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创伤性脊髓损伤修复过程中少突胶质细胞的作用

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摘　要

临床上脊髓损伤对国家、社会和个人产生重大身体、心理和经济负担。脊髓损伤后，血脑屏障被破坏，血细胞渗入损伤部位，神经元和胶质细胞发生死亡，进而引起受损轴突的脱髓鞘病变，这一系列生理病理反应导致不可逆转的神经功能损伤。少突胶质细胞是中枢神经系统的髓鞘形成细胞，并且少突胶质前体细胞(oligodendrocyte precursor cells, OPCs)是已知的成熟少突胶质细胞唯一来源，具有保护损伤轴突的作用。本文将对少突胶质细胞在脊髓损伤后发生的生理病理变化，以及对其在脊髓损伤修复中发挥的作用的研究现状进行综述，并且对脊髓损伤修复未来发展方向进行展望。

关键词

少突胶质细胞，脊髓损伤，神经再生

Oligodendrocytes and Its Role in Spinal Cord Traumatic Injury

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Abstract

Spinal cord injury (SCI) is a severe emergency that causes personal physical, psychological problems and social economic burdens among individuals, communities and countries. In SCI, unal-

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terable neuronal dysfunction occurs due to a series of physiopathologic processes, including penetration of blood cells in the injury site following blood-brain barrier (BBB) disruption and demyelination of injured axons following the apoptotic cascade of neuronal and glial cells. Oligodendrocytes form the myelin sheaths in the central nervous system (CNS). Oligodendrocyte precursor cells (OPCs) are the main source of mature oligodendrocytes that protects neuronal axons from the injury site. This literature review outlines the physiopathological traits of oligodendrocytes after SCI, summarizes recent research on its role in the traumatic spinal cord injury and repair, and demonstrates future efforts on the management of SCI.

Keywords

Oligodendrocyte, Spinal Cord Injury, Neural Regeneration

1. 前言

脊髓由白质和灰质组成，其中包含神经元胞体、上行和下行纤维束，其作为大脑与周围神经之间的联系通路至关重要，因此，脊髓损伤的不同部位和程度导致不同程度的残疾，最严重的后果就是失去生命。作为一种中枢神经系统创伤性疾病，脊髓损伤具有高发病率、高致残率和医疗费用昂贵等特点。根据脊髓损伤的病理生理过程我们一般将其分为原发性脊髓损伤和继发性脊髓损伤两种[1]。原发性损伤是指外力直接或间接作用于脊髓组织造成脊髓损伤。而继发性损伤是指在原发性损伤后，随着损伤时间的延长，损伤部位出现的一系列破坏性级联病理生理变化，如：水肿、局部出血、炎症反应、电解质平衡失调、脂质过氧化、自由基形成、神经元轴突断裂、神经元凋亡、轴突脱髓鞘等，最终导致纤维胶质瘢痕、囊肿的形成[2]。到目前为止，所研究的治疗脊髓损伤的方法主要是从神经保护和神经再生两个方面进行[3]。神经保护方面分为药理学疗法和非药物疗法。药理学疗法目前包括采用利鲁唑、米诺环素、GM-1神经节苷脂、成纤维细胞生长因子、粒细胞集落刺激因子、肝细胞生长因子等治疗脊髓损伤，而非药物疗法的主要手段是低温治疗和脑脊液引流。神经再生关键治疗包括使用 Rho-ROCK 抑制剂和 Anti-NOGO 抗体的药理学疗法和利用脊髓刺激、细胞疗法等的非药物疗法[4]。基于神经元的不可再生，寻找有效的治疗方法，减少继发性损伤过程中神经元的死亡是神经保护策略的主要手段。

在中枢神经系统中少突胶质细胞(oligodendrocyte, OL)是唯一能够通过分化形成髓鞘的胶质细胞，也是成年中枢神经系统中主要的增殖类细胞，约占胶质细胞总数的 5%~10% [5]，它是由少突胶质祖细胞分化而来[6]。在个体发育过程中，少突胶质系细胞首先起源于脊髓和大脑室管膜下区的神经祖细胞[7]。成熟的少突胶质细胞会形成髓鞘包裹轴突，促进轴突动作电位的快速传导[8]，同时他们还会影响神经元稳态，为神经元提供代谢支持[9] [10]。在脊髓损伤后，少突胶质祖细胞会迅速增殖，成为新生少突胶质细胞的主要来源[11]，因此，尝试用少突胶质细胞重塑髓鞘保护轴突的特性来治疗脊髓损伤是一个可行性非常高的办法[12]。因此，本篇综述中主要为了阐明在脊髓损伤后修复的过程中少突胶质细胞的贡献及之后可能的研究方向。

