胁NSC的生存空间, 抑制NSC的生长发育。通过阻断AS变异促进NSC增殖和分化, 分化成熟的新神经元和胶质细胞代替受损的细胞, 抑制炎症反应和神经毒素产生, 促进神经再生与修复, 减弱脱髓鞘反应和局部的胶质瘢痕形成, 重建神经元的部分环路和功能, 改善AD患者认知能力[58]。

综上, 利用NSC多向分化潜能, 可为中枢神经系统疾病临床细胞治疗和基因治疗提供新的细胞来源。因此, 从AS角度探索利用AS调控NSC的再生能力和定向分化潜能, 将NSC诱导产生特定分化的细胞替代损伤和病变的神经细胞, 可能达到阻止或逆转AD的效果。

4 AD发病进程中AS对神经元的影响

神经元主要负责接受、整合、传导和传输兴奋[59]。在中枢神经系统中, AS包绕着神经元, 不仅为神经元胞体和突触提供支架结构, 而且还能调节神经元的活动和突触信号传递[60-62]。在AD病理中, 激活型AS产生和释放神经递质、细胞因子和毒性物质, 通过突触、缝隙连接和细胞信号交流, 在受体、离子通道、信使、基因转录等水平影响和调节神经元的功能。

突触是神经元之间信息传递的特化结构, 是形成神经活动的结构基础。AS释放神经递质如谷氨酸、ATP、γ-氨基丁酸(γ-aminobutyric acid, GABA)、肽、生长因子等, 参与神经元突触传递调节[63]。AS释放谷氨酸对突触传递起兴奋作用, 谷氨酸激活神经元NMDA受体上的谷氨酸位点, 增强神经元间的突触传递[64]。Aβ低聚物可导致AS与谷氨酸相关蛋白(excitatory amino acid transporter 1/2, EAAT1/2)表达水平降低, 从而削弱神经元突触可塑性[65]。AS释放ATP对突触传递起抑制作用, ATP代谢产物腺嘌呤与神经元嘌呤P2Y受体结合, 抑制神经元突触传递[66]。AS释放的生长因子(如TGF、FGF-2、IGF)促进神经元形成新的突触, 参与突触形成和重塑。AS细胞膜有钠钾泵和钙泵, 调节细胞内外K^+、Na^+和Ca^{2+}离子浓度、pH值等, 对维持内环境稳定和神经元正常电生理活动起着重要的作用[67]。破坏神经元和AS之间钙离子平衡, 会引起突触传递抑制和神经毒性的发生[68]。

AS和神经元之间通过缝隙连接交流钙离子, 从而对神经元功能发挥作用。研究表明, AS膜上存在谷氨酸、GABA和转运蛋白, GABA可以刺激AS上Ca^{2+}信号通道诱导自身释放能量与腺苷[69-70], 降低神经突触兴奋性[71]。另外, 神经元上电信号产生的放电频率与时间可激活AS膜上GABA进而提升神经元处理信息能力[71-72]。

AS是合成和释放炎症因子的主要场所, 不仅是炎症因子的主要来源, 而且具有炎症因子的受体。当氨基酸、NO、ATP、炎症因子、LPS等因素激活AS后, AS合成和释放炎症因子(IL-1、TNF-α等)反过来调节自身的功能, 也影响相邻脑细胞的功能。炎症因子刺激AS, 异常活化的AS聚集和增生形成胶质瘢痕, 形成的胶质瘢痕一方面构成了神经元再生修复的物理屏障, 另一方面分泌炎症因子构成了阻碍神经元再生的化学屏障[46]。从代谢方面而言, AS对神经元调控主要途径是糖酵解通路。乳酸作为促进神经元存活的能量原料, 是由AS在厌氧条件下产生和释放的[73]。AD发生过程中, 激活型AS降低乳酸释放, 神经元内不能有效利用乳酸合成自身能量, 损害神经元功能[74]。

AS与神经元之间存在着广泛的信号交流。激活型AS通过炎症因子和毒性蛋白(如Aβ、Tau等

蛋白)直接破坏神经元的功能, 或借助其他物质(如Ca^{2+}、ATP、乳酸等)间接调控神经元。因此, 通过阻断AS激活或利用药物抑制激活型AS释放杀伤神经元的毒素是目前治疗AD的新策略。

