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中枢神经系统中的星形胶质细胞通过多种机制调控髓鞘发育和再生*

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摘要 在中枢神经系统（central nervous system，CNS）中，髓鞘是包裹轴突的重要结构，由少突胶质细胞发育而来，其主要功能是加速神经信号的转导并保护神经纤维免受损伤。髓鞘的损伤或丧失会导致神经转导异常，进而引发多发性硬化症等神经退行性疾病。因此，深入研究髓鞘的发育和再生机制不仅是揭示神经系统功能调控的重要环节，也是治疗相关疾病的关键突破口。研究表明，星形胶质细胞作为CNS中数量最丰富的胶质细胞群，通过建立动态的神经-胶质网络，在髓鞘发育与再生过程中发挥多维度的调控作用。在发育阶段，星形胶质细胞通过分泌一系列细胞因子，调控少突胶质前体细胞的增殖、分化和迁移。在病理条件下，星形胶质细胞的反应呈现双相性特征：急性期释放的白血病抑制因子（leukemia inhibitory factor，LIF）和脑源性神经营养因子（brain-derived neurotrophic factor，BDNF）起促进作用；而慢性激活状态则可能通过产生硫酸软骨素蛋白聚糖（chondroitin sulfate proteoglycans，CSPGs）形成抑制性微环境，从而阻碍髓鞘形成。本文综述了星形胶质细胞调节中枢神经系统髓鞘发育和再生的机制，重点分析了星形胶质细胞在此过程中的多层次作用，旨在为多发性硬化症等神经退行性疾病的治疗提供新的策略。

关键词 星形胶质细胞，少突胶质细胞，髓鞘发育，髓鞘再生
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髓鞘是中枢神经系统（central nervous system，CNS）中的重要结构，由少突胶质细胞（oligodendrocytes，OLs）包裹轴突形成，通过增加轴突的电绝缘性显著加速神经信号转导[1]。髓鞘的发育与再生是一个高度复杂且精密调控的过程，涉及多种调节机制。在CNS中，少突胶质前体细胞（oligodendrocyte precursor cells，OPCs）分化为成熟的OLs，并沿着轴突形成髓鞘[2-5]。这一过程受多种生长因子和信号通路的调节。当神经系统因损伤或疾病导致脱髓鞘时，OPCs在多种细胞因子作用下通过激活、迁移和分化等一系列步骤，在受损区域形成新的髓鞘，恢复神经信号的转导功能。值得注意的是，在髓鞘再生过程中，星形胶质细胞作为CNS中最丰富的胶质细胞类型，发挥着关键作用。它们不仅通过分泌细胞因子和生长因子直接调控OPCs的增殖与分化，还通过调节局部微环境，为髓鞘再生提供支持，甚至在某些情况下抑制再髓鞘化的发生。本文聚焦星形胶质细胞在髓鞘发育与再生中的作用，探讨其在支持和调控过程中的具体机制。

1 星形胶质细胞的分类及其功能

星形胶质细胞（astrocytes）是中枢神经系统中数量最为丰富的胶质细胞类型之一，约占胶质细胞总量的50%，并在脑内分布广泛，体积较大。根据其分布和形态，星形胶质细胞分为两类：原浆性星形胶质细胞（protoplasmic astrocytes）主要位于灰质中，突起短而粗，参与维持血脑屏障和调节神经

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递质浓度；纤维性星形胶质细胞（fibrous astrocytes）分布于白质中，突起细长，主要负责结构支持和维持神经元的代谢平衡[6-7]。

星形胶质细胞在中枢神经系统中具有多方面的重要功能。它们通过分泌血小板源性生长因子（platelet-derived growth factor，PDGF）和血管内皮生长因子（vascular endothelial growth factor，VEGF），调控血脑屏障的紧密连接，防止有害物质渗透；在突触可塑性中，星形胶质细胞释放三磷酸腺苷（adenosine triphosphate，ATP）和D-丝氨酸等信号分子，调控受体活性，从而影响长时程增强（long-term potentiation，LTP）和长时程抑制（long-term depression，LTD）的形成[8]。在病理状态下，星形胶质细胞通过分泌白介素（interleukin，IL）-6、肿瘤坏死因子α（tumor necrosis factor-α，TNF-α）等参与免疫反应和炎症调控。在阿尔茨海默病（Alzheimer's disease，AD）中，星形胶质细胞通过反应性增生清除β-淀粉样蛋白（amyloid β-protein，Aβ）斑块，减缓病理进程；在帕金森病（Parkinson's disease，PD）动物模型中，其分泌神经营养因子如胶质细胞源性神经营养因子（glial cell-derived neurotrophic factor，GDNF）和脑源性神经营养因子（brain-derived neurotrophic factor，BDNF），保护黑质多巴胺神经元免受退化[9]。此外，星形胶质细胞在脑内的不同区域发挥特定功能：在皮层中，它们调节血管与神经元间的能量供应；在小脑中，调节突触活动以支持精细运动控制；在基底神经节内，通过调控多巴胺代谢平衡影响运动信号传递；在视网膜中，为视神经提供营养和代谢支持[7，10-17]。