2. 脊髓损伤后少突胶质细胞发生的生理变化

髓鞘是神经细胞的保护层，当发生脱髓鞘之后，会使轴突和少突胶质细胞受到破坏，从而导致一系

列的生理病理过程[13]。脊髓损伤后引起少突胶质细胞坏死和凋亡会导致轴突脱髓鞘，从而影响轴突的功能和稳定性。在原发性损伤后，大量少突胶质细胞死亡，引起此现象发生的原因在动物模型中，是由于髓鞘碎片中含有轴突生长抑制因子，如 Nogo-A 蛋白、OMgp 或髓鞘相关糖蛋白 MAG [14] [15] [16]。而继发性损伤后细胞所处微环境发生的巨大改变，不利于促进轴突再生，持续的恶化最终导致感觉和运动功能障碍。脊髓外部机械损伤后外周循环蛋白和各种炎症因子如一氧化氮、TNF-α、自由基等浸润损伤部位，加重局部微环境的炎症反应和缺血性损伤，导致组织 pH 值急剧下降，损伤部位产生酸性微环境[17] [18]。损伤后微环境的失衡包括分子、细胞和组织在时间和位置上发生的病理生理变化，如：有益因子的减少、有害因子表达的升高等。例如：硫酸酯酶 2 (Sulf2)是 OPC 分泌的一种细胞外硫化酶，Sulf2 通过调节小鼠腹侧脊髓中的 Sonic Hedgehog (Shh)信号传导与 Sulf1 协调调节从运动神经元到少突胶质前体细胞的命运转化[19]，OPC 中 Sulf2 的表达升高会损害祖细胞的募集和 OL 的产生，Sulf1/2 通过促进 OPC 中的 BMP 和 WNT 信号传导增强抑制性微环境的产生，从而抑制髓鞘再生[20]。另外，小胶质细胞的表型主要依赖于微环境，微环境的改变会使小胶质细胞激活，形态改变，增殖、迁移通过分泌更多炎症因子和趋化因子发挥吞噬、炎症性增殖等各种效应功能[21] [22]。

在继发性损伤过程中产生的活性氧、兴奋性毒性、细胞外 ATP 和促炎细胞因子等都会对少突胶质细胞产生极大的损伤，从而引起少突胶质细胞大量死亡。最重要的是继发性损伤后，细胞膜上的离子泵/转运体的离子电解稳态被破坏，细胞外钾离子浓度增加，而胞内钠离子和钙离子的浓度也增加[23] [24]，导致神经元信号传输障碍。钙离子流入细胞内空间激活蛋白酶，破坏线粒体功能和细胞骨架，产生自由基，轴突变性，最终激活凋亡途径[25]。另外，少突胶质细胞自噬的特异性缺失对 OPCs/OL 的功能有害，导致更多的髓鞘丢失和运动障碍[26]。

在脊髓损伤中参与损伤和修复的细胞主要有两大类：1) 神经和非神经固有细胞，神经固有细胞包括神经元和胶质细胞如：少突胶质祖细胞、少突胶质细胞、小胶质细胞、星形胶质细胞等，而非神经固有细胞包括成纤维细胞、内皮祖细胞等[27]。脊髓损伤的第一阶段是炎症反应，其中小胶质细胞、星形胶质细胞和巨噬细胞等都参与了炎症反应。据报道，小胶质细胞/巨噬细胞在 SCI 后 7 天内达到募集高峰，小胶质细胞/巨噬细胞能够转化为 M2 表型并减少炎症，促进神经元的生长和存活，这对脊髓损伤后修复过程中神经发生、轴突重塑、血管生成和少突胶质细胞存活和髓鞘再生至关重要[28] [29] [30]。第二阶段是细胞的增殖。在脊髓损伤后胶质细胞和神经前体细胞会通过增殖反应来进行补救。中枢神经系统损伤后，神经干细胞会从静息状态转变为活跃状态，活化的干细胞会增殖分化并迁移至损伤部位，促进局部组织再生[31]。脊髓损伤后，星形胶质细胞活化形成纤维性胶质瘢痕，但最新研究表明，小胶质细胞也是脊髓损伤过程中形成胶质瘢痕的重要组成成分，小胶质细胞的缺失会减少脊髓损伤后神经元和少突胶质细胞数量的丢失和损害的功能的恢复[32]。星形胶质细胞除了激活为反应性星形胶质细胞形成纤维性胶质瘢痕外，它还会释放一些促进少突胶质前体细胞增殖、迁移和分化的细胞生长因子[33] [34]。PDGF-AA 就是由星形胶质细胞和神经元分泌的一种 OPC 的有丝分裂原和生长因子，它的过表达会促进 OPC 数量增多[35]。第三个阶段是组织重塑，这可能会长达数几年。脊髓损伤后，少突胶质祖细胞迅速增殖分化为少突胶质细胞和再髓鞘化的雪旺细胞，促进髓鞘再生[36] [37]。