5 AD发病进程中AS对MG的影响

在正常生理状态下, MG主要起到监视周围环境变化和吞噬异常分子的作用[75-76]。MG被激活后表现出2种形态类型: M1和M2[77]。其中, M1型MG释放神经毒性因子、炎症因子等有害物质[78-79], 当处于较长时间或持续处于刺激环境时, M1型MG产生级联反应, 导致神经元受损、突触丢失, 最终使患者的认知和记忆能力进一步退化[80]。M2型MG可通过吞噬作用清除异常蛋白或炎症因子, 并且由损伤边缘向中心区进行移动清除[81], 从而修复受损组织, 维持体内生理环境的稳态[82-83]。研究发现, 增加血红素氧化酶(hemeoxidase, HO-1)的活性或使其表达水平升高, 降低了IFN-γ诱导产生的ROS量, 并且iNOS和NO的释放随之减少, MG引起的炎症反应也随之降低[84]。在AD中MG与AS之间形成了相互制约的关系。活化的MG通过分泌神经毒素(如IL-1α和TNF-γ)和补体成分(complement component 1q, C1q)促使AS转化为具有神经毒性的A1表型, 从而导致神经元和OL死亡, 最终加剧了AD病理特征[85]。活化的MG也可通过释放促炎因子(如IL-1β、IL-6和TNF-α)或产出Aβ诱导AS转化成A1型, 其结果导致大脑内神经胶质细胞清除Aβ能力下降、Aβ累积和神经炎症发生[86]。研究发现, 一种强效胰高血糖素样肽1受体(glucagon-like peptide-1 receptor, GLP1R)激动剂——NLY01可直接阻止MG介导AS向神经毒性A1表型转化, 具有神经保护作用[87]。调节MFG-E8(milk fat globule epidermal growth factor 8)水平可以阻止MG介导AS向神经毒性A1型的转化[88]。活化的MG释放炎症因子诱导AS激活, 而激活型AS既可改变MG的形态和抑制其吞噬功能, 又可释放相关的炎症因子诱导MG激活。钙介导细胞间通讯也是AS和MG相互通讯的网络。激活型AS释放ATP、ATP代谢产物腺嘌呤和MG上嘌呤P2X7受体, 使MG膜对钙离子通透性大大增加, 最终造成MG凋亡[89]。另外, 在AD小鼠中发现Aβ可以诱导AS内NF-κB通路的激活, AS释放C3补体与CaR3(carbonic anhydrase III)受体结合改变MG对Aβ的吞噬清除能力[90]。另外, AS也可以通过释放趋化因子CCL2/CXCL10等提高MG的清除作用。AS释放趋化因子诱导MG由M1向M2型细胞转化以及增强MG向病灶区迁移和清除有害物质能力[91]。MG释放的1L-10与AS的受体结合, 抑制或降低MG的激活, 进而抑制神经炎症反应的发生[92]。

AS和MG存在静息态和激活态, 都属于免疫类型的细胞, 具有释放和吞噬能力, 因而两者相互影响是双向的制约。一方面, AS释放神经营养因子、趋化因子等保护和修复MG的正常生理功能, 提高其清除能力和降低炎症反应; 另一方面, AS释放炎症因子和毒性物质使MG活化, 活化的MG自身释放炎症因子或补体成分不断刺激AS, 最终进一步加重AD程度。

6 AD发病进程中AS对OL的影响

OL是由少突胶质前体细胞(oligodendrocyte precursor cells, OPCs)分化形成的一类高度特化的神经胶质细胞, 在维持中枢神经系统正常功能中发挥重要作用。OL主要负责髓鞘的形成, 维持神经元轴突结构完整, 增加神经传导速度, 增强电信号在大脑中的传递效率[93]。此外, OL还能分泌神经营养因子(BDNF、IGF-1等)、生长因子(TGF-β、FGF-9、HB-EGF)和代谢物(乳酸盐、丙酮酸盐、酮体等), 维护神经元轴突的长期功能和存活[94]。研究发现, OL可借助单羧酸转运蛋白-1(monocarboxylic acid transporter-1, MCT-1)为神经元提供必需的能量物质, 下调或抑制MCT-1导致乳酸不能有效转运入神经元, 造成神经元能量供应紊乱, 引发轴突损伤甚至神经元凋亡[95-96]。

AD患者大部分存在髓鞘缺失的现象, 且髓鞘缺失程度与AD患者认知功能障碍严重程度呈正相关。在正常环境下, OL与AS协同作用, 释放神经营养因子、生长因子或趋化因子促进少突胶质前体细胞增殖、迁移和分化成熟, 分化成熟的OL包绕轴突, 完成髓鞘的新生或再生修复[97]。在AD病理状态下, 首先, 激活型AS产生神经炎症因子, 引起OL功能障碍和髓鞘的缺失。其次, 激活型AS分泌产生的Aβ毒性蛋白破坏OL和髓鞘上膜结构的功能, 并伴随着Aβ沉淀累积诱导脱髓鞘的发生和抑制损伤区髓鞘二次再生[98]。当髓鞘的含量不断降低又促进Aβ沉积加速, 导致Aβ破坏力不断增强[99]。再次, OL对氧化应激非

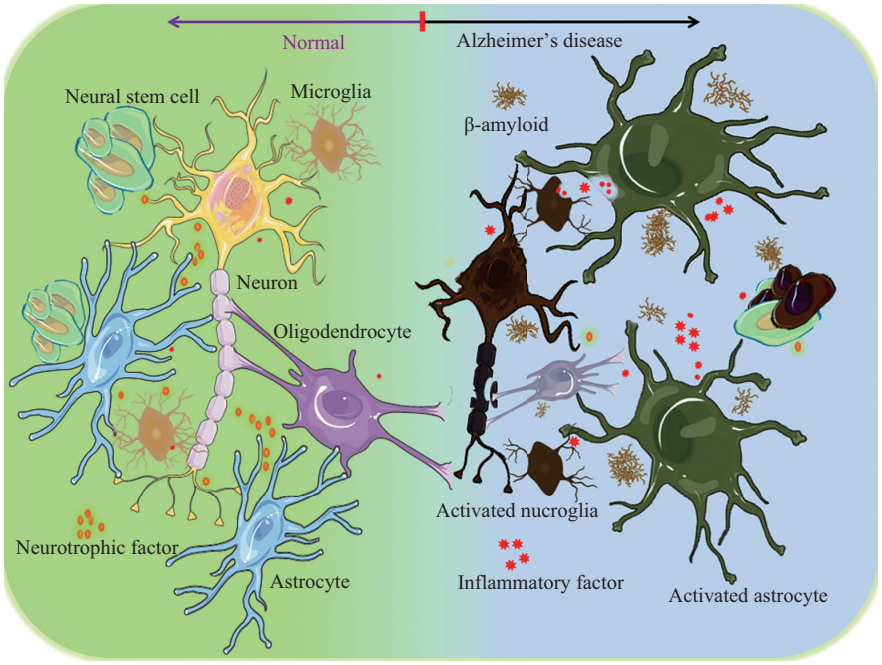
常敏感, Aβ可诱导OL发生氧化应激反应而导致脱髓鞘[100], 并随着AD病理进程释放活性氧增加, 少突细胞前体细胞分化发育受损, 髓鞘再生修复受阻, 造成神经元功能障碍和神经电冲动传导异常[101]。此外, OL及其祖细胞的亚群具有类似免疫细胞的特性, 参与清除疾病损害的髓鞘, 通过细胞通讯改变免疫细胞行为[102]。

