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缺血性脑卒中与生物标志物的相关性研究

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摘 要

近年来研究发现生物标志物可通过神经保护、神经修复、抗炎等方式对缺血性脑卒中的发生、发展及预后造成影响。了解各生物标志物在缺血性脑卒中中的表达变化及潜在作用，为缺血性脑卒中的防治及预后提供新的方向。

关键词

缺血性脑卒中，炎症反应，生物标志物，脑血管疾病

Correlation between Biomarkers and Ischemic Stroke

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Abstract

In recent years, studies have found that biomarkers can affect the occurrence, development and prognosis of ischemic stroke through neuroprotection, nerve repair and other means. Understanding the expression changes and potential role of each biomarker in ischemic stroke, provides a new direction for the prevention, treatment and prognosis of ischemic stroke.

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Keywords

Ischemic Stroke, Inflammatory Reaction, Biomarker, Cerebrovascular Disease

1. 引言

缺血性脑卒中是一类由于脑血管病变所致脑内血液供应不足，继而出现血管供应部位的脑组织坏死和相应的神经功能缺损，并伴各类脑细胞不同程度损伤的临床综合征，是较为重要的血管事件，也是神经系统疾病中主要的致残和致死性疾病。由于缺血性脑卒中常导致患者终身残疾的疾病特点，以及该病的发病率和患病率持续增加，这一现象成为家庭和社会的巨大负担。2019 全球疾病负担组于近期公布的最新疾病负担调查结果显示，卒中的疾病负担已从第五位上升至第三位[1]，此外，流行病学调查分析显示：中国属于全球卒中年龄标化发病率较高的国家，且中国的死亡率和卒中伤残调整生命年仍均处于中等水平[2]，未来我国仍持续面临着卒中的预防、治疗、康复等多方面的挑战。因此，对于该疾病我们应采取以预防为主的态度，减少疾病的发生。大量研究表明，该疾病的发病过程中有多种生物标志物参与炎症反应，生物标志物的浓度可影响炎症反应的程度，炎症反应程度可直接影响脑损伤程度。本综述旨在讨论研究多种生物标志物与缺血性脑卒中的关系。

2. 褪黑素(Melatonin)

褪黑素是一种神经激素，由松果体分泌，研究表明，除改善睡眠，延缓衰老等作用外，在缺血性脑卒中时还可表现出强有力的抗炎反应。首先可减少卒中后的炎症反应、脑水肿和脑血屏障通透性[3]，并抑制卒中后白细胞外渗到大脑区域；其次可降低凋亡率，增加神经元细胞的存活率，以维持大脑的神经功能[4]。在正常情况下，自由基和抗氧化酶的产生保持在微妙的平衡，由于缺血、缺氧等原因造成脑损伤，使中枢神经系统的内源性抗氧化系统能力减弱，最终导致氧化应激损伤和细胞凋亡[5]。脑缺血诱导的氧化应激、谷氨酸盐应激、自由基形成等都会导致神经细胞受损[6]。褪黑素的代谢产物也能作为自由基清除剂来改善神经炎症和加速脑组织恢复[7]，减少脑细胞氧化应激，提高神经细胞的活性，并改善认知和行为能力[8] [9] [10]，同时减轻抗兴奋性毒性和抗线粒体功能障碍。褪黑素有效地降低大脑皮质和海马中促炎细胞因子的水平[11]，降低胶质细胞在反应中的激活程度[12]，通过褪黑素受体将胶质细胞转化为在缺血脑组织中的有利形式[7]，还可上调抗氧化蛋白，降低活性氧和过氧化脂质浓度，增加细胞活力和增殖能力。褪黑素还能通过另一机制有效的抑制细胞凋亡，并完全改善突触损伤、记忆丧失、神经炎症和神经退化[13]。在既往的临床前和临床研究发现，褪黑素被证明能有效地减少血脂指标，趋于正常，并且可延缓血管病变进程，很大程度上减少该疾病的发生。褪黑素的具体影响机制尚未完全了解，但该激素的神经保护及改善预后的作用的肯定的，可为缺血性卒中的治疗提供新的靶点。