完整的髓鞘结构对中枢神经系统有效的神经元信号传导至关重要，脊髓损伤后轴突脱髓鞘可能会抑制或减缓动作电位的传导，并导致功能缺陷。少突胶质前体细胞对中枢神经系统损伤后的髓鞘再形成和少突胶质细胞再生过程至关重要，但是少突胶质前体细胞非常脆弱，脊髓损伤后的脱髓鞘会增加 OPCs 内的兴奋电流，导致神经传导通路中断。

3. 脊髓损伤后修复过程中少突胶质细胞的贡献

少突胶质祖细胞是产生髓鞘化的少突胶质细胞的主要来源，髓鞘的形成会保护、支持隔离和维持轴

突电传导，从而支持中枢神经系统功能的正常发挥[38]。而脊髓损伤后少突胶质细胞的大量死亡会导致轴突脱髓鞘，损伤后 OPCs 会迅速增殖产生新的再髓鞘化少突胶质细胞和大部分髓鞘化雪旺细胞[39]，同时影响神经胶质细胞的生长，甚至调节免疫反应[40]。

脊髓损伤导致严重的运动、感觉和自主功能障碍，目前尚无根治的临床方法，而少突胶质前体细胞因为其独特的潜力被认为是治疗脊髓损伤疾病的潜力细胞[41]。在脊髓损伤后，关于应用少突胶质细胞来促进再髓鞘化主要包含两种手段：1) 少突胶质细胞保护疗法，主要是指对已存在的少突胶质细胞进行保护，使其免受凋亡或坏死；2) 诱导再髓鞘化，即通过为病变部位的内源性少突胶质前体细胞提供合适的生存环境，促进其迁移、增殖及分化形成新的髓鞘[42]。在保护已有的少突胶质细胞方面，中草药展现出对未来临床应用的巨大发展潜力，例如：槲皮素能显著降低脊髓损伤后少突胶质细胞的坏死，改善大鼠脊髓损伤后运动功能的恢复[43]。小檗碱能够通过触发损伤后少突胶质细胞自噬，减轻损伤脊髓的炎症反应，减少神经元凋亡，从而减轻神经损伤[44]。Agathisflavone 能够促进神经再生，增加神经营养因子(NGF、GDNF)的表达，调节炎症反应，治疗大鼠急性脊髓损伤[45]。

之前的研究认为脊髓损伤后髓鞘再生的少突胶质细胞是由少突胶质祖细胞增殖、迁移所产生，但最近的研究表明，髓鞘再生可以由脱髓鞘区域幸存的成熟少突胶质细胞直接产生[46]。这一发现为我们了解髓鞘再生开辟了新的机会。但是，新的少突胶质细胞形成髓鞘的能力比幸存的少突胶质细胞形成髓鞘的能力强，大量髓鞘可以正确靶向轴突，但幸存的少突胶质细胞很少产生新的髓鞘[46]，以上证据说明促进新生少突胶质细胞的增殖、迁移至病变部位，分化为成熟少突胶质细胞对再髓鞘化极其重要，这也为我们的研究重点指出方向。

另有研究表明，在脊髓损伤动物模型中，移植 OPCs 可以增加病灶中心有髓轴突的百分比减小损伤脊髓空洞的大小[47] [48]，促进脊髓损伤后功能的恢复[49] [50]。同时移植成功的 OPCs 能够分化为成熟的少突胶质细胞，促进损伤部位再髓鞘化包裹轴突，使其存活[51] [52]。同时，移植的 OPCs 可以释放 IGF-1、BDNF、GDNF 等细胞因子，促进神经元的存活，维持存活轴突中突触的可塑性[53]。虽然细胞移植技术可以代替受损部位的细胞，但是其也存在细胞存活率低、与宿主有排斥反应等缺点，因此另一种产生成熟少突胶质细胞的方法是通过其他细胞转化，如：通过体内重编程将神经祖细胞、反应性星形胶质细胞转化为少突胶质祖细胞修复脊髓损伤[54] [55]，利用 SOX2 蛋白转导直接将人成纤维细胞转化为少突胶质细胞样细胞促进脊髓损伤修复[56]等。