综上, 在AD中AS和OL相互作用影响神经元轴突髓鞘发生和修复, 因此, 探索调节AS功能刺激受损区域内髓鞘再生, 或调节AS功能促进少突胶质前体细胞分化发育, 可能是AD治疗的新思路。

7 AD发病进程中AS与其他细胞的相互作用

脑部神经细胞的形态和生理功能对于中枢神经系统的正常功能至关重要。当大脑处于健康状态时, 各类神经细胞有条不紊地进行分工作业, 保证大脑正常运转。中枢神经系统由健康状态转变为病理状态是由多种细胞共同参与导致, 并非某单一细胞决定, 而且各细胞之间表现出复杂的相互作用网络(图1)。

在AD病理初期, NSC、神经元、神经胶质细胞仍发挥正常生理功能, 维持中枢神经系统的稳定性。此时, NSC定向迁移并分化为成熟的神经元和各类神经胶质细胞; AS和MG分泌大量神经营养因子和生长因子, 维持NSC增殖分化和神经元存活, 并为清除神经毒性蛋白(Aβ和Tau蛋白)与抑制炎症因子(1L-1β和TNF-α)创造有利的生理环境; OL分泌神经营养因子、生长因子和代谢物促进髓鞘的形成和维持神经元存活, 保证并增强神经元突触结构的完



星形胶质细胞与其他类型脑细胞间相互关系图。正常健康状态(左侧绿色区域)下, NSC增殖并分化为神经元、AS、小胶质细胞和OL, 且各细胞间紧密连接, 形成神经系统网络结构。此时, 脑部微环境中存在大量营养因子和少量炎症因子, 可促进神经发生。AD病理状态(右侧蓝色区域)下, 各类型脑细胞的形态和生理发生了变化。神经元和激活型AS分泌Aβ, 从而诱导AS和小胶质细胞激活, 而激活型AS和小胶质细胞产生大量炎症因子, 造成Aβ和炎症因子不断积累, 导致脑部微环境不断恶化。此时, AS异常形态抑制NSC生长, 促进神经元和OL凋亡, 加重AD病理进程。The nervous system diagram depicts the interactions between astrocytes and other brain cells. In the normal healthy brain (green area on the left), neural stem cells proliferate and differentiate into neurons, AS, microglia and oligodendrocytes, and the cells are closely connected with each other to form a neural network system. In this brain state, there are a great deal of neurotrophic factors and a very few inflammatory factors in the microenvironment that can promote adult neurogenesis. In the AD pathological state (blue area on the right), the morphology and physiology of brain cells have changed. Both neurons and activated AS secrete Aβ, which thereby induces activation of other AS and microglial cells. Moreover, AS and microglial cells under activated condition can release a large amount of inflammatory cytokines, which also leads to an increasing accumulation of Aβ and inflammatory factors that will further deteriorate the brain microenvironment. Additionally, the abnormal morphology of AS greatly inhibits the growth of neural stem cells as well as promotes the apoptosis of neurons and oligodendrocytes, and eventually exacerbates the pathological process of AD.

图1 星形胶质细胞与其他类型脑细胞间的相互作用

Fig.1 Interactions between astrocytes and other brain cells in health and Alzheimer's disease

整及信息传导速度和效率。另外, 神经元通过突触、缝隙连接和细胞信号交流等不同层面调节NSC和神经胶质细胞的生理功能。在AD发病过程中, 脑部环境发生微变化, 神经元、免疫细胞(AS和MG)率先感受并表现出异常活跃的现象, 尤其是MG对环境刺激最敏感。当刺激累加达到临界值时导致免疫细胞被激活, 产生免疫应答, 最初MG和AS的激活有利于参与Aβ清除[86]。首先被激活的MG表现为M1型, 此时具有促炎功能, 能释放少量的炎症因子, 同时也存在M2型MG, 并通过吞噬作用清除异常蛋白或炎症因子。当M2型MG清除量小于M1型MG释放量, 导致环境不断恶化, 激活AS为A1型, 大多数MG转变为M1型。此时, 胶质细胞形态出现异常, 并释放出大量炎症因子, 丧失吞噬能力。激活型AS和神经元释放Aβ和Tau毒性蛋白, 而毒性蛋白反过来刺激脑细胞, 导致AS和MG不断释放炎症因子, 而炎症因子又刺激AS和神经元分泌毒性蛋白, 不断的“连锁效应”使AD的程度加重。

