星形胶质细胞的反应性及其在代表性神经疾病中的作用

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摘要 星形胶质细胞是中枢神经系统中最为丰富的神经胶质细胞, 其在中枢神经系统的发育、稳态和损伤修复过程中起着重要作用。当中枢神经系统遭受疾病或创伤时, 损伤部位星形胶质细胞的形态和分子特征会发生改变, 转化为反应性星形胶质细胞。反应性星形胶质细胞具有异质性, 其中最具有代表性的是具有神经毒性的A1亚型和具有神经保护性的A2亚型。该文系统地总结了星形胶质细胞的基本功能和反应性星形胶质细胞的异质性, 并详细阐述了反应性星形胶质细胞在脑卒中、阿尔茨海默病、帕金森病、抑郁症等中枢神经系统疾病中的作用, 旨在为研发利用星型胶质细胞治疗神经系统疾病的新策略提供理论基础。

关键词 星形胶质的功能; 星形胶质细胞异质性; 反应性星形胶质细胞; 神经系统疾病

The Reactivity of Astrocytes and Its Role in Representative Neurological Diseases

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Abstract Astrocytes are the most abundant glial cells in the central nervous system, and they play important roles in the development, homeostasis and damage repair of the central nervous system. When the central nervous system suffers disease or trauma, the morphological and molecular characteristics of astrocytes at the site of injury are altered and transformed into reactive astrocytes. Reactive astrocytes are heterogeneous, with the most representative being the overview of the basic functions of astrocytes and the heterogeneity of reactive astrocytes, and delves into the role of reactive astrocytes in central nervous system diseases such as stroke, Alzheimer's disease, Parkinson's disease, and depression. This review aims to provide a theoretical basis for the development of new strategies for the treatment of neurological diseases using astrocytes.

Keywords astrocyte function; astrocyte heterogeneity; reactive astrocytes; neurological diseases

随着全球人口数量的增长和老龄化进程的加剧, 中枢神经系统疾病已成为世界范围内主要的死亡和致残因素。在过去30年里, 因中枢神经系统疾病而死亡的人数增加了39%, 残疾人数增加了15%, 这给人们的日常生活和社会医疗负担带来了巨大挑战[1]。近年来各国虽然对中枢神经系统疾病的治疗和预后康复的相关药物研发投入了大量资源和努力, 但收效甚微, 如目前用于治疗阿尔茨海默病

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(Alzheimer's disease, AD)的药物并不能阻止疾病的进程, 只能暂时改善临床症状[2]。因此, 从其他方面研究发病机理和寻找药物开发靶点将是非常必要的。星形胶质细胞是中枢神经系统内的主要胶质细胞类型。在以往的研究中, 星形胶质细胞主要被认为可起到支撑和营养的作用, 但随着研究的深入, 越来越多的功能被揭示出来。在某些刺激下星形胶质细胞会发生活化。几乎所有的中枢神经系统疾病发病过程中都伴随着星形胶质细胞的活化。最新的研究认为星形胶质细胞的活化并非只是中枢神经系统病变的结果, 还可能是中枢神经系统病变的原因[3]。因此, 了解星形胶质细胞的基本功能、反应特性及其在中枢神经系统疾病中的作用, 将为研发利用星型胶质细胞治疗神经系统疾病的新策略提供理论基础。

1 星形胶质细胞的基本功能

中枢神经系统主要由两类细胞组成: 神经元和胶质细胞。小鼠大脑中神经元约占大脑细胞总数的65%[4], 而在人类大脑中, 胶质细胞和神经元的比例约为1:1[5-6]。最近的研究表明, 胶质细胞和神经元的比例随物种等级的升高而逐渐增加[3]。这也反映出了胶质细胞的重要性。大脑内的胶质细胞主要包括小胶质细胞、寡突胶质细胞和星形胶质细胞。小胶质细胞是大脑内的免疫细胞[7]。寡突胶质细胞的树突末端包裹神经元的轴突形成髓鞘结构[8]。星形胶质细胞以往被认为仅仅是对神经元有支持作用的填充细胞。然而, 现在对星形胶质细胞的功能, 包括离子稳态的维持和神经递质的循环、血脑屏障的维持和调节、神经元的突触发生调节等基本功能已有更广泛的研究。除此以外, 星形胶质细胞在受到环境刺激之后还会发生结构和功能的转换, 进一步释放营养因子、传导免疫信号并参与到神经系统的损伤修复过程中。