在髓鞘发育和再生方面，星形胶质细胞也起着重要作用。髓鞘形成早期，原浆性星形胶质细胞调节神经递质浓度，间接调控OPCs的增殖和迁移，纤维性星形胶质细胞则引导OPCs寻找目标轴突；髓鞘形成中期，原浆性星形胶质细胞通过释放D-丝氨酸等物质，调节突触后神经元的兴奋性，进而影响神经元与OLs之间的信号交流，为髓鞘的有序形成提供了必要的信号调控，纤维性星形胶质细胞则将葡萄糖转化为乳酸，作为能量底物参与合成髓鞘脂质和蛋白质；在髓鞘形成后期，原浆性星形胶质细胞通过调节胞外钾离子浓度维持神经元的正常兴奋性，以确保髓鞘的稳定和功能完整，而纤维性星形胶质细胞在髓鞘损伤时被激活，分泌因子促进再髓鞘化，维持髓鞘结构和功能[18-21]。

总体而言，星形胶质细胞不仅是中枢神经系统正常功能的核心调节者，还在髓鞘的发育和损伤后的再生中发挥重要作用。深入研究星形胶质细胞的作用机制，将为多发性硬化症（multiple sclerosis，MS）等脱髓鞘疾病的治疗提供新的思路和依据。

2 CNS髓鞘的发育与再生

2.1 CNS髓鞘发育

CNS中的髓鞘由OPCs分化而来。OPCs通过一系列分化和成熟过程，最终形成OLs，后者包裹神经元轴突，从而形成髓鞘，为神经信号的高效转导提供支持。在胚胎发育早期，PDGF和成纤维细胞生长因子（fibroblast growth factor，FGF）等生长因子与OPCs细胞表面受体结合，激活Ras/MAPK和PI3K/Akt信号通路[22-24]，促进细胞增殖并维持其未分化状态。同时，OPCs与神经元和星形胶质细胞的相互作用激活Notch信号通路，通过Hes和Id家族蛋白的负反馈机制调节与OLs分化相关的关键基因（*Olig2*和*Sox10*）的表达，从而抑制分化并进一步增殖，以确保有足够数量的OPCs参与后续分化和髓鞘形成[25-26]。在增殖过程中，OPCs通过延伸细胞突起在CNS内迁移，寻找未被髓鞘包裹的神经元轴突作为髓鞘化的靶点。C-X-C基序趋化因子配体（C-X-C motif chemokine ligand，CXCL）1和CXCL12在这一过程中发挥关键作用，引导OPCs迁移并准确定位。同时，胞外基质中的纤维连接蛋白和层黏连蛋白也通过提供机械支持促进细胞迁移[27]。当OPCs迁移至目标区域后，PDGF、FGF、胰岛素样生长因子1（insulin like growth factor-1，IGF-1）和CXCL12等信号分子结合细胞表面受体，进一步激活mTOR和Wnt信号通路。mTOR通过PI3K/Akt通路调控细胞代谢，促进髓鞘相关蛋白（MBP和PLP）的合成；经典Wnt信号通过激活β联蛋白（β-catenin），调控与OLs分化相关基因（*Olig2*、*Sox10*和*Nkx2.2*）的表达；非经典Wnt信号与mTORC2共同作用，调控细胞骨架重组，增强OPCs的迁移能力和突起延伸[2，28-35]。这些信号通路的协同作用，确保OPCs顺利分化为成熟的OLs。成熟的OLs通过突起识别接触神经元轴突。一旦突起与轴突接触，OLs的突起膜会围绕轴突螺旋状缠绕，形成多层膜结构。随着膜层数的增加，髓鞘逐渐增厚并压实，内部的细胞质被排

除，最终形成一种高度致密的脂质结构。这一过程被称为髓鞘化[36-37]。

2.2 CNS髓鞘再生

髓鞘损伤是指髓鞘的结构破坏或功能异常。在MS等脱髓鞘疾病，表现为运动无力、动作不协调、感觉异常及认知障碍等症状，免疫攻击是发病的主要原因之一，免疫系统误将髓鞘视为“入侵者”进行攻击；此外，基因突变如佩梅病（Pelizaeus-Merzbacher disease，PMD）、异染性脑白质营养不良（metachromatic leukodystrophy，MLD）以及代谢异常也可导致髓鞘稳定性受损；毒性物质和机械损伤也是潜在致病因素[38-43]。衰老也会造成髓鞘损伤，衰老过程中氧化应激水平升高，活性氧类（reactive oxygen species，ROS）等自由基的大量产生会直接损伤髓鞘脂质和蛋白质使其结构和功能受损，炎症反应在此过程中增强，IL-1β、IL-6和TNF-α等抑制髓鞘形成相关基因的表达，线粒体出现功能异常等情况，影响能量供应，脂质代谢紊乱影响髓鞘的组成和再生[44-45]。此外，神经疾病也会影响髓鞘的维持。在AD中，Aβ寡聚体干扰神经元与OLs之间的信号交流，激活小胶质细胞，引发炎症反应，释放炎症因子和神经毒性物质，损伤髓鞘，tau蛋白异常磷酸化后形成神经原纤维缠结，影响轴突的物质运输，使髓鞘得不到足够的营养支持[46]；在PD中，α突触核蛋白聚集物干扰OLs内的蛋白质稳态，导致内质网应激，引发细胞凋亡，进而影响髓鞘的正常代谢和更新，多巴胺能神经元变性也会间接影响髓鞘的完整性[47-48]。