脊髓损伤的修复主要包括微环境的重塑和促进内源性神经干细胞/祖细胞的募集和神经元分化[57]。在成年中枢神经系统中，髓鞘的自然再生过程在损伤后开始，即少突胶质前体细胞(OPCs)将迁移到损伤区域并分化为 OLs 并恢复髓鞘。因此，少突胶质细胞是脊髓损伤后细胞治疗的首选细胞。细胞移植主要实现脊髓组织的置换，促进轴突生长和髓鞘形成，最终实现功能恢复。通过移植神经干细胞衍生的少突胶质细胞促进轴突髓鞘化已有研究，在 Wistar 大鼠体内模型中，移植骨髓间充质干细胞来源的少突胶质前体细胞 4 周后，移植细胞分化为神经元细胞和少突胶质细胞，导致髓鞘再生和运动功能的改善，但是由于它们的生态位不同，使其并不能够成为治疗脊髓损伤的最佳选择[31]。组织工程化的深入研究吸引了我们的目光，少突胶质细胞和生物材料结合进行移植可能会成为最有前景的治疗策略[58] [59]。应用生物材料不仅可以为轴突生长提供定向支持同时还会提供一个良性的微环境，对少突胶质祖细胞分化为成熟少突胶质细胞和神经元再生至关重要[60]。将 OPC 和 NPC 的组合与水凝胶一起 3D 打印有助于重建中枢神经损伤区域的功能性轴突连接[61]。已有研究证明，移植过表达 microRNA-219 的少突胶质祖细胞会促进 OPC 分化为成熟少突胶质细胞并改善运动功能恢复[62] [63] [64]。人胚胎来源的少突胶质祖细胞移植 SCI 裸鼠模型可以显著改善运动功能，且不会引起任何不良临床反应[65]。

4. 展望

脊髓损伤由于其病理后果和缺乏自我修复能力的原因对患者产生极大的影响。脊髓损伤不仅包括外伤性的损伤，还有一些病理导致的脊髓损伤，例如：多发性硬化症、阿尔茨海默症等，目前可用的治疗方法不能恢复失去的神经功能，随着脊髓损伤人数的逐年增加，寻找有效的治疗方法对整个人类的发展都至关重要[66]。

对于脊髓损伤修复的方法，虽然已经有大量文献报道，但是缺乏一致的认可，目前尚未发现完全修复 SCI 和改善功能恢复的有效治疗方法。在这方面，据报道，应用干细胞移植、生物材料、生物分子和药物等策略均对 SCI 恢复有一定的效果，但是髓鞘再生效率低是脊髓损伤疾病难以恢复的主要原因，严重影响轴突和功能恢复，而再髓鞘化是由来自于中枢神经系统的前体细胞分化而来的内源性少突胶质细胞和雪旺细胞完成。在再髓鞘化的过程中，少突胶质前体细胞会迁移至病变部位，逐渐分化为成熟的少突胶质细胞，包裹在损伤中幸存的轴突上，防止轴突退化，恢复正常的神经元传导[67]，因此，利用他们的这种特性，通过保护已有的少突胶质细胞或采用细胞移植等方法来治疗脊髓损伤是一种很有前景的研究手段。

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参考文献

[1] 田婷, 李晓光. 脊髓损伤再生修复中的问题与挑战[J]. 中国组织工程研究, 2021, 25(19): 3039-3048.

[2] 李建平, 何留民, 吴武田. 脊髓损伤的病理改变及修复策略[J/OL]. 中国科学: 生命科学, 1-12. https://kns.cnki.net/kcms/detail/detail.aspx?dbcode=CJFD&dbname=CJFDAUTO&filename=JCXK202210005&uniplatform=NZKPT&v=iy2zHdHGOOHSzCF9_dsaT40bDi_smcre4tMuYWdv21neGTh25wukAYerW5RGKmJS, 2022-03-21.

[3] Anjum, A., Yazid, M.D., Fauzi, D.M., *et al*. (2020) Spinal Cord Injury: Pathophysiology, Multimolecular Interactions, and Underlying Recovery Mechanisms. *International Journal of Molecular Sciences*, **21**, Article No. 7533. https://doi.org/10.3390/ijms21207533

[4] Ahuja, C.S., Nori, S., Tetreault, L., *et al*. (2017) Traumatic Spinal Cord Injury-Repair and Regeneration. *Neurosurgery*, **80**, S9-S22. https://doi.org/10.1093/neuros/nyw080

[5] Barateiro, A., Brites, D. and Fernandes, A. (2016) Oligodendrocyte Development and Myelination in Neurodevelopment: Molecular Mechanisms in Health and Disease. *Current Pharmaceutical Design*, **22**, 656-679. https://doi.org/10.2174/1381612822666151204000636

[6] Kuhn, S., Gritti, L., Crooks, D., *et al*. (2019) Oligodendrocytes in Development, Myelin Generation and beyond. *Cells*, **8**, Article No. 1424. https://doi.org/10.3390/cells8111424

[7] Elbaz, B. and Popko, B. (2019) Molecular Control of Oligodendrocyte Development. *Trends in Neurosciences*, **42**, 263-277. https://doi.org/10.1016/j.tins.2019.01.002