正常生理状况下, 除营养和支持之外, 星形胶质细胞在血脑屏障的调节和维持, 突触的形成、消融和神经递质循环中也具有重要作用。血脑屏障是中枢神经系统内独特的微血管结构, 由星形胶质细胞包裹大脑内的微血管形成。血脑屏障能够严格调节分子、离子和细胞在血液和大脑组织之间的转移, 从而保护大脑免受病原体、毒素等的伤害[9]。星形胶质细胞在血脑屏障的功能维持中起着关键作用。研究表明, 星形胶质细胞能够通过多种途径调节血脑屏障, 例如, 星形胶质细胞释放的前列腺素E2(prostaglandin E2, PGE2)调节血管舒张[10], 也能够在谷氨酸(Glutamic acid, Glu)的刺激下释放花生四烯酸(arachidonic acid)。花生四烯酸可被细胞色素P-450(cytochrome P-450, CYP450)转化为血管扩张剂环氧二碳三烯酸(epoxyeicosatrienoic acid, EETs)[11]; 同时释放的花生四烯酸也会被脑血管平滑肌细胞内CYP450的亚型细胞色素P4A(cytochrome P-4A, CYP4A)合成为血管收缩物质20羟基二十碳四烯酸(20-hydroxyeicosatetraenoic acid, 20-HETE)[12]调节血管的舒张和收缩。此外, 星形胶质细胞也能够通过胞内内质网释放Ca^{2+}调节血管的舒张或收缩, 如低浓度的Ca^{2+}能够引起血管的舒张, 高浓的Ca^{2+}则会引起血管的收缩。研究发现, 提高星形胶质细胞端足结构处的Ca^{2+}浓度能够激活其自身的大电导钙激活钾通道(large conductance calcium activated potassium channels, BKCa), 导致K^+释放到血管周围空间, 引起血管平滑肌的过度极化, 从而引起血管扩张[12]。除了上述机制外, 星形胶质细胞也通过音猬因子(sonic hedgehog, shh)、血管生成素(angiopoetins)、血管紧缩素(angiopoetins)、载脂蛋白E(apolipoprotein E, ApoE)等来调节血脑屏障的功能[13]。因此, 星形胶质细胞能够通过整合自身和微环境中的相关成分积极参与调控和维持血脑屏障的功能。

突触是神经元之间的特殊结构, 在神经元间传递信息。早期对突触的认识仅仅局限于神经元到神经元。后来研究发现, 突触不仅存在于神经元之间, 还存在于神经元和星形胶质细胞之间。这种同时存在于两个神经元和一个星形胶质细胞之间的结构被称为三方突触[14]。三方突触中的星形胶质细胞在突触的形成、消融及神经递质循环中起着重要作用。星形胶质细胞的多种分泌因子在三方突触中发挥着重要作用, 如血栓反应蛋白(thrombospondin, TSP)(包括thrombospondin 1、thrombospondin 2)和hevin(SPARC-like protein 1)能够诱导突触结构的成熟[15]; 胆固醇能够增强突触前膜的功能[16]; 肿瘤坏死因子-α(tumor necrosis factor-α, TNF-α)和Glypican4&6能够通过招募AMPA受体(alpha-amino-3-hyroxy-5-methyl-4-isoxazolepropionicacid receptors, AMPARs)提高突触后膜AMPA受体密度, 进而增强突触后膜的功能[17-19]; 雌二醇(estradiol)、伽玛原钙蛋白(pro-

tocadherins)、整合素(integrins)等也通过不同途径增强突触的功能或促进突触的发生[20]; 富含半胱氨酸的酸性分泌糖蛋白(secreted protein acidic and rich in cysteine, SPARC)通过阻断Hevin的活性来抑制突触的形成[21]。与突触发生的调节机制相比, 目前我们对突触的消融知之甚少。最近的研究表明, 星形胶质细胞可以直接通过多重表皮生长因子样结构域蛋白10(multiple EGF like domains 10, Megf10)和Mer受体酪氨酸激酶(tyrosine-protein kinase Mer, Mertk)通路吞噬弱突触, 以及通过分泌转化生长因子β(transforming growth factor-β, TGF-β)间接调节突触的消除[18-22], 从而促进中枢神经系统中正常神经回路的修剪和细化。星形胶质细胞的端足包裹突触结构使得突触在空间上成为一个相对独立的结构。这种结构更有利于突触内神经递质的回收和转运, 如突触前膜释放的神经递质Glu或γ-氨基丁酸(gamma-aminobutyric acid, GABA)进入突触间隙, 并被突触后膜的递质受体接收。在此过程中, 大量的Glu或GABA被星形胶质细胞转运吸收。约80%的Glu被星形胶质细胞膜上的兴奋性氨基酸转运蛋白1/2(excitatory amino acid transporters 1/2, EAAT1/2)转运吸收, 并被转化为谷氨酰胺, 随后被谷氨酰胺转运系统转移到神经元, 在神经元内转化为Glu或GABA, 从而维持突触外低浓度的Glu, 防止兴奋性神经毒性的发生[23]。GABA的转运主要是由位于神经元轴突末端的GABA转运蛋白1(GABA transporter 1, GAT1)和位于星形胶质细胞膜上的GAT1/3完成的[24-26], 转运进入神经元的GABA储存于递质囊泡内进行循环利用[27]。转运进入星形胶质细胞内的GABA被GABA转氨酶(GABA transaminase, GABA-T)和琥珀酸半醛脱氢酶(succinate semialdehyde dehydrogenase, SSADH)分解代谢为琥珀酸, 琥珀酸进入三羧酸循环(tricarboxylic acid cycle, TCA)进行氧化代谢[28]。综上所述, 星形胶质细胞通过分泌大量的因子调节突触的发生、维持和修剪, 并且参与突触信息的传递, 这对于机体的正常认知和学习具有重大意义(图1)。