髓鞘再生对于恢复CNS功能至关重要，是多种脱髓鞘疾病治疗的重点。当髓鞘受损时，局部组织释放ATP、高迁移率族蛋白B1（high mobility group box-1 protein，HMGB1）和热休克蛋白（heat shock proteins，HSPs）等危险信号及促炎性细胞因子（如IL-1β、TNF-α、IL-6），招募OPCs迁移至损伤部位，小胶质细胞和巨噬细胞通过清除髓鞘碎片并释放生长因子IGF-1和BDNF促进再生[49-56]。星形胶质细胞对髓鞘再生也有重要作用，最新研究表明[57]，星形胶质细胞衍生的簇蛋白（clusterin，CLU）抑制PI3K-Akt-mTOR信号通路进一步使OPCs和OLs凋亡，而敲低或敲除星形胶质细胞中的CLU，能增加炎症性脱髓鞘病变中OPCs数量，增加髓鞘厚度。此外，也有研究表明，在PD等与年龄相关的神经退行性疾病中，星形胶质细胞衰老表现明显，其细胞形态增大，p16表达增强，衰老相关β半乳糖苷酶活性升高，衰老相关分泌表型（senescence-associated secretory phenotype，SASP）分泌增加，进一步加重神经炎症[58]。因此，深入研究髓鞘的发育与再生机制，不仅有助于理解CNS疾病的病理，还为脱髓鞘疾病的临床治疗提供重要的理论依据和全新思路。

3 星形胶质细胞在髓鞘发育过程中的调控作用

在髓鞘发育过程中，OPCs的存活、增殖和分化起着重要作用，研究表明，星形胶质细胞通过分泌各种细胞因子促进这一过程（图1）。BDNF通过与TrkB受体结合，激活PI3K/Akt和MAPK/ERK信号通路，促进OPCs的存活和分化并增强神经可塑性；睫状神经营养因子（ciliary neuronotrophic factor，CNTF）通过其受体复合体激活JAK-STAT信号通路，促进OPCs的增殖、分化和髓鞘形成；FGF-2同样激活MAPK/ERK通路促进细胞增殖并维持其在未分化状态；IGF-1调控Akt信号通路抑制细胞凋亡促进细胞的生长和存活。此外，星形胶质细胞还可以通过调节细胞外基质（extracellular matrix，ECM）成分和离子环境以及提供代谢支持间接影响OPCs；星形胶质细胞的星状突起可以延伸到OLs周围[10，59]，与OLs通过由连接蛋白Cx32和Cx47形成的通道形成紧密的接触，从而直接影响OLs的行为，这种直接的通讯方式使得两种胶质细胞能够快速响应局部环境变化，并协调其功能；星形胶质细胞突起上的钾离子通道能调节细胞外钾离子的浓度，维持离子平衡，影响OLs的膜电位和兴奋性，乳酸转运体从血液或脑脊液中获取和输送代谢物（如乳酸、葡萄糖）给OLs，这些代谢物对于OLs的能量供应和功能维护至关重要；同时，星形胶质细胞突起能够清除突触间隙中的神经递质（如谷氨酸），防止其在细胞间隙中过量积累，从而避免毒性效应，其释放的神经调节因子（如腺苷、神经肽等）还可通过调节OLs的信号转导通路，影响其增殖、分化和髓鞘形成过程[15，28-31，60-63]。