[8] Allen, N.J. and Lyons, D.A. (2018) Glia as Architects of Central Nervous System Formation and Function. *Science*, **362**, 181-185. https://doi.org/10.1126/science.aat0473

[9] Philips, T. and Rothstein, J.D. (2017) Oligodendroglia: Metabolic Supporters of Neurons. *Journal of Clinical Investigation*, **127**, 3271-3280. https://doi.org/10.1172/JCI90610

[10] Plemel, J.R., Keough, M.B., Duncan, G.J., *et al*. (2014) Remyelination after Spinal Cord Injury: Is It a Target for Repair? *Progress in Neurobiology*, **117**, 54-72. https://doi.org/10.1016/j.pneurobio.2014.02.006

[11] Duncan, G.J., Manesh, S.B., Hilton, B.J., *et al*. (2018) Locomotor Recovery Following Contusive Spinal Cord Injury Does Not Require Oligodendrocyte Remyelination. *Nature Communications*, **9**, Article No. 3066. https://doi.org/10.1038/s41467-018-05473-1

[12] Ahuja, C.S., Mothe, A., Khazaei, M., *et al*. (2020) The Leading Edge: Emerging Neuroprotective and Neuroregenerative Cell-Based Therapies for Spinal Cord Injury. *Stem Cells Translational Medicine*, **9**, 1509-1530.

https://doi.org/10.1002/sctm.19-0135

[13] Wang, J.T., Medress, Z.A. and Barres, B.A. (2012) Axon Degeneration: Molecular Mechanisms of a Self-Destruction Pathway. *Journal of Cell Biology*, **196**, 7-18. https://doi.org/10.1083/jcb.201108111

[14] Schwab, M.E. (2004) Nogo and Axon Regeneration. *Current Opinion in Neurobiology*, **14**, 118-124. https://doi.org/10.1016/j.conb.2004.01.004

[15] Schwab, M.E. and Strittmatter, S.M. (2014) Nogo Limits Neural Plasticity and Recovery from Injury. *Current Opinion in Neurobiology*, **27**, 53-60. https://doi.org/10.1016/j.conb.2014.02.011

[16] Ueno, R., Takase, H., Suenaga, J., *et al*. (2020) Axonal Regeneration and Functional Recovery Driven by Endogenous Nogo Receptor Antagonist LOTUS in a Rat Model of Unilateral Pyramidotomy. *Experimental Neurology*, **323**, Article ID: 113068. https://doi.org/10.1016/j.expneurol.2019.113068

[17] Xi, K., Gu, Y., Tang, J., *et al*. (2020) Microenvironment-Responsive Immunoregulatory Electrospun Fibers for Promoting Nerve Function Recovery. *Nature Communications*, **11**, Article No. 4504. https://doi.org/10.1038/s41467-020-18265-3

[18] 朱正桓, 邹红军, 宋志文, 刘锦波. 脊髓损伤后神经修复过程中的细胞微环境[J]. 中国组织工程研究, 2023, 27(1): 114-120.

[19] Jiang, W., Ishino, Y., Hashimoto, H., *et al*. (2017) Sulfatase 2 Modulates Fate Change from Motor Neurons to Oligodendrocyte Precursor Cells through Coordinated Regulation of Shh Signaling with Sulfatase 1. *Developmental Neuroscience*, **39**, 361-374. https://doi.org/10.1159/000464284

[20] Saraswat, D., Shayya, H.J., Polanco, J.J., *et al*. (2021) Overcoming the Inhibitory Microenvironment Surrounding Oligodendrocyte Progenitor Cells Following Experimental Demyelination. *Nature Communications*, **12**, Article No. 1923. https://doi.org/10.1038/s41467-021-22263-4

[21] Li, Z., Wei, H., Piirainen, S., *et al*. (2016) Spinal versus Brain Microglial and Macrophage Activation Traits Determine the Differential Neuroinflammatory Responses and Analgesic Effect of Minocycline in Chronic Neuropathic Pain. *Brain, Behavior, and Immunity*, **58**, 107-117. https://doi.org/10.1016/j.bbi.2016.05.021

[22] Li, Y., He, X., Kawaguchi, R., *et al*. (2020) Microglia-Organized Scar-Free Spinal Cord Repair in Neonatal Mice. *Nature*, **587**, 613-618. https://doi.org/10.1038/s41586-020-2795-6

[23] Gazdic, M., Volarevic, V., Harrell, C.R., *et al*. (2018) Stem Cells Therapy for Spinal Cord Injury. *International Journal of Molecular Sciences*, **19**, Article No. 1039. https://doi.org/10.3390/ijms19041039

[24] Hayta, E. and Elden, H. (2018) Acute Spinal Cord Injury: A Review of Pathophysiology and Potential of Non-Steroidal Anti-Inflammatory Drugs for Pharmacological Intervention. *Journal of Chemical Neuroanatomy*, **87**, 25-31. https://doi.org/10.1016/j.jchemneu.2017.08.001