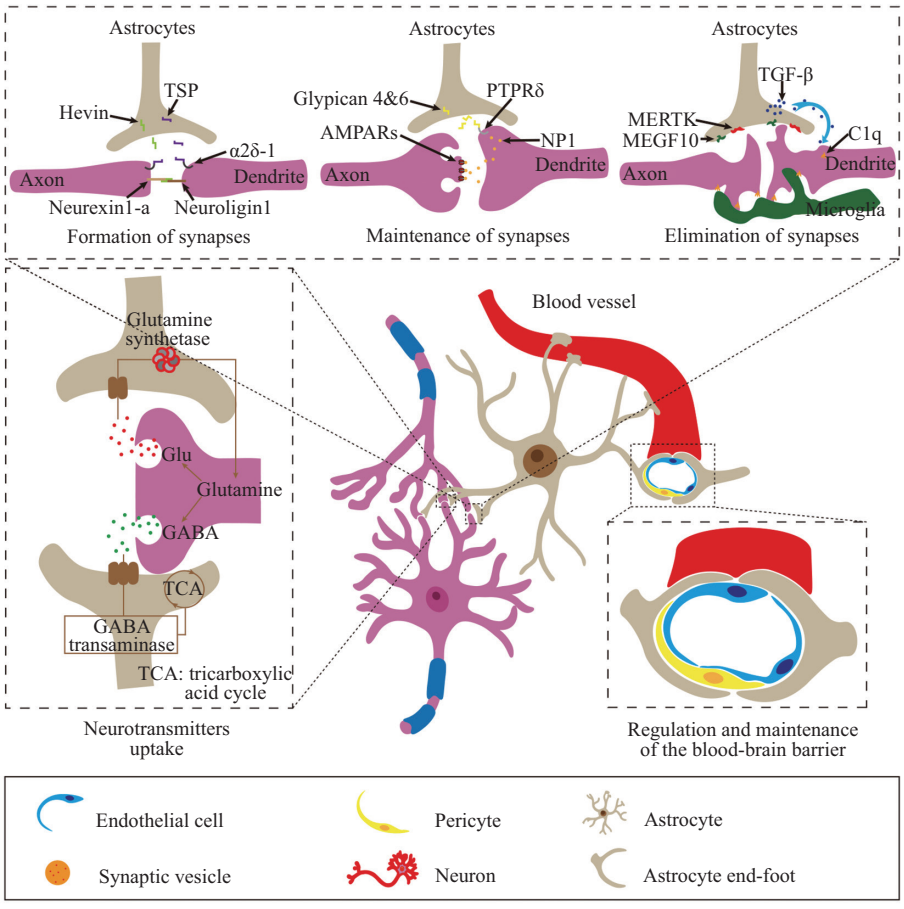

图1 星形胶质细胞的多种功能

Fig.1 The multiple functions of astrocytes

2 星形胶质细胞的反应特性和异质性

2.1 星形胶质细胞的反应特性

星形胶质细胞对中枢神经系统疾病和损伤的反应被称为星形胶质细胞的反应性。20世纪70年代, 科学家们从部分星形胶质细胞中发现了胶质纤维酸性蛋白(glial fibrillary acidic protein, GFAP)并首次提出了反应性星形胶质细胞的概念。反应性星形胶质细胞通常会发生结构和功能的改变, 包括细胞肥大、增殖增强、炎症介质和神经营养因子的分泌, 以及中间丝表达的增加, 如GFAP和波形蛋白(vimentin)[29]。反应性星形胶质细胞具有很强的增殖能力, 被称为星形胶质细胞增生。反应性星形胶质细胞增生和疤痕形成是中枢神经系统损伤的突出特征, 在刺伤或严重挫伤中星形胶质细胞的反应特征随距离损伤中心区域的位置不同而不同, 在损伤中心区域星形胶质细胞大量增殖, 新增殖的星形胶质细胞呈细长形并聚集在损伤组织的边缘形成致密的疤痕, 从而划定强烈炎症的范围, 限定炎症细胞和感染因子扩散到附近的健康组织中, 而消融和减弱由反应性星形胶质细胞形成的疤痕都会加剧炎症细胞的扩散, 加重疾病的进程[30-31]。因此, 在脑和脊髓损伤后, 星形胶质细胞形成的疤痕发挥了重要的神经保护功能[31-33]。随着距离损伤中心区域越来越远, 反应性星形胶质细胞的增殖能力和细胞密度逐渐降低, 星形胶质细胞形态由细长转变为肥大, *GFAP*等基因的表达升高[34]。这些肥厚的反应性星形胶质细胞与损伤周围区域突触的重塑、神经回路调节、降低炎症反应等过程有关[35]。在炎症、感染和损伤状态下, 星形胶质细胞会呈现不同的反应特性, 并发挥不同的作用, 但其相关的分子机制仍不清楚, 需要进一步深入研究。