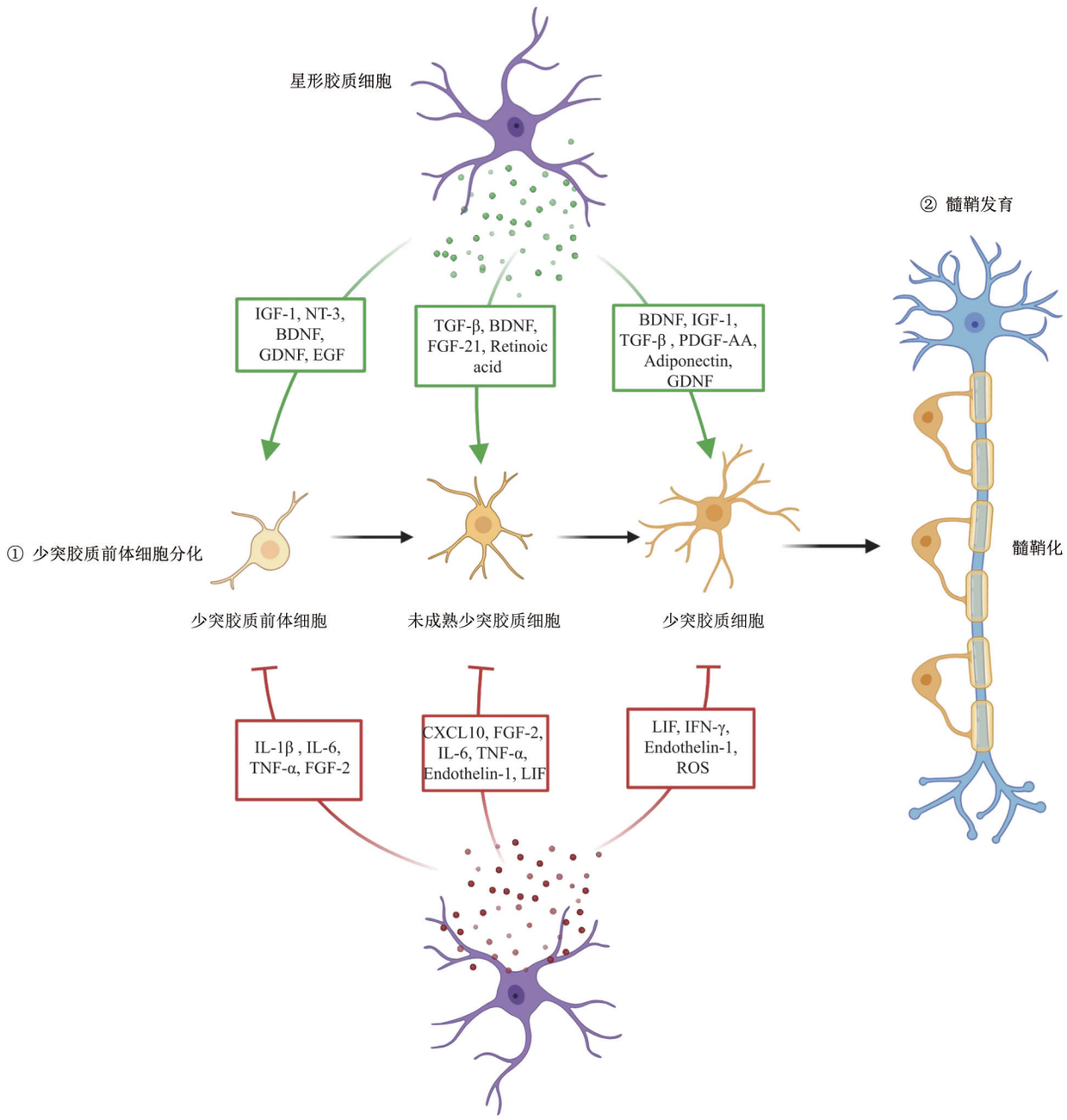

Fig. 1　The regulatory role of astrocytes in myelin development

图1　星形胶质细胞在髓鞘发育中的调控作用

在中枢神经系统中，OPC增殖、迁移到目标区域后分化为成熟的OL，最终形成髓鞘。在此过程中，星形胶质细胞通过分泌IGF-1、BDNF以及IL-1、TNF-α和FGF-2等因子调控OPC的增殖、迁移和分化以及髓鞘形成。绿色箭头及方框内的因子：在神经元活动正常且营养充足以及一些特定的发育阶段，星形胶质细胞分泌一系列促进髓鞘发育的因子。红色箭头及方框内的因子：在炎症和免疫反应以及氧化应激条件下，星形胶质细胞分泌一系列抑制性因子阻碍髓鞘形成。IGF-1：胰岛素样生长因子1（insulin-like growth factor 1）；NT-3：神经营养因子3（neurotrophin-3）；BDNF：脑源性神经营养因子（brain-derived neurotrophic factor）；GDNF：胶质细胞源性神经营养因子（glial cell-derived neurotrophic factor）；EGF：表皮细胞生长因子（epidermal growth factor）；TGF-β：转化生长因子β（transforming growth factor beta）；FGF：成纤维细胞生长因子（fibroblast growth factor）；Retinoic acid：维A酸；PDGF-AA：血小板源性生长因子-AA（platelet-derived growth factor-AA）；Adiponectin：脂联素；IL：白介素（interleukin）；TNF-α：肿瘤坏死因子α（tumor necrosis factor-α）；CXCL10：C-X-C基序趋化因子配体10（C-X-C motif chemokine ligand 10）；Endothelin-1：内皮素1；LIF：白血病抑制因子（leukemia inhibitory factor）；IFN-γ：干扰素γ（interferon-γ）；ROS：活性氧类（reactive oxygen species）。

4 星形胶质细胞在髓鞘再生过程中的调控作用

4.1 星形胶质细胞的活化

在神经系统受到损伤或炎症时，细胞会释放出多种分子，包括损伤相关的分子模式（damage associated molecular patterns，DAMPs）、炎症因子以及神经营养因子。这些分子与星形胶质细胞表面的Toll样受体（Toll like receptors，TLRs）和NOD样受体（nucleotide-binding oligomerization domain-like receptors，NLRs）结合，激活信号转导通路，触发星形胶质细胞的活化过程[64-65]。当神经系统遭受轻微损伤时，星形胶质细胞通常仅表现出轻度活化；而在严重损伤或慢性疾病（如中风、创伤性脑损伤和MS）中，星形胶质细胞会进入更显著的反应性状态，发生形态和功能上的改变，表现为细胞形态的变大、细胞突起的增多、细胞内蛋白质（如神经胶质纤维酸性蛋白）的增加，以及分泌因子表达的变化，这种状态下的星形胶质细胞被称为反应性星形胶质细胞，在实验性自身免疫性脑脊髓炎（experimental autoimmune encephalomyelitis，EAE）小鼠模型中，反应性星形胶质细胞的缺失会加重神经炎症，而在慢性EAE小鼠模型中，清除反应性星形胶质细胞可以减轻炎症反应[66]，这表明，在不同状态下，反应性星形胶质细胞有双重作用，因此，根据反应性表型可以进一步分为A1型和A2型（图2）。