长时间暴露在病理环境下, NSC定向分化潜能受到抑制, 存活和增殖受到威胁, 激活型AS异常形态和胶质瘢痕影响其发育和迁移, 阻碍病灶区域神经修复和细胞再生。随着病理程度不断加深, 神经元功能性结构不断丧失, 出现树突棘丢失、树突退化, 甚至神经元死亡等现象, 中断神经元与神经胶质细胞广泛的双向信号交流, 导致突触传递和轴突传导异常, 由此引发一系列病理改变。神经元释放Aβ毒性蛋白, 使得AS和MG被活化, 过度激活使AS和MG形态和功能发生改变, 从而由最初对神经元的保护作用变为加剧对神经元的损伤。OL在炎症因子或Aβ双重刺激下发生脱髓鞘甚至凋亡, 影响神经元结构和电信号的传导功能, 导致神经元出现电生理紊乱和功能异常, 加剧脑细胞产生毒性蛋白和炎症因子且抑制NSC增殖分化功能, 使内环境稳态发生改变。脱髓鞘所致的神经元轴突损伤提示胶质细胞–神经元间持续联系对维持神经系统稳定具有重要的作用。

因此, 中枢神经系统中各类神经细胞“交互、协同”作用影响AD的发生发展, 说明神经退行性疾病发病机制的复杂性。与此同时, 在AD病理进程中AS通过直接或间接作用制约其他脑细胞的正常生理功能, 其他脑细胞也通过“负反馈调节”影响AS在脑部环境中的生理作用, 使其在发育、炎症反应、氧化应激、组织修复与再生等方面都发挥着重要作用。

8 展望

AS作为中枢神经系统中重要的胶质细胞, 在AD中扮演多重角色, 一方面可通过自身免疫机制清除有害物质或分泌神经营养因子抑制AD发生; 另一方面又可释放毒性蛋白和炎症因子促进AD发生。AS与其他脑细胞以直接或间接作用联系, 支配着AD的病理进程。因此, 针对AD中AS与其他脑细胞错综复杂的作用关系, 通过流式细胞筛选A1型AS和M1型MG的数量或其他脑细胞表型和形态的改变(如OL脱髓鞘程度), 可作为未来诊断AD病理程度的依据。迄今为止, 市场上AD治疗药物只是缓解和改善AD症状并不能完全治愈。同时, 现有AD药物研发多数以单一靶点为治疗导向。虽然单一靶点在AD药物治疗中起着一定作用, 但并不代表该靶点是导致AD发病的决定性靶点, 因此, 导致药物治疗进入临床期检验时不能达到预期目标。联合生物化学、分子生物学、动物行为学、基因遗传学等多种领域共同研发同一“多靶点”药物, 依靠减轻炎症、修复AS生理功能或提高毒性蛋白清除率, 可能是未来预防和治疗AD等神经退行性疾病的潜在方向。例如, 在AD发病潜伏期或早期阶段, 使用受体激动剂或炎症因子拮抗剂, 抑制AS介导炎症反应或阻止AS向神经毒性A1型转化。利用营养因子激活剂提升A2型AS分泌神经营养物质, 提高NSC增殖分化功能, 进而保证正常神经元、胶质细胞来源不受抑制, 有效地改善AD病理环境中细胞间的负面作用, 最终阻止或逆转AD发生。另外, 还可研发先导小分子抗炎药物, 促使活化的胶质细胞向A2或M2型胶质细胞转变, 增强清除或降解毒性蛋白、炎症因子的能力。还可采用干细胞移植治疗法修复AS, 获得功能正常的AS, 避免激活型AS增多而形成胶质瘢痕的症状。

综上所述, 总结AS在AD发病进程中与其他脑细胞间的作用关系, 将有助于更好地从细胞层面了解AD的发病机制。最终, 探究通过AS调节其他脑细胞功能, 进而阻止或逆转AD可行性。从AS角度探索研究AD的发病机制, 可为了解AD提供新思路和开发有针对性的新药物。

目前, 在动物模型中进行不同水平的研究表明, AS在AD的发病过程中发挥着重要的作用。但是AS在AD中发挥的作用近几年才逐渐引起重视, 因而以

AS为靶点诊断和治疗AD的方法还处于探索阶段。AS通过多种途径维护和防御大脑神经系统网络, 其在AD发病机制中错综复杂的作用尚未完全阐明, 因此以AS为靶点的药物极其匮乏。另外, 由于动物模型与人类脑组织中的神经细胞在基因组成、细胞形态及作用等方面依旧存在较大差异性, 以及人类神经系统在发育过程中形成了更加复杂神经网络结构, 因而, 从动物研究转化到人体应用还有很长路要走。随着研究深入, AS在AD发病机制中的重要作用使其有希望成为AD新的治疗靶点。

参考文献 (References)

[1] ANGELOVA P R, ABRAMOV A Y. Interaction of neurons and astrocytes underlies the mechanism of Abeta-induced neurotoxicity [J]. Biochem Soc Trans, 2014, 42(5): 1286-90.

[2] SHANKAR G M, LI S, MEHTA T H, et al. Amyloid-beta protein dimers isolated directly from Alzheimer's brains impair synaptic plasticity and memory [J]. Nat Med, 2008, 14(8): 837-42.

[3] LI H L, WANG H H, LIU S J, et al. Phosphorylation of tau antagonizes apoptosis by stabilizing beta-catenin, a mechanism involved in Alzheimer's neurodegeneration [J]. Proc Natl Acad Sci USA, 2007, 104(9): 3591-6.

[4] PATTERSON C. World Alzheimer report 2018-the state of the art of dementia research: new frontiers [J]. Alzheimer Dis Int, 2018: 1-48.

[5] ALZHEIMER'S A. 2016 Alzheimer's disease facts and figures [J]. Alzheimers Dement, 2016, 12(4): 459-509.