2.2 反应性星形胶质细胞的异质性

众多研究表明, 星形胶质细胞的反应性并不仅仅是一个全或无的应答现象, 而是一种精细分级的连续变化。反应性的星形胶质细胞在细胞形态、位置分布、基因表达等多个水平上表现出极大的异质性。胞体和主要突起的肥大化是星形胶质细胞反应性的典型特征。但这种胞体的肥大并不是一致的, 它们的肥大程度呈现出异质性和高度可变, 并且这种异质性与距离损伤区域的远近密切相关。如在机械损伤等疾病形成的胶质疤痕中, 在损伤中心区域, 重度反应性星形胶质细胞形态呈现细长并相互交织重叠, 但中心区域周围的轻中度反应性星形胶质细胞则呈现胞体肥大并基本上不重叠[36-37]。因此, 在损伤区域不同位置的反应性星形胶质细胞在细胞形态上存在明显差异。

另外, 不同类型的中枢神经系统损伤刺激会引起反应性星形胶质细胞中基因表达的不同。例如, GFAP在大部分星形胶质细胞中表达; 脂质运载蛋白2(lipocalin-2, Lcn2)和serpina3n仅在反应性星形胶质细胞中强烈表达, 并被作为反应性星形胶质细胞的标志物; 而正五聚蛋白(pentraxin 3, Ptx3)、鞘氨醇-1-磷酸受体3(sphingosine-1-phosphate receptor 3, S1pr3)、tweak受体Tnfrsf12a在大脑中动脉栓塞(middle cerebral artery occlusion, MCAO)诱导的反应性星形胶质细胞中特异性高表达; H2-D1、serpin家族G成员1(serpin family G member 1, Serping1)在脂多糖(lipopolysaccharide, LPS)诱导的星形胶质细胞亚型中特异性高表达[38]。

2.3 反应性星形胶质细胞的两大类型(A1型和A2型)

根据产生条件和基因表达的不同, LIDDELOW等[39]参照小胶质细胞的命名方法将LPS诱导的与神经毒性有关的反应性星形胶质细胞命名为A1型, 将缺血诱导的与神经保护有关的反应性星形胶质细胞命名为A2型。A1型反应性星形胶质细胞主要由炎症刺激诱导分化而来。在神经炎症中, 活化的小胶质细胞通过产生TNF-α、白介素-1α(interleukin-1α, IL-1α)、补体成分1q(complement, C1q)诱导星形胶质细胞极化为A1表型。在基因表达方面, A1型反应性星形胶质细胞的许多免疫和炎症相关基因上调, 如: 组织相容性2(histocompatibility 2, *H-2*)、补体C3(complement C3, *C3*)、D区位点1(D region locus 1)、*Serping1*等[40]。C3被大多数研究者用来鉴定A1表型。在功能方面, A1型反应性星形胶质细胞失去了许多正常星形胶质细胞的功能, 包括: 促进神经元存活和生长、突触的形成和吞噬等。A1型反应性星形胶质细胞通过释放某种神经毒性介质诱导多种神经元及成熟分化的寡突胶质细胞凋亡[39]。此外, A1型反应性星形胶质细胞能释放多种经典补体级联成分(如: C3), 诱导突触数量减少和介导突触消除[41]。如视网膜神经节细胞(retinal ganglion cells, RGCs)与A1型星形胶质细胞共培养后产生的突触数量比与非反应性星形胶质细胞共培养时减少了50%, 且突触的功能较弱[39]。与A1型反应性星形胶质细胞不同, A2型主要由缺血诱导分化而来, 具体诱导机制尚不