在急性损伤早期的抗炎和神经营养因子微环境驱动下，星形胶质细胞通常分化为A2型反应性星形胶质细胞，分泌BDNF、GDNF、NT-3、TGF-β、FGF、IGF-1、LIF、VEGF等因子，调控局部炎症、清除损伤碎片、支持髓鞘再生，帮助中枢神经系统恢复正常功能。而在严重或慢性神经损伤情况下，则可能分化为A1型反应性星形胶质细胞，在小胶质细胞等免疫细胞分泌的促炎因子作用下，星形胶质细胞释放TNF-α、IL-1β、ROS、一氧化氮（nitric oxide，NO）等神经毒性因子，直接或间接损害神经元，并通过分泌谷氨酸等神经递质诱导神经元过度兴奋，增加OLs凋亡，阻碍髓鞘再生[67-70]，此外，还会在损伤区域增生形成胶质瘢痕（glial scar）[71-73]，该结构可以隔离损伤，防止病理扩散，但同时也会阻碍神经再生和髓鞘再生。胶质瘢痕中含有的硫酸软骨素蛋白聚糖（chondroitin sulfate proteoglycans，CSPGs）等抑制因子会阻止OPCs的迁移，抑制它们进入损伤区域并形成髓鞘，从而使神经功能恢复受阻。在神经退行性疾病或慢性炎症条件下，反应性星形胶质细胞更倾向于分化为A1型，从而导致神经损伤的加剧[67-70]。

4.2 星形胶质细胞的能量供应

髓鞘再生是一个高能耗的过程，OLs需要充足的线粒体能量来生成新的髓鞘。星形胶质细胞通过葡萄糖转运蛋白（glucose transporters，GLUTs）从血液中摄取葡萄糖，随后将其代谢为乳酸或其他代谢底物，传递给神经元和OLs使用[74]。乳酸作为星形胶质细胞产生的主要代谢产物，能够通过单羧酸转运体（monocarboxylate transporters，MCTs）传递给OLs和神经元[75-77]。OLs和神经元摄取乳酸后，通过乳酸氧化生成ATP，满足髓鞘形成和神经功能的能量需求。这种代谢互作模式也被称为星形胶质细胞-神经元乳酸穿梭（astrocyte-neuron lactate shuttle，ANLS）[78-79]。

4.3 星形胶质细胞的吞噬作用

在髓鞘再生过程中，星形胶质细胞发挥着重要作用，特别是在吞噬髓鞘碎片的过程中。损伤后的髓鞘碎片影响局部环境稳定，星形胶质细胞通过吞噬作用识别并清除这些碎片，维持损伤区域的清洁与稳定，避免有害物质（如髓鞘碎片中的脂质和蛋白质降解产物）积累[80]。在这一过程中，星形胶质细胞会释放一系列细胞因子（如TGF-β、IL-1β等），这些因子在局部免疫反应中起到重要调节作用，TGF-β能够抑制过度的免疫反应，减少炎症介质的释放，促进修复，而IL-1β则在早期的免疫应答中起到推动作用，有助于激活其他胶质细胞，此外，星形胶质细胞通过分泌神经营养因子（如IGF-1和BDNF），进一步促进OPCs的增殖、迁移与分化，并促进它们分化为成熟的OLs，从而推动髓鞘的再生[80-81]。然而，星形胶质细胞的吞噬作用在某些情况下也可能对髓鞘再生产生不利影响。尤其是在某些慢性或持续的神经损伤状态下，过度的吞噬反应可能会导致星形胶质细胞的持续激活，这时，星形胶质细胞释放过多的炎症因子，导致局部炎症反应加重，进一步抑制髓鞘再生，同时，持续激活会使星形胶质细胞过度活化，导致胶质瘢痕形成[82]，胶质瘢痕通过物理屏障的方式阻碍OPCs的迁移与分化，并且抑制OLs的增殖，从而影响髓鞘的再生。