[6] ALZHEIMER'S A. Alzheimer's Association (2019) Alzheimer's disease facts and figures [J]. Alzheimers Dement, 2019, 15: 321-87.

[7] MOSSELLO E, BALLINI E. Management of patients with Alzheimer's disease: pharmacological treatment and quality of life [J]. Ther Adv Chronic Dis, 2012, 3(4): 183-93.

[8] MOREL L, CHIANG M S R, HIGASHIMORI H, et al. Molecular and functional properties of regional astrocytes in the adult brain [J]. J Neurosci, 2017, 37(36): 8706-17.

[9] CHEN Y, LIANG Z, BLANCHARD J, et al. A non-transgenic mouse model (icv-STZ mouse) of Alzheimer's disease: similarities to and differences from the transgenic model (3xTg-AD mouse) [J]. Mol Neurobiol, 2013, 47(2): 711-25.

[10] ROBEL S, SONTHEIMER H. Glia as drivers of abnormal neuronal activity [J]. Nat Neurosci, 2016, 19(1): 28-33.

[11] LIDDELOW S, BARRES B. SnapShot: astrocytes in health and disease [J]. Cell, 2015, 162(5): 1170, e1.

[12] LOPEZ-HIDALGO M, SCHUMMERS J. Cortical maps: a role for astrocytes [J]. Curr Opin Neurobiol, 2014, 24(1): 176-89.

[13] ANDERSON M A, BURDA J E, REN Y, et al. Astrocyte scar formation aids central nervous system axon regeneration [J]. Nature, 2016, 532(7598): 195-200.

[14] HALASSA M M, HAYDON P G. Integrated brain circuits: astrocytic networks modulate neuronal activity and behavior [J]. Annu Rev Physiol, 2010, 72: 335-55.

[15] SIDORYK-WEGRZYNOWICZ M, STRUZYNSKA L. Astroglial contribution to tau-dependent neurodegeneration [J]. Biochem J, 2019, 476(22): 3493-504.

[16] KOISTINAHO M, LIN S, WU X, et al. Apolipoprotein E promotes astrocyte colocalization and degradation of deposited amyloid-beta peptides [J]. Nat Med, 2004, 10(7): 719-26.

[17] ZHANG Y W, WANG Z, XIE W, et al. Acetylation enhances TET2 function in protecting against abnormal DNA methylation during oxidative stress [J]. Mol Cell, 2017, 65(2): 323-35.

[18] KIDANA K, TATEBE T, ITO K, et al. Loss of kallikrein-related peptidase 7 exacerbates amyloid pathology in Alzheimer's disease model mice [J]. EMBO Mol Med, 2018, 10(3): e8184.

[19] DOMINGUEZ-PRIETO M, VELASCO A, TABERNERO A, et al. Endocytosis and transcytosis of amyloid-beta peptides by astrocytes: a possible mechanism for amyloid-beta clearance in Alzheimer's disease [J]. J Alzheimers Dis, 2018, 65(4): 1109-24.

[20] CHEN Y, QIN C, HUANG J, et al. The role of astrocytes in oxidative stress of central nervous system: a mixed blessing [J]. Cell Prolif, 2020, 53(3): e12781.

[21] NAVARRETE M, PEREA G, MAGLIO L, et al. Astrocyte calcium signal and gliotransmission in human brain tissue [J]. Cereb Cortex, 2013, 23(5): 1240-6.

[22] ALVAREZ J I, KATAYAMA T, PRAT A. Glial influence on the blood brain barrier [J]. Glia, 2013, 61(12): 1939-58.

[23] OKSANEN M, HYÖTYLÄINEN I, TRONTTI K, et al. NF-E2-related factor 2 activation boosts antioxidant defenses and ameliorates inflammatory and amyloid properties in human Presenilin-1 mutated Alzheimer's disease astrocytes [J]. Glia, 2020, 68(3): 589-99.

[24] SCHMöLE A C, LUNDT R, TOPOROWSKI G, et al. Cannabinoid receptor 2-deficiency ameliorates disease symptoms in a mouse model with Alzheimer's disease-like pathology [J]. J Alzheimers Dis, 2018, 64(2): 379-92.

[25] LIMA T Z, SARDINHA L R, SAYOS J, et al. Astrocytic expression of the immunoreceptor CD300f protects hippocampal neurons from amyloid-β oligomer toxicity *in vitro* [J]. Curr Alzheimer Res, 2017, 14(7): 778-83.

[26] TAO L, ZHU Y, WANG R, et al. N-myc downstream-regulated gene 2 deficiency aggravates memory impairment in Alzheimer's disease [J]. Behav Brain Res, 2020, 379: 112384.

[27] DRESSELHAUS E, DUERR J M, VINCENT F, et al. Class I HDAC inhibition is a novel pathway for regulating astrocytic apoE secretion [J]. PLoS One, 2018, 13(3): e0194661.

[28] LUO R, SU L Y, LI G, et al. Activation of PPARA-mediated autophagy reduces Alzheimer disease-like pathology and cognitive decline in a murine model [J]. Autophagy, 2020, 16(1): 52-69.

[29] LEE H T, LEE K I, CHEN C H, et al. Genetic deletion of soluble epoxide hydrolase delays the progression of Alzheimer's disease [J]. J Neuroinflammation, 2019, 16(1): 267.

[30] RUAN C S, LIU J, YANG M, et al. Sortilin inhibits amyloid pathology by regulating non-specific degradation of APP [J]. Exp Neurol, 2018, 299(Pt A): 75-85.