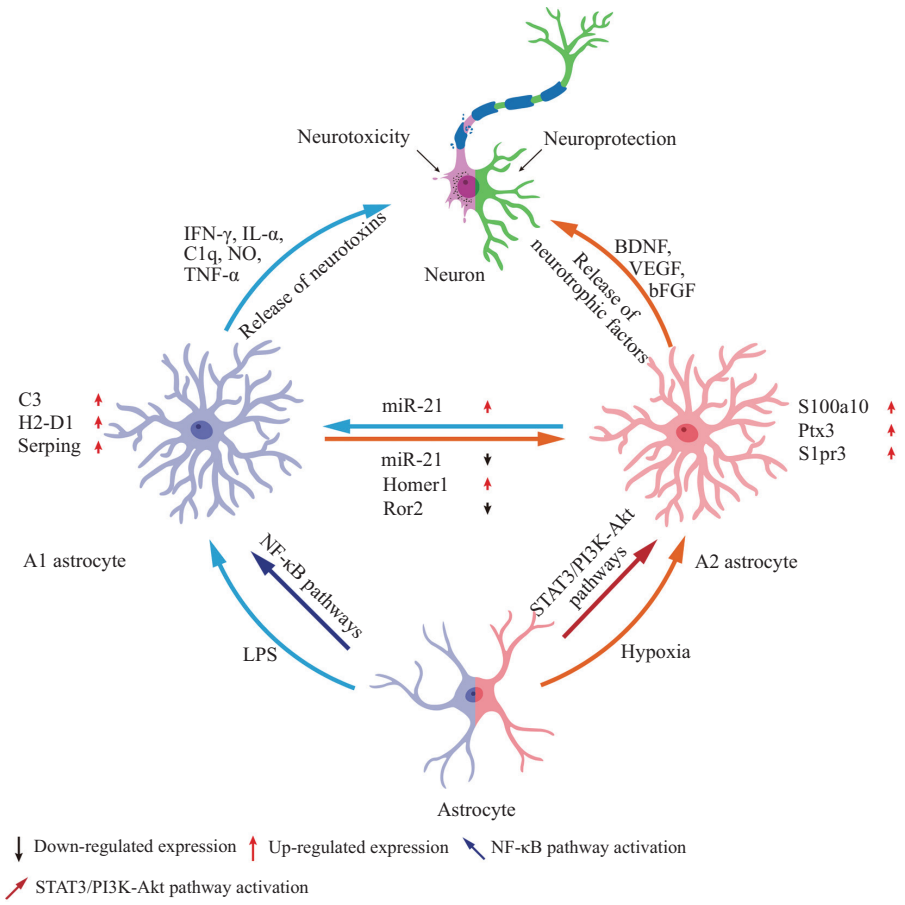

图2 反应性星形胶质细胞亚型及其特征

Fig.2 The subtypes of Reactive astrocytes and their features

清楚。在基因表达方面, A2型星形胶质细胞上调许多特征性基因, 例如: *Ptx3*、*S1pr3*、和S100钙结合蛋白A10(S100 calcium binding protein A10, *S100a10*)[40]。其中S100a10被认为是A2型星形胶质细胞的特异性标志物。在功能方面, 脑缺血时诱导而来的A2型反应性星形胶质细胞的吞噬作用和突触重塑的能力增强, 并促进了神经元的存活和组织修复[40]。A2型反应性星形胶质细胞通过ATP结合盒转运体A1(ATP-binding cassette transporter A1, ABCA1)介导的途径在脑缺血后发挥吞噬作用。这种吞噬作用与小胶质细胞的吞噬存在时空差异, 即小胶质细胞的吞噬作用在缺血核心内发生较早, 而A2星形胶质细胞的吞噬作用在缺血半暗区发生较晚, 这种时空差异可能有助于缺血半暗区脑微环境的重塑和恢复[42]。A2也可以通过STAT3-GPC6和STAT3-GNDF通路促进突触的形成和生长[40]。此外, A2可以通过上调多种神经营养因子及相关调控因子促进神经元的保护和组织修复。A2的主要调节因子可能包括信号转导和转录激活因子3(signal transducers and activators of transcription 3, STAT3)[43]、ras-同源家族A(Ras homolog family member A, RhoA)[44]、缺氧诱导因子(hypoxia inducible factor-1α, HIF-1α)[45-46]和促红细胞生成素(hemopoietin, EPO)[47-48]等。在某些情况下A1、A2表型能够发生转化, 如miR-21能够通过靶向STAT3来调节反应性星形胶质细胞的极化, 下调miR-21可以促进A1向A2转化, 而上调miR-21可能导致A2向A1的极化[40]。此外, 有研究表明前动力蛋白2(prokineticin-2, PK-2)能够促进星形胶质细胞向损伤部位迁移并转化为有益的A2表型[49]。综上所述, 我们推测在中枢神经系统损伤后, 抑制星形胶质细胞转化为A1表型, 或者促进星形胶质细胞转化为A2表型将对神经功能的恢复有着积极意义(图2)。