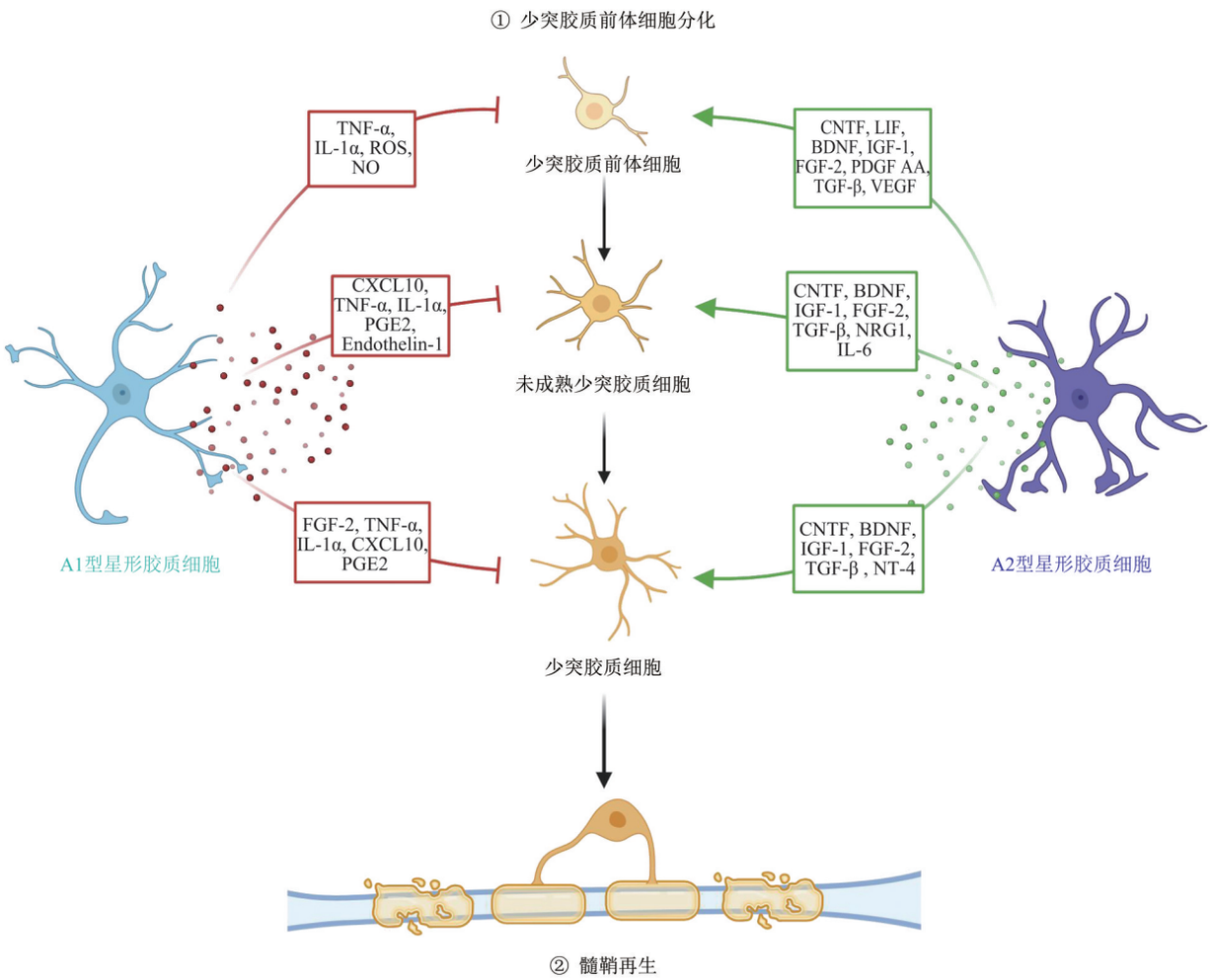

Fig. 2　Regulatory role of astrocytes in remyelination

图2　星形胶质细胞在髓鞘再生中的调控作用

星形胶质细胞在不同的病理生理条件下会极化为具有不同功能特性的A1型和A2型。在神经退行性疾病中，星形胶质细胞分化为A1型，而在轻微损伤或修复初期，则主要为A2型。红色箭头及方框内的因子：A1型星形胶质细胞分泌一系列因子抑制OPC的增殖和分化，阻碍髓鞘再生。绿色箭头及方框内的因子：A2型星形胶质细胞分泌一系列因子促进髓鞘再生。TNF-α：肿瘤坏死因子α（tumor necrosis factor-α）；IL：白介素（interleukin）；ROS：活性氧类（reactive oxygen species）；NO：一氧化氮（nitric oxide）；CXCL10：C-X-C基序趋化因子配体10（C-X-C motif chemokine ligand 10）；PGE2：前列腺素E2（prostaglandin E2）；Endothelin-1：内皮素1；FGF-2：成纤维细胞生长因子2（fibroblast growth factor 2）；CNTF：睫状神经营养因子（ciliary neuronotrophic factor）；LIF：白血病抑制因子（leukemia inhibitory factor）；BDNF：脑源性神经营养因子（brain-derived neurotrophic factor）；IGF-1：胰岛素样生长因子1（insulin-like growth factor 1）；PDGF-AA：血小板源性生长因子-AA（platelet-derived growth factor-AA）；TGF-β：转化生长因子β（transforming growth factor beta）；VEGF：血管内皮生长因子（vascular endothelial growth factor）；NRG-1：神经调节蛋白1（neuregulin 1）；NT-4：神经营养因子4（neurotrophin-4）。

4.4　星形胶质细胞与其他细胞间的相互作用

脱髓鞘后，小胶质细胞可以通过限制外周单核细胞的募集来促进髓鞘再生，而单核细胞则抑制小胶质细胞对髓鞘碎片的吞噬作用[83]。星形胶质细胞可能在髓鞘再形成过程中与小胶质细胞相互作用，影响其募集以清除碎片。星形胶质细胞和小胶质细胞在中枢神经系统中的相互作用对髓鞘再生具有关键影响。两种细胞通过相互调节炎症反应、碎片清除过程中的信号转导等机制，共同促进髓鞘再生。

小胶质细胞首先响应髓鞘损伤，通过识别DAMPs[52]启动炎症反应。释放促炎性细胞因子如TNF-α、IL-1β和IL-6等，促进免疫反应，以清除受损组织和髓鞘碎片。星形胶质细胞在小胶质细胞