[25] Quadri, S.A., Farooqui, M., Ikram, A., *et al*. (2020) Recent Update on Basic Mechanisms of Spinal Cord Injury. *Neurosurgical Review*, **43**, 425-441. https://doi.org/10.1007/s10143-018-1008-3

[26] Saraswat, O.S., Bankston, A.N., Mullins, S.A., *et al*. (2018) Blocking Autophagy in Oligodendrocytes Limits Functional Recovery after Spinal Cord Injury. *Journal of Neuroscience*, **38**, 5900-5912. https://doi.org/10.1523/JNEUROSCI.0679-17.2018

[27] Tuszynski, M.H. and Steward, O. (2012) Concepts and Methods for the Study of Axonal Regeneration in the CNS. *Neuron*, **74**, 777-791. https://doi.org/10.1016/j.neuron.2012.05.006

[28] Rodríguez-Barrera, R., Rivas-González, M., García-Sánchez, J., *et al*. (2021) Neurogenesis after Spinal Cord Injury: State of the Art. *Cells*, **10**, Article No. 1499. https://doi.org/10.3390/cells10061499

[29] Kuboyama, T., Kominato, S., Nagumo, M., *et al*. (2021) Recovery from Spinal Cord Injury via M2 Microglial Polarization Induced by Polygalae Radix. *Phytomedicine*, **82**, Article ID: 153452. https://doi.org/10.1016/j.phymed.2020.153452

[30] Van Broeckhoven, J., Sommer, D., Dooley, D., *et al*. (2021) Macrophage Phagocytosis after Spinal Cord Injury: When Friends Become Foes. *Brain*, **144**, 2933-2945. https://doi.org/10.1093/brain/awab250

[31] Saremi, J., Mahmoodi, N., Rasouli, M., *et al*. (2022) Advanced Approaches to Regenerate Spinal Cord Injury: The Development of Cell and Tissue Engineering Therapy and Combinational Treatments. *Biomedicine & Pharmacotherapy* **146**, Article ID: 112529. https://doi.org/10.1016/j.biopha.2021.112529

[32] Bellver-Landete, V., Bretheau, F., Mailhot, B., *et al*. (2019) Microglia Are an Essential Component of the Neuroprotective Scar That Forms after Spinal Cord Injury. *Nature Communications*, **10**, Article No. 518. https://doi.org/10.1038/s41467-019-08446-0

[33] Xu, L., Tang, Y.Y., Ben, X.L., *et al*. (2020) Ginsenoside Rg1-Induced Activation of Astrocytes Promotes Functional Recovery via the PI3K/Akt Signaling Pathway Following Spinal Cord Injury. *Life Sciences*, **252**, Article ID: 117642. https://doi.org/10.1016/j.lfs.2020.117642

[34] Cheng, Y.Y., Zhao, H.K., Chen, L.W., *et al*. (2020) Reactive Astrocytes Increase Expression of proNGF in the Mouse Model of Contused Spinal Cord Injury. *Neuroscience Research*, **157**, 34-43. https://doi.org/10.1016/j.neures.2019.07.007

[35] Cherchi, F., Bulli, I., Venturini, M., *et al*. (2021) Ion Channels as New Attractive Targets to Improve Re-Myelination Processes in the Brain. *International Journal of Molecular Sciences*, **22**, Article No. 7277. https://doi.org/10.3390/ijms22147277

[36] Assinck, P., Duncan, G.J., Plemel, J.R., *et al*. (2017) Myelinogenic Plasticity of Oligodendrocyte Precursor Cells Following Spinal Cord Contusion Injury. *Journal of Neuroscience*, **37**, 8635-8654. https://doi.org/10.1523/JNEUROSCI.2409-16.2017

[37] Ma, D., Wang, B., Zawadzka, M., *et al*. (2018) A Subpopulation of Foxj1-Expressing, Nonmyelinating Schwann Cells of the Peripheral Nervous System Contribute to Schwann Cell Remyelination in the Central Nervous System. *Journal of Neuroscience*, **38**, 9228-9239. https://doi.org/10.1523/JNEUROSCI.0585-18.2018

[38] Tsata, V., Kroehne, V., Reinhardt, S., *et al*. (2019) Electrophysiological Properties of Adult Zebrafish Oligodendrocyte Progenitor Cells. *Frontiers in Cellular Neuroscience*, **13**, Article No. 102. https://doi.org/10.3389/fncel.2019.00102

[39] Barnabé-Heider, F., Göritz, C., Sabelström, H., *et al*. (2010) Origin of New Glial Cells in Intact and Injured Adult Spinal Cord. *Cell Stem Cell*, **7**, 470-482. https://doi.org/10.1016/j.stem.2010.07.014