[31] WANG Y, WU Z, BAI Y T, et al. Gad67 haploinsufficiency reduces amyloid pathology and rescues olfactory memory deficits in a mouse model of Alzheimer's disease [J]. Mol Neurodegener, 2017, 12(1): 73.

[32] LUO H, XIANG Y, QU X, et al. Apelin-13 suppresses neuroinflammation against cognitive deficit in a streptozotocin-induced rat model of Alzheimer's disease through activation of BDNF-TrkB

signaling pathway [J]. Front Pharmacol, 2019, 10: 395.
[33] CARLOCK C, WU J, SHIM J, et al. Interleukin33 deficiency causes tau abnormality and neurodegeneration with Alzheimer-like symptoms in aged mice [J]. Transl Psychiatry, 2017, 7(7): e1164.
[34] BURFEIND K G, MURCHISON C F, WESTAWAY S K, et al. The effects of noncoding aquaporin-4 single-nucleotide polymorphisms on cognition and functional progression of Alzheimer's disease [J]. Alzheimers Dement (NY), 2017, 3(3): 348-59.
[35] ZHOU Y, SONG W M, ANDHEY P S, et al. Human and mouse single-nucleus transcriptomics reveal TREM2-dependent and TREM2-independent cellular responses in Alzheimer's disease [J]. Nat Med, 2020, 26(1): 131-42.
[36] BYMAN E, SCHULTZ N, NETHERLANDS BRAIN B, et al. Brain alpha-amylase: a novel energy regulator important in Alzheimer disease [J]? Brain Pathol, 2018, 28(6): 920-32.
[37] LIU C C, HU J, ZHAO N, et al. Astrocytic LRP1 mediates brain Aβ clearance and impacts amyloid deposition [J]. J Neurosci, 2017, 37(15): 4023-31.
[38] REICHENBACH N, DELEKATE A, PLESCHER M, et al. Inhibition of Stat3-mediated astrogliosis ameliorates pathology in an Alzheimer's disease model [J]. EMBO Mol Med, 2019, 11(2): e9665.
[39] RODRIGUEZ J J, YEH C Y, TERZIEVA S, et al. Complex and region-specific changes in astroglial markers in the aging brain [J]. Neurobiol Aging, 2014, 35(1): 15-23.
[40] ARRANZ A M, DE STROOPER B. The role of astroglia in Alzheimer's disease: pathophysiology and clinical implications [J]. Lancet Neurol, 2019, 18(4): 406-14.
[41] BEAUQUIS J, VINUESA A, POMILIO C, et al. Neuronal and glial alterations, increased anxiety, and cognitive impairment before hippocampal amyloid deposition in PDAPP mice, model of Alzheimer's disease [J]. Hippocampus, 2014, 24(3): 257-69.
[42] KEREN-SHAUL H, SPINRAD A, WEINER A, et al. A unique microglia type associated with restricting development of Alzheimer's disease [J]. Cell, 2017, 169(7): 1276-90, e17.
[43] TYKHOMYROV AA P A, NEDZVETSKY V S. Glial fibrillary acidic protein (GFAP): on the 45th anniversary of its discovery [J]. Neurophysiolog 2016, 48: 54-71.
[44] LI J W, ZONG Y, CAO X P, et al. Microglial priming in Alzheimer's disease [J]. Ann Transl Med, 2018, 6(10): 176.
[45] ZAMANIAN J L, XU L, FOO L C, et al. Genomic analysis of reactive astrogliosis [J]. J Neurosci, 2012, 32(18): 6391-410.
[46] LIDDELOW S A, GUTTENPLAN K A, CLARKE L E, et al. Neurotoxic reactive astrocytes are induced by activated microglia [J]. Nature, 2017, 541(7638): 481-7.
[47] BHAT R, CROWE E P, BITTO A, et al. Astrocyte senescence as a component of Alzheimer's disease [J]. PLoS One, 2012, 7(9): e45069.
[48] VERKHRATSKY A, ZOREC R, PARPURA V. Stratification of astrocytes in healthy and diseased brain [J]. Brain Pathol, 2017, 27(5): 629-44.
[49] ZHAO J, O'CONNOR T, VASSAR R. The contribution of activated astrocytes to Abeta production: implications for Alzheimer's disease pathogenesis [J]. J Neuroinflammation, 2011, 8: 150.
[50] OBERSTEIN T J, SPITZER P, KLAFKI H W, et al. Astrocytes and microglia but not neurons preferentially generate N-terminally truncated Abeta peptides [J]. Neurobiol Dis, 2015, 73: 24-35.
[51] OLABARRIA M, NORISTANI H N, VERKHRATSKY A, et al. Concomitant astroglial atrophy and astrogliosis in a triple transgenic animal model of Alzheimer's disease [J]. Glia, 2010, 58(7): 831-8.
[52] HOU L, LIU Y, WANG X, et al. The effects of amyloid-beta42 oligomer on the proliferation and activation of astrocytes *in vitro* [J]. *In Vitro* Cell Dev Biol Anim, 2011, 47(8): 573-80.
[53] FROST G R, LI Y M. The role of astrocytes in amyloid production and Alzheimer's disease [J]. Open Biol, 2017, 7(12): 170228.
[54] SETOGUCHI T, KONDO T. Nuclear export of OLIG2 in neural stem cells is essential for ciliary neurotrophic factor-induced astrocyte differentiation [J]. J Cell Biol, 2004, 166(7): 963-8.
[55] CASSE F, RICHETIN K, TONI N. Astrocytes' contribution to adult neurogenesis in physiology and Alzheimer's isease [J]. Front Cell Neurosci, 2018, 12: 432.
[56] HARA M, KOBAYAKAWA K, OHKAWA Y, et al. Interaction of reactive astrocytes with type I collagen induces astrocytic scar formation through the integrin-N-cadherin pathway after spinal cord injury [J]. Nat Med, 2017, 23(7): 818-28.
[57] LEE H J, LEE J K, LEE H, et al. Human umbilical cord blood-derived mesenchymal stem cells improve neuropathology and cognitive impairment in an Alzheimer's disease mouse model through modulation of neuroinflammation [J]. Neurobiol Aging, 2012, 33(3): 588-602.
[58] MANTLE J L, LEE K H. A differentiating neural stem cell-derived astrocytic population mitigates the inflammatory effects of TNF-alpha and IL-6 in an iPSC-based blood-brain barrier model [J]. Neurobiol Dis, 2018, 119: 113-20.
[59] SONG H, STEVENS C F, GAGE F H. Astroglia induce neurogenesis from adult neural stem cells [J]. Nature, 2002, 417(6884): 39-44.
[60] SMIT A B, SYED N I, SCHAAP D, et al. A glia-derived acetylcholine-binding protein that modulates synaptic transmission [J]. Nature, 2001, 411(6835): 261-8.
[61] OLIET S H, PIET R, POULAIN D A. Control of glutamate clearance and synaptic efficacy by glial coverage of neurons [J]. Science, 2001, 292(5518): 923-6.
[62] HAYDON P G. GLIA: listening and talking to the synapse [J]. Nat Rev Neurosci, 2001, 2(3): 185-93.
[63] LIDDELOW S A, BARRES B A. Reactive astrocytes: production, function, and therapeutic potential [J]. Immunity, 2017, 46(6): 957-67.
[64] HINKLE J T, DAWSON V L, DAWSON T M. The A1 astrocyte paradigm: new avenues for pharmacological intervention in neurodegeneration [J]. Mov Disord, 2019, 34(7): 959-69.
[65] HUANG S, TONG H, LEI M, et al. Astrocytic glutamatergic transporters are involved in Abeta-induced synaptic dysfunction [J]. Brain Res, 2018, 1678: 129-37.
[66] PARRI H R, GOULD T M, CRUNELLI V. Spontaneous astrocytic Ca^{2+} oscillations in situ drive NMDAR-mediated neuronal excitation [J]. Nat Neurosci, 2001, 4(8): 803-12.
[67] MORONI R F, INVERARDI F, REGONDI M C, et al. Developmental expression of Kir4.1 in astrocytes and oligodendrocytes of rat somatosensory cortex and hippocampus [J]. Int J Dev Neurosci, 2015, 47(Pt B): 198-205.
[68] PALOTAS A, KALMAN J, PALOTAS M, et al. Fibroblasts and lymphocytes from Alzheimer patients are resistant to beta-amyloid-induced increase in the intracellular calcium concentration [J].