炎症启动后，通过分泌抗炎性细胞因子IL-10、IL-4等调控局部的炎症反应，防止过度炎症造成的神经损伤。在清除碎片的过程中，小胶质细胞释放的促炎因子，吸引其他免疫细胞，进一步促进碎片的清除。星形胶质细胞还能分泌调节性分子，如基质金属蛋白酶，通过重塑细胞外基质，帮助小胶质细胞更好地进入损伤部位，清除碎片并启动修复。此外，小胶质细胞释放的抗炎性因子调节星形胶质细胞的活性，减少星形胶质细胞的持续激活，从而控制胶质疤痕的扩展。在病理状态下，小胶质细胞功能的异常会导致星形胶质细胞过度活化和疤痕形成，进一步阻碍髓鞘再生[80，83-84]。

星形胶质细胞与神经元之间的相互作用在髓鞘再生过程中也起到至关重要的作用。星形胶质细胞分泌BDNF、FGF-2等神经营养因子，这些营养因子通过激活神经元表面的受体，启动神经元的保护性信号通路，如TrkB受体的激活，促进神经元修复和神经突生长，保护神经元免受损伤，并促进神经元的存活和功能恢复。此外，星形胶质细胞通过γ氨基丁酸（γ-aminobutyric acid，GABA）[85]和谷氨酸（glutamate）[86]等神经递质对神经元活性进行实时精细调控，星形胶质细胞参与GABA代谢，维持其浓度稳定，保障神经元抑制性传递，其异常会致神经元过度兴奋，并通过转运体摄取和释放谷氨酸，维持神经元兴奋性平衡，转运异常会引发兴奋性毒性，常见于神经退行性疾病[84，87-89]。

髓鞘再生需要良好的血液供应以提供氧气和能量，星形胶质细胞通过与血管系统的相互作用，帮助调节血流量和营养供应。星形胶质细胞的末端围绕在毛细血管周围，形成所谓的“血管足”（endfeet）[90]，帮助维持血脑屏障的完整性，确保在髓鞘再生过程中CNS能够获取充足的血液供应，并防止有害物质进入大脑。同时通过钙离子信号调节毛细血管的扩张或收缩，确保髓鞘再生过程中血流和氧气供应的平衡。星形胶质细胞还通过分泌CCL2、CCL3、CCL5、CXCL10、CXCL12等趋化因子，引导外周免疫细胞（如单核细胞和淋巴细胞）进入中枢神经系统，参与髓鞘损伤后的清除工作，同时，星形胶质细胞通过调节免疫细胞的活性，防止过度的免疫反应引发进一步的神经损伤[91-92]。

5 总结与展望

星形胶质细胞在髓鞘发育和再生中起着关键作用，尽管已有许多研究揭示了其在中枢神经系统中的功能，但仍有诸多重要问题需要深入探索。首先，星形胶质细胞与OPCs之间的相互作用机制尚不完全清楚。研究表明，星形胶质细胞通过分泌生长因子和细胞因子调控OPCs的增殖、分化和迁移，但具体的信号通路、关键调控分子及其在不同发育阶段或病理条件下的动态变化仍需进一步研究。其次，星形胶质细胞的异质性及其对髓鞘发育和再生的影响值得深入探讨。星形胶质细胞并非单一功能的细胞类型，其在不同脑区及病理条件下表现出显著差异。例如，A2型星形胶质细胞可能有助于支持髓鞘形成和再髓鞘化，而A1型星形胶质细胞在某些病理状态下可能起抑制作用。深入理解其异质性，将有助于明确不同亚型在髓鞘形成与再生中的具体功能。此外，星形胶质细胞在某些病理条件下可能具有负面作用。例如，在MS等脱髓鞘疾病中，星形胶质细胞可能通过释放促炎性因子或形成胶质瘢痕，抑制再髓鞘化。虽然已有研究揭示了这些负面效应的存在，但如何有效调控或逆转这些作用，以促进髓鞘再生，是未来研究的重要方向。星形胶质细胞在调节局部代谢环境方面的作用也亟待进一步研究。尽管已知它们通过提供代谢底物（如乳酸、葡萄糖、脂肪酸）支持神经元和少突胶质细胞的功能，但其在髓鞘发育和再生中的具体代谢支持机制尚不明确。未来研究需要聚焦星形胶质细胞如何通过调控局部代谢环境影响OPCs的分化，以及这种代谢调节在髓鞘再生中的作用机制。同时，星形胶质细胞与其他细胞类型的相互作用在髓鞘再生过程中也扮演重要角色。星形胶质细胞与小胶质细胞、神经元及血管内皮细胞共同组成复杂的细胞网络，但该网络在不同病理状态下如何影响髓鞘再生仍需深入研究。

总体而言，尽管星形胶质细胞在髓鞘发育与再生中展现出重要作用，但在异质性、代谢调节、负面效应以及与其他细胞类型相互作用等方面仍有许多未解之谜。未来的研究将进一步揭示星形胶质细胞如何通过精确调控机制介导髓鞘形成与再生，为脱髓鞘疾病的治疗提供新的思路和策略。

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Astrocytes in The Central Nervous System Regulate Myelination and Remyelination Through Multiple Mechanisms*