3 反应性星型胶质细胞在代表性神经疾病中的作用

3.1 反应性星型胶质细胞在脑卒中恢复过程中的作用

脑卒中是指由各种原因引起的大脑局部供血

紊乱, 包括缺血性卒中和出血性卒中, 其发病率、致残率、死亡率、复发率高, 是导致全球居民死亡和残疾的主要原因之一。在脑卒中损伤后星形胶质细胞的基因表达、形态、增殖和功能逐渐变化, 并表现出异质性, 即星形胶质细胞被激活并发挥相关作用。激活的星形胶质细胞能够通过以下途径发挥有益的作用。①通过合成和释放谷胱甘肽(glutathione, GSH)保护神经元, 减轻氧化应激的损伤[50]。②释放神经营养因子(如神经生长因子(nerve growth factor, NGF)[51]、脑源性神经营养因子(brain derived neurotrophic factor, BDNF)[52]、胶质源性神经营养因子(glial-derived neurotrophic factor, GDNF)[53-54]、睫状神经营养因子(ciliary neurotrophic factor, CNTF)[55-56]等)保护神经元的存活和促进神经再生。③通过介导卒中后不同时间点水通道蛋白4(aquaporin-4, AQP4)的活性减轻脑水肿[57]。④通过HIF-1介导脑内促红细胞生成素(erythropoietin, EPO)的上调, 从而保护神经元, 减小梗死体积[58-59]。然而, 反应性星形胶质细胞也会诱导神经元兴奋性毒性(如Glu释放)[60], 以及引起过度的炎症反应对卒中预后产生不利影响。以往的研究认为, 反应性星形胶质细胞的增生和胶质疤痕的形成抑制了卒中后的轴突再生和神经修复[61], 但WILLIAMSON等[62]发现反应性星形胶质细胞能够促进卒中后的血管修复和行为恢复, 这可能与星形胶质细胞的异质性有关。因此, 进一步深入研究脑卒中后星形胶质细胞的作用机制, 减少反应性星形胶质细胞对神经系统的不利影响, 同时加强其神经保护作用, 可能为卒中后的治疗提供新的方案。

3.2 反应性星型胶质细胞在AD进程中的作用

AD是一种进行性的神经退行性疾病, 也是老年人中最突出的认知障碍。AD的临床表现为渐进性的认知功能障碍, 包括: 记忆丧失、意识混乱和行为改变, 其原因是β淀粉样蛋白(β-amyloid protein, Aβ)的积累和异常磷酸化蛋白的聚集。AD以大脑内存在细胞外淀粉样斑块(amyloid plaques, APs)和细胞内神经纤维缠结(neurofibrillary tangles, NFTs)为标志。APs由聚集的Aβ组成, 而NFTs由细胞内tau蛋白的异常磷酸化和聚集组成。以往的研究表明, 反应性星形胶质细胞围绕着APs和携带NFTs的神经元[63], 并发挥相关功能。星形胶质细胞能够通过产生脑啡肽酶(neprilysin)、胰岛素降解酶(insulin degrading enzyme)、内皮转化酶(endothelin-converting enzymes)等蛋白酶切割水解Aβ, 也可通过其表达的载脂蛋白(apolipoproteins)、AQP4、α2巨球蛋白(α2 macroglobulin)和α1抗凝乳胰蛋白酶(α1-antichymotrypsin)促进Aβ进入血液循环从而清除Aβ[64]。Aβ斑块周围的星形胶质细胞上调了连接蛋白30(connexins 30, Cx30)和连接蛋白43(connexins 43, Cx43)的表达, Aβ诱导的炎症或细胞内钙浓度增加的情况可触发Cx43连接蛋白半通道(hemichannels, HCs)的打开, 造成星形胶质细胞内ATP和Glu的释放[65]。过量的ATP释放可通过刺激小胶质细胞分泌IL-1β介导神经毒性效应[66]或通过分泌IL-6产生神经保护作用[67], 而Glu的释放可通过激活突触外*N*-甲基-*D*-天冬氨酸(*N*-methyl-*D*-aspartic acid, NMDA)受体导致突触丢失[68]。同时, 过量的Glu会造成神经元兴奋性毒性, 导致神经元的死亡。有研究表明, 淀粉样斑块周围的反应性星形胶质细胞产生更多的腐胺。星形胶质细胞通过单胺氧化酶B(monoamine oxidase B, MAOB)将腐胺转化为抑制性GABA, 并通过Best1(bestrophin 1)通道异常释放, 而导致AD动物模型的突触可塑性减弱, 学习和记忆受损。值得注意的是, 抑制合成GABA或阻断GABA转运蛋白可恢复这些小鼠的相关表型[69]。但GABA的释放也能够保护神经元免受由于Glu异常释放引起的过度兴奋。因此, 星形胶质细胞的反应性在AD病程中具有两面性, 如何发挥其有益作用, 抑制其有害作用, 是未来AD治疗中所需要关注的问题。