Prog Neuropsychopharmacol Biol Psychiatry, 2002, 26(5): 971-4.

[69] MARIOTTI L, LOSI G, SESSOLO M, et al. The inhibitory neurotransmitter GABA evokes long-lasting Ca^{2+} oscillations in cortical astrocytes [J]. Glia, 2016, 64(3): 363-73.

[70] SERRANO A, HADDJERI N, LACAILLE J C, et al. GABAergic network activation of glial cells underlies hippocampal heterosynaptic depression [J]. J Neurosci, 2006, 26(20): 5370-82.

[71] COVELO A, ARAQUE A. Neuronal activity determines distinct gliotransmitter release from a single astrocyte [J]. Elife, 2018, 7: e32237.

[72] PEREA G, GÓMEZ R, MEDEROS S, et al. Activity-dependent switch of GABAergic inhibition into glutamatergic excitation in astrocyte-neuron networks [J]. Elife, 2016, 5: e20362.

[73] CHIH C P, ROBERTS E L, J R. Energy substrates for neurons during neural activity: a critical review of the astrocyte-neuron lactate shuttle hypothesis [J]. J Cereb Blood Flow Metab, 2003, 23(11): 1263-81.

[74] 罗程, 夏贞焰, 赵永华. 脑内神经元–星形胶质细胞能量代谢偶联研究进展[J]. 重庆医学(LUO C, XIA Z Y, ZHAO Y H. Research progress of energy metabolism coupling of neuron-AS in brain [J]. Chongqing Medicine), 2018, 47(9): 1244-7.

[75] KIM W G, MOHNEY R P, WILSON B, et al. Regional difference in susceptibility to lipopolysaccharide-induced neurotoxicity in the rat brain: role of microglia [J]. J Neurosci, 2000, 20(16): 6309-16.

[76] SALTER M W, BEGGS S. Sublime microglia: expanding roles for the guardians of the CNS [J]. Cell, 2014, 158(1): 15-24.

[77] SICA A, SCHIOPPA T, MANTOVANI A, et al. Tumour-associated macrophages are a distinct M2 polarised population promoting tumour progression: potential targets of anti-cancer therapy [J]. Eur J Cancer, 2006, 42(6): 717-27.

[78] MICHELL-ROBINSON M A, TOUIL H, HEALY L M, et al. Roles of microglia in brain development, tissue maintenance and repair [J]. Brain, 2015, 138(Pt 5): 1138-59.

[79] WALKER D G, LUE L F. Immune phenotypes of microglia in human neurodegenerative disease: challenges to detecting microglial polarization in human brains [J]. Alzheimers Res Ther, 2015, 7(1): 56.