[40] Duncan, G.J., Manesh, S.B., Hilton, B.J., *et al*. (2020) The Fate and Function of Oligodendrocyte Progenitor Cells after Traumatic Spinal Cord Injury. *Glia*, **68**, 227-245. https://doi.org/10.1002/glia.23706

[41] Antonios, J.P., Farah, G.J., Cleary, D.R., *et al*. (2019) Immunosuppressive Mechanisms for Stem Cell Transplant Survival in Spinal Cord Injury. *Neurosurgical Focus*, **46**, E9. https://doi.org/10.3171/2018.12.FOCUS18589

[42] Mekhail, M., Almazan, G. and Tabrizian, M. (2012) Oligodendrocyte-Protection and Remyelination Post-Spinal Cord Injuries: A Review. *Progress in Neurobiology*, **96**, 322-339. https://doi.org/10.1016/j.pneurobio.2012.01.008

[43] Fan, H., Tang, H.B., Shan, L.Q., *et al*. (2019) Quercetin Prevents Necroptosis of Oligodendrocytes by Inhibiting Macrophages/Microglia Polarization to M1 Phenotype after Spinal Cord Injury in Rats. *Journal of Neuroinflammation*, **16**, Article No. 206. https://doi.org/10.1186/s12974-019-1613-2

[44] Wang, H., Liu, C., Mei, X., *et al*. (2017) Berberine Attenuated Pro-Inflammatory Factors and Protect against Neuronal Damage via Triggering Oligodendrocyte Autophagy in Spinal Cord Injury. *Oncotarget*, **8**, 98312-98321. https://doi.org/10.18632/oncotarget.21203

[45] Do Nascimento, R.P., De Jesus, L.B., Oliveira-Junior, M.S., *et al*. (2022) Agathisflavone as a Single Therapy or in Association with Mesenchymal Stem Cells Improves Tissue Repair in a Spinal Cord Injury Model in Rats. *Frontiers in Pharmacology*, **13**, Article ID: 858190. https://doi.org/10.3389/fphar.2022.858190

[46] Franklin, R.J.M., Frisén, J. and Lyons, D.A. (2021) Revisiting Remyelination: Towards a Consensus on the Regeneration of CNS Myelin. *Seminars in Cell & Developmental Biology*, **116**, 3-9. https://doi.org/10.1016/j.semcdb.2020.09.009

[47] Priest, C.A., Manley, N.C., Denham, J., *et al*. (2015) Preclinical Safety of Human Embryonic Stem Cell-Derived Oligodendrocyte Progenitors Supporting Clinical Trials in Spinal Cord Injury. *Regenerative Medicine*, **10**, 939-958. https://doi.org/10.2217/rme.15.57

[48] Chen, H., Zhang, Y., Yang, Z., *et al*. (2013) Human Umbilical Cord Wharton's Jelly-Derived Oligodendrocyte Precursor-Like Cells for Axon and Myelin Sheath Regeneration. *Neural Regeneration Research*, **8**, 890-899.

[49] Fu, H., Hu, D., Zhang, L., *et al*. (2018) Efficacy of Oligodendrocyte Progenitor Cell Transplantation in Rat Models with Traumatic Thoracic Spinal Cord Injury: A Systematic Review and Meta-Analysis. *Journal of Neurotrauma*, **35**, 2507-2518. https://doi.org/10.1089/neu.2017.5606

[50] Yang, J., Xiong, L.L., Wang, Y.C., *et al*. (2018) Oligodendrocyte Precursor Cell Transplantation Promotes Functional Recovery Following Contusive Spinal Cord Injury in Rats and Is Associated with Altered microRNA Expression. *Molecular Medicine Reports*, **17**, 771-782. https://doi.org/10.3892/mmr.2017.7957

[51] Jin, M.C., Medress, Z.A., Azad, T.D., *et al*. (2019) Stem Cell Therapies for Acute Spinal Cord Injury in Humans: A Review. *Neurosurgical Focus*, **46**, E10. https://doi.org/10.3171/2018.12.FOCUS18602

[52] Yao, Z.F., Wang, Y., Lin, Y.H., *et al*. (2017) Transplantation of PDGF-AA-Overexpressing Oligodendrocyte Precursor Cells Promotes Recovery in Rat Following Spinal Cord Injury. *Frontiers in Cellular Neuroscience*, **11**, Article No. 79. https://doi.org/10.3389/fncel.2017.00079

[53] Wilkins, A., Majed, H., Layfield, R., *et al*. (2003) Oligodendrocytes Promote Neuronal Survival and Axonal Length by Distinct Intracellular Mechanisms: A Novel Role for Oligodendrocyte-Derived Glial Cell Line-Derived Neurotrophic Factor. *Journal of Neuroscience*, **23**, 4967-4974. https://doi.org/10.1523/JNEUROSCI.23-12-04967.2003

[54] El Waly, B., Cayre, M. and Durbec, P. (2018) Promoting Myelin Repair through *in Vivo* Neuroblast Reprogramming.