3.3 反应性星型胶质细胞在PD进程中的作用

帕金森病(Parkinson's disease, PD)是第二大神经退行性疾病, 在人口老龄化进程中其发病率持续升高。PD的临床表现通常为静止性震颤、强直、运动迟缓和姿势不稳[70]。病理特征是神经元细胞内含有α-突触核蛋白(α-synuclein, α-SYN)的包涵体的积累、黑质致密部多巴胺神经元的丢失和神经炎症[71-72]。在对PD病人死亡样本的研究中发现, 在黑质致密部中的星形胶质细胞的数量轻度增加, 并且GFAP免疫反应性也轻微增强[73]。星形胶质细胞在PD中主要通过清除病变的α-SYN减轻神经炎症、释放神经营养因子、降低氧化应激以及清除损伤的线粒体来发挥作用。α-SYN的编码基因*SNCA*的突变与α-SYN在神经元细胞内的异常聚集有关。星形胶质细胞会吞噬神经元释放到细胞外空间中的α-SYN。星形胶质细胞内过量积累的α-SYN能够诱导产生具有神经毒

性的促炎细胞因子, 如IL-1、IL-6和TNF-α, 以及一些趋化因子, 如C-X-C基序配体1(CXCL1)。同时细胞外空间积累的α-SYN也能够激活小胶质细胞。最近一项研究表明, 激活的小胶质细胞可通过分泌IL-1α、TNF-α和C1q诱导神经毒性A1星形胶质细胞的产生[74]。研究表明, 使用辛伐他汀(simvastatin)抑制星形胶质细胞转化为A1表型, 能够显著降低1-甲基-4-苯基-1,2,3,6-四氢吡啶(1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, MPTP)诱导的小鼠PD模型中多巴胺能神经元的丢失和行为缺陷[75]。同时, 激活的小胶质细胞和星形胶质细胞所启动的神经炎症也被认为是PD发病的关键。对PD动物模型给予各种抗炎药物(如地塞米松、布洛芬、金刚胺、米诺环素、垂体腺苷酸环化酶激活肽、血管活性肠肽、IL-10和TGF-β等)治疗均显示出对多巴胺能细胞死亡的预防作用[73]。星形胶质细胞氧化/亚硝化应激也在PD的发病机制中发挥重要作用。星形胶质细胞通过产生抗氧化剂GSH和超氧化物歧化酶(superoxide dismutase, SOD)合并来保护神经元免受活性氧(reactive oxygen species, ROS)和活性氮(reactive nitrogen species, RNS)的损伤[76], 也能通过PINK1依赖的Parkin通路靶向降解损伤的线粒体, 从而减少活性氧和神经炎症的产生[77]。此外, 星形胶质细胞还能释放神经营养因子, 如胶质细胞系来源的GDNF和NGF, 维持神经元存活[78]。因此, 星形胶质细胞功能的正常化和神经保护能力的上调是预防和治疗PD的有效方法。

3.4 反应性星型胶质细胞在抑郁症中的作用

抑郁症(depression)是世界范围内最广泛的精神疾病, 影响着全球约4%的人口, 表现为情绪低落、快感缺失、认知障碍、睡眠障碍等生物学症状。抑郁症的发病率随着年龄的增长而增长[79], 女性的发病率约为男性的两倍[80], 并且重度抑郁症患者常伴有自杀倾向。在临床中星形胶质细胞的特异性蛋白S100β一般被认为是抑郁症的血清生物标志物, 因为它的表达水平在抑郁症患者的血清中显著升高[81]。抑郁症患者死后的组织病理学研究显示, 额叶皮质[82]、海马[83]、蓝斑(locus coeruleus)[84]以及杏仁核[85]中星形胶质细胞的数量和基因表达水平如GFAP显著降低。抑郁症患者通常伴有神经炎症特征, 包括外周血、脑脊液和脑结构中促炎细胞因子水平升高, 以及小胶质细胞和星形胶质细胞的激活[86]。以往的研究表明, 在抑郁症模型中, 通过抑制A1反应性星形胶质细胞的激活能够改善小鼠的抑郁样行为和认知功能[87]。在对选择性血清素受体抑制剂(selective serotonin reuptake inhibitors, SSRIs)氟西汀(fluoxetine)的抗抑郁机制研究表明, 氟西汀不仅通过阻断5-羟色胺的再摄取发挥抗抑郁作用, 同时还可以抑制A1反应性星形胶质细胞的激活[86], 促进自噬小体的形成, 清除受损的线粒体, 减少星形胶质细胞的死亡[88], 从而改善小鼠模型的抑郁样表型。因此, 对星形胶质细胞与抑郁症相关性的研究有望为抗抑郁药物的开发提供一些有潜力的分子靶点。