[80] JIANG T, YU J T, TAN L. Novel disease-modifying therapies for Alzheimer's disease [J]. J Alzheimers Dis, 2012, 31(3): 475-92.

[81] 邓之婧, 郭哲, 庞逸敏, 等. 小鼠脑缺血后星形胶质细胞和小胶质细胞的活化规律比较[J]. 中华老年心脑血管病杂志(DENG Z J, GUO Z, PANG Y M, et al. Activating rules of astrocytes and microglias in mice after cerebral ischemia [J]. Chinese Journal of Geriatric Heart Brain and Vessel Diseases), 2016, 18(1): 77-80.

[82] LUO X G, CHEN S D. The changing phenotype of microglia from homeostasis to disease [J]. Transl Neurodegener, 2012, 1(1): 9.

[83] CHEN Z, JALABI W, HU W, et al. Microglial displacement of inhibitory synapses provides neuroprotection in the adult brain [J]. Nat Commun, 2014, 5: 4486.

[84] MIN K J, YANG M S, KIM S U, et al. Astrocytes induce hemeoxygenase-1 expression in microglia: a feasible mechanism for preventing excessive brain inflammation [J]. J Neurosci, 2006, 26(6): 1880-7.

[85] LIDDELOW S A, GUTTENPLAN K A, CLARKE L E, et al. Neurotoxic reactive astrocytes are induced by activated microglia [J]. Nature, 2017, 541(7638): 481-7.

[86] KAUR D, SHARMA V, DESHMUKH R. Activation of microglia and astrocytes: a roadway to neuroinflammation and Alzheimer's disease [J]. Inflammopharmacology, 2019, 27(4): 663-77.

[87] YUN S P, KAM T I, PANICKER N, et al. Block of A1 astrocyte conversion by microglia is neuroprotective in models of Parkinson's disease [J]. Nat Med, 2018, 24(7): 931-8.

[88] XU X, ZHANG A, ZHU Y, et al. MFG-E8 reverses microglial-induced neurotoxic astrocyte (A1) via NF-κB and PI3K-Akt pathways [J]. J Cell Physiol, 2018, 234(1): 904-14.

[89] VERDERIO C, MATTEOLI M. ATP mediates calcium signaling between astrocytes and microglial cells: modulation by IFN-gamma [J]. J Immunol, 2001, 166(10): 6383-91.

[90] LIAN H, YANG L, COLE A, et al. NFkappaB-activated astroglial release of complement C3 compromises neuronal morphology and function associated with Alzheimer's disease [J]. Neuron, 2015, 85(1): 101-15.

[91] HE M, DONG H, HUANG Y, et al. Astrocyte-derived CCL2 is associated with M1 activation and recruitment of cultured microglial cells [J]. Cell Physiol Biochem, 2016, 38(3): 859-70.

[92] NORDEN D M, FENN A M, DUGAN A, et al. TGFbeta produced by IL-10 redirected astrocytes attenuates microglial activation [J]. Glia, 2014, 62(6): 881-95.

[93] 张臻, 陈文利. 少突胶质细胞在神经退行性疾病中的研究进展[J]. 云南大学学报(自然科学版)(ZHANG Z, CHEN W L. Research progress of oligodendrocytes in neurodegenerative diseases [J]. Journal of Yunnan University)(Natural Sciences Edition), 2019, 41(2): 404-10. .

[94] BERTO S, MENDIZABAL I, USUI N, et al. Accelerated evolution of oligodendrocytes in the human brain [J]. Proc Natl Acad Sci USA, 2019, 116 (48): 24334-42.

[95] CHAMBERLAIN K A, NANESCU S E, PSACHOULIA K, et al. Oligodendrocyte regeneration: its significance in myelin replacement and neuroprotection in multiple sclerosis [J]. Neuropharmacology, 2016, 110(Pt B): 633-43.

[96] NAVE K A, WERNER H B. Myelination of the nervous system: mechanisms and functions [J]. Annu Rev Cell Dev Biol, 2014, 30: 503-33.

[97] MEKHAIL M, ALMAZAN G, TABRIZIAN M. Oligodendrocyte-protection and remyelination post-spinal cord injuries: a review [J]. Prog Neurobiol, 2012, 96(3): 322-39.

[98] XU J, CHEN S, KU G, et al. Amyloid beta peptide-induced cerebral endothelial cell death involves mitochondrial dysfunction and caspase activation [J]. J Cereb Blood Flow Metab, 2001, 21(6): 702-10.

[99] HORIUCHI M, MAEZAWA I, ITOH A, et al. Amyloid beta1-42 oligomer inhibits myelin sheet formation *in vitro* [J]. Neurobiol Aging, 2012, 33(3): 499-509.

[100] ZENG C, LEE J T, CHEN H, et al. Amyloid-b peptide enhances tumor necrosis factor-a-induced iNOS through neutral sphingomyelinase/ceramide pathway in oligodendrocytes [J]. J Neurochem, 2005, 94: 703-12.

[101] DESAI M K, MASTRANGELO M A, RYAN D A, et al. Early oligodendrocyte/myelin pathology in Alzheimer's disease mice constitutes a novel therapeutic target [J]. Am J Pathol, 2010, 177(3): 1422-35.

[102] FALCAO A M, VAN BRUGGEN D, MARQUES S, et al. Disease-specific oligodendrocyte lineage cells arise in multiple sclerosis [J]. Nat Med 2018, 24(12): 1837-44.