Stem Cell Reports, **10**, 1492-1504. https://doi.org/10.1016/j.stemcr.2018.02.015

[55] Ding, Z., Dai, C., Zhong, L., *et al*. (2021) Neuregulin-1 Converts Reactive Astrocytes Toward Oligodendrocyte Lineage Cells via Upregulating the PI3K-AKT-mTOR Pathway to Repair Spinal Cord Injury. *Biomedicine & Pharmacotherapy*, **134**, Article ID: 111168. https://doi.org/10.1016/j.biopha.2020.111168

[56] Pouya, A., Rassouli, H., Rezaei-Larijani, M., *et al*. (2020) SOX2 Protein Transduction Directly Converts Human Fibroblasts into Oligodendrocyte-Like Cells. *Biochemical and Biophysical Research Communications*. https://doi.org/10.1016/j.bbrc.2020.02.047

[57] Xu, Y., Zhou, J., Liu, C., *et al*. (2021) Understanding the Role of Tissue-Specific Decellularized Spinal Cord Matrix Hydrogel for Neural Stem/Progenitor Cell Microenvironment Reconstruction and Spinal Cord Injury. *Biomaterials*, **268**, Article ID: 120596. https://doi.org/10.1016/j.biomaterials.2020.120596

[58] Zarepour, A., Hooshmand, S., Gökmen, A., *et al*. (2021) Spinal Cord Injury Management through the Combination of Stem Cells and Implantable 3D Bioprinted Platforms. *Cells*, **10**, Article No. 3189. https://doi.org/10.3390/cells10113189

[59] Li, J., Ji, Z., Wang, Y., *et al*. (2022) Human Adipose-Derived Stem Cells Combined with Nano-Hydrogel Promote Functional Recovery after Spinal Cord Injury in Rats. *Biology* (*Basel*), **11**, Article No. 781. https://doi.org/10.3390/biology11050781

[60] Liu, X., Hao, M., Chen, Z., *et al*. (2021) 3D Bioprinted Neural Tissue Constructs for Spinal Cord Injury Repair. *Biomaterials*, **272**, Article ID: 120771. https://doi.org/10.1016/j.biomaterials.2021.120771

[61] Joung, D., Truong, V., Neitzke, C.C., *et al*. (2018) 3D Printed Stem-Cell Derived Neural Progenitors Generate Spinal Cord Scaffolds. *Advanced Functional Materials*, **28**, Article ID: 1801850. https://doi.org/10.1002/adfm.201801850

[62] Nazari, B., Namjoo, Z., Moradi, F., *et al*. (2021) miR-219 Overexpressing Oligodendrocyte Progenitor Cells for Treating Compression Spinal Cord Injury. *Metabolic Brain Disease*, **36**, 1069-1077. https://doi.org/10.1007/s11011-021-00701-y

[63] Bai, G., Jiang, L., Meng, P., *et al*. (2021) LncRNA Neat1 Promotes Regeneration after Spinal Cord Injury by Targeting miR-29b. *Journal of Molecular Neuroscience*, **71**, 1174-1184. https://doi.org/10.1007/s12031-020-01740-3

[64] Li, F., Zhou, M.W., Liu, N., *et al*. (2019) MicroRNA-219 Inhibits Proliferation and Induces Differentiation of Oligodendrocyte Precursor Cells after Contusion Spinal Cord Injury in Rats. *Neural Plasticity*, **2019**, Article ID: 9610687. https://doi.org/10.1155/2019/9610687

[65] Manley, N.C., Priest, C.A., Denham, J., *et al*. (2017) Human Embryonic Stem Cell-Derived Oligodendrocyte Progenitor Cells: Preclinical Efficacy and Safety in Cervical Spinal Cord Injury. *Stem Cells Translational Medicine*, **6**, 1917-1929. https://doi.org/10.1002/sctm.17-0065

[66] Bradbury, E.J. and Burnside, E.R. (2019) Moving beyond the Glial Scar for Spinal Cord Repair. *Nature Communications*, **10**, Article No. 3879. https://doi.org/10.1038/s41467-019-11707-7

[67] Spaas, J., Van Veggel, L., Schepers, M., *et al*. (2021) Oxidative Stress and Impaired Oligodendrocyte Precursor Cell Differentiation in Neurological Disorders. *Cellular and Molecular Life Sciences*, **78**, 4615-4637. https://doi.org/10.1007/s00018-021-03802-0