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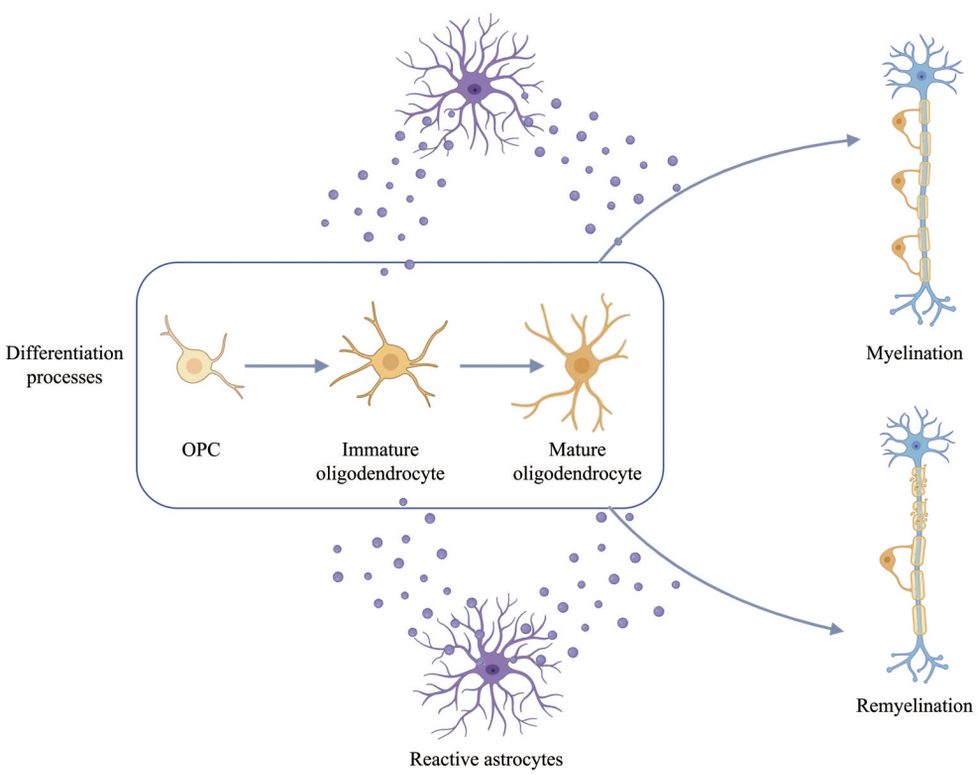
Graphical abstract



Abstract In the central nervous system (CNS), the myelin sheath, a specialized membrane structure that wraps around axons, is formed by oligodendrocytes through a highly coordinated spatiotemporal developmental program. The process begins with the directed differentiation of neural precursor cells into oligodendrocyte

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precursor cells (OPCs), followed by their migration, proliferation, differentiation, and maturation, ultimately leading to the formation of a multi-segmental myelin sheath structure. Recent single-cell sequencing research has revealed that this process involves the temporal regulation of over 200 key genes, with a regulatory network composed of transcription factors such as Sox10 and Olig2 playing a central role. The primary function of the myelin sheath is to accelerate nerve signal transmission and protect nerve fibers from damage. Its insulating properties not only increase nerve conduction speed by 50−100 times but also ensure the long-term functional integrity of the nervous system by maintaining axonal metabolic homeostasis and providing mechanical protection. The pathological effects of myelin sheath injury exhibit a cascade amplification pattern: acute demyelination leads to action potential conduction block, while chronic lesions may cause axonal damage and neuronal death in severe or long-term cases, ultimately resulting in irreversible neurological dysfunction with neurodegenerative characteristics. Multiple sclerosis (MS) is a neurodegenerative disease characterized by chronic inflammatory demyelination of the CNS. Clinically, the distribution of lesions in MS exhibits spatial heterogeneity, which is closely related to differences in the regenerative capacity of oligodendrocytes within the local microenvironment. Emerging evidence suggests that astrocytes form a dynamic “neural-immune-metabolic interface” and play a multidimensional regulatory role in myelin development and regeneration by forming heterogeneous populations composed of different subtypes. During embryonic development, astrocytes induce the targeted differentiation of OPCs in the ventricular region through the Wnt/β-catenin pathway. In the mature stage, they secrete platelet-derived growth factor AA (PDGF-AA) to establish a chemical gradient that guides the precise migration of OPCs along axonal bundles. Notably, astrocytes also provide crucial metabolic support by supplying energy substrates for high-energy myelin formation through the lactate shuttle mechanism. In addition, astrocytes play a dual role in myelin regulation. During the acute injury phase, reactive astrocytes establish a triple defense system within 72 h: upregulating glial fibrillary acidic protein (GFAP) to form scars that isolate lesions, activating the JAK-STAT3 regeneration pathway in oligodendrocytes *via* leukemia inhibitory factor (LIF), and releasing tumor necrosis factor-stimulated gene-6 (TSG-6) to inhibit excessive microglial activation. However, in chronic neurodegenerative diseases, the phenotypic transformation of astrocytes contributes to microenvironmental deterioration. The secretion of chondroitin sulfate proteoglycans (CSPGs) inhibits OPC migration *via* the RhoA/ROCK pathway, while the persistent release of reactive oxygen species (ROS) leads to mitochondrial dysfunction and the upregulation of complement C3-mediated synaptic pruning. This article reviews the mechanisms by which astrocytes regulate the development and regeneration of myelin sheaths in the CNS, with a focus on analyzing the multifaceted roles of astrocytes in this process. It emphasizes that astrocytes serve as central hubs in maintaining myelin homeostasis by establishing a metabolic microenvironment and signaling network, aiming to provide new therapeutic strategies for neurodegenerative diseases such as multiple sclerosis.

Key words astrocytes, oligodendrocytes, myelination, remyelination
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