综上所述, 星形胶质细胞密切参与调节中枢神经系统疾病的病理过程并表现出双重作用: 一方面, 星形胶质细胞通过释放神经营养因子、减轻氧化应激、清除异常聚集物等去保护神经细胞, 减缓疾病进程; 另一方面, 在疾病的诱导下, 星形胶质细胞也会丧失正常的稳态功能并释放炎性因子产生毒性作用, 加剧中枢神经系统疾病的进程。在不同的神经疾病进程和微环境条件下, 星形胶质细胞的反应性也会发生转变, 产生不同的效果(表1)。因此, 如何在中枢神经系统疾病中减轻星形胶质细胞的有害作用, 增强有益作用, 将是未来亟待解决的问题。

4 总结与展望

星形胶质细胞作为大脑内一类重要的胶质细胞类型, 其作用越来越受到研究者的关注。近年来, 对星形胶质细胞相关功能的研究已经取得了较大进展, 星形胶质细胞在神经系统的发育、稳态以及中枢神经系统疾病的病变过程中都发挥了重要作用。目前已有研究指出, 通过干预星形胶质细胞的极化能够减缓中枢神经系统疾病的进程、改善临床症状。然而, 目前的研究仍需要进一步探索: (1) 星形胶质细胞在中枢神经系统疾病和损伤修复中的变异机制, 即如何由“好”变“坏”, 以及由“坏”变“好”; (2) 反应性星形胶质细胞的异质性在不同微环境中的复杂度和主导类型, 尤其是明确促进神经组织修复的星形胶质分子特征。相信随着空间转录组学和蛋白组学相关技术的发展, 在不同类型中枢神经系统疾病中反应性星形胶质细胞的异质性和对应的分子特征将会得到进一步的解析。许多神经疾病也可以通过阻断星形胶质细胞有害反应变异或对抗星形胶质细胞分泌的神经毒素来治疗, 因此, 发掘调节星形胶质

表1 星形胶质细胞在不同中枢神经系统疾病中的作用

Table 1 The roles of the reactive astrocytes in different neurological diseases

疾病 Diseases	有益作用 Promoting effects	有害作用 Suppressing effects
Stroke	Astrocyte protect neurons by synthesizing and releasing GSH to alleviate oxidative stress damage[57] Astrocyte derived neurotrophin protects the survival of neurons and promotes nerve regeneration[51-56,89-91] After stroke, astrocytes alleviate brain edema by mediating AQP4 activity at different time points[92-94] Astrocytes mediate the upregulation of EPO in the brain through HIF-1α, which is involved in neuroprotection and neuroinflammation, leading to reduced infarct volume[58-59] The glial scar formed by astrocyte proliferation prevents the diffusion of inflammatory factors and limits the damaged tissue area[30,95-96]	Astrocyte reduce the uptake of Glu to induce excitotoxicity of neurons[57,97] The glial scar formed by astrocyte proliferation inhibits axonal regeneration and neural repair after stroke[61] Activation of NF-κB patway in astrocytes can lead to neuronal death by inducing the production and release of inflammatory cytokines and neurotoxins[91,98-100]
Alzheimer's disease	Astrocytes have been involved in the degradation of Aβ, by secreting neprilysin, insulin degrading enzymes and endothelin-converting enzyme[64-101] Astrocytes promote the clearance of Aβ by facilitating its entry into the bloodstream through lipoproteins, AQP4, α2-macroglobulin, and α1-antichymotrypsin[64,102-103] Astrocytes prevent Aβ-induced synaptic loss by producing TGF-β1[104-105]	Astrocytes abnormally release GABA through the Best1 channel, which leads to impaired synaptic plasticity and memory ability in AD[69] NF-kB activation and complement C3 release in astrocytes impair the morphology and function of neurons in AD[106] Astrocytes promote brain inflammation and Aβ accumulation by releasing inflammatory mediators and inducing oxidative stress[107-108]
Parkinsin's disease	Astrocytes respond to oxidative stress in the early stage of PD by releasing antioxidants, thus providing neuroprotection[109] Astrocytes protect dopaminergic neurons in the early stages of PD by reducing the misfolding and aggregation of α-SYN[110-111] Astrocytes protect neurons from ROS and RNS damage by producing antioxidants GSH and SOD[76] Astrocytes target and degrade damaged mitochondria via the PINK1-dependent Parkin pathway to reduce the production of ROS and neuroinflammation[77]	The aggregation of α-SYN in astrocytes induces the production of neuroinflammation, thereby accelerating the pathological process of PD[112-113]
Depression	Lactic acid secreted by astrocytes has some effects to antidepressant[114-115]	A1 astrocytes can aggravate depression-like behavior and cognitive dysfunction[86-87,116-117]

细胞异质性和反应特征的关键因子能够为治疗脑卒中、阿尔茨海默病、帕金森病、抑郁症等中枢神经系统疾病提供新的策略和希望。

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