3. 脑源性神经营养因子(BDNF)

脑源性神经营养因子(BDNF)是一种对神经系统的生长和分化至关重要的蛋白质[14]，不仅如此，还可有效防止细胞凋亡[15]，促进现有神经元的存活以及促进神经发生[16]，并调节皮层兴奋性[17]。BDNF

作用涉及诸多方面，如：突触成熟、突触可塑性以及正常认知功能的维持。神经突触的再生和神经发生是脑损伤后大脑再生能力的标志，研究表明，BDNF 可促进卒中后康复的神经突触再生[18]，对其他生长因子的表达和新生血管的生成具有促进作用[19]。JR 等人经免疫测定实验证实，静脉注射后 4 小时，BDNF 在卒中病灶中的水平显著增加[20]，以及在调节凋亡细胞死亡中充当重要的神经保护因子[21]，并且通过星形胶质细胞核因子——E2 的昼夜节律来保护神经元[22]。研究发现 BDNF 的前体和神经保护功能主要来自于两种由 TrkB 激活的信号通路，它们都可通过调节转录因子的水平和活性在细胞周期、分裂和存活中发挥重要作用[23]，FH 等人观察到 BDNF 还可通过高亲和力的激动性抗体抑制神经元细胞凋亡和坏死，在大鼠实验模型中减少梗塞面积并促进功能恢复[24]。另有研究表明 BDNF 缺乏可能与更严重的卒中机制密切相关[25]。因此，BDNF 对缺血性卒中的病情和预后改善是至关重要的。

4. 粒细胞集落刺激因子(G-CSF)

粒细胞集落刺激因子(G-CSF)是细胞造血生长因子家族的一种糖苷配基蛋白，此因子具有多种神经保护作用：抗凋亡活性、神经原性、免疫调节作用以及血管生成能力[26]，还可通过其多效性作用激活干细胞存活、神经生成、抗凋亡和抗炎作用[27]。G-CSF 是具有双重活性的内源性配体，有利于减轻神经元变性和增加缺血后的神经可塑性，通过抑制内质网应激和线粒体应激对受损神经元发挥神经保护作用，并通过减少促凋亡蛋白和增加抗凋亡蛋白来维持细胞内环境稳定[28]。Huang 等人的一项研究的数据表明，给予 G-CSF 治疗后的缺血性脑卒中患者的改良 Barthel 指数量表评分有所改善[29]。在既往的动物实验研究中证明 G-CSF 蛋白在缺氧缺血动物模型中的神经元保护作用部分是由于抗炎细胞因子白细胞介素-10 的表达水平升高而表达其抗炎作用[30]。G-CSF 改善神经功能还可通过减轻缺血性卒中后血脑屏障破坏[31]，有利于内皮细胞的迁徙和增生[32]，从而增加中风后新血管的形成，增加神经营养因子的表达。ML W 等人研究表明，G-CSF 使患者获得了更好的神经系统量表评分、更好的运动协调恢复以及梗死体积显著减少[33]，故该因子可作为保护性因子进行更深入的研究。

5. 微小核糖核酸(microRNA)

微小核糖核酸(简称 miRNA)，是一种单链核糖核酸分子[34]，主要作用机制有氧化应激、线粒体障碍、卒中后炎症性肿胀、神经原性损伤和细胞兴奋性毒性等[35]。在疾病的发展过程中，血脑屏障(BBB)受损也是一个重要的病理特征。MicroRNA-126 (miR-126)可维持 BBB 的完整性，还可以减轻卒中后的 BBB 破坏、脑水肿和神经元损伤[36]。在实验模型的急性期缺血小鼠脑内 miR-126-3p/-5p 的过度表达降低了促炎细胞因子和粘附分子的释放，可明显减轻缺血性卒中后 BBB 的破坏，保护 BBB 的完整性[37]。K X 等人研究表明，miR-874-3p 的过度表达可以促进缺血性中风小鼠的血管生成、抑制炎症因子的释放和脑组织凋亡[38]。另一项动物研究中，miR-384-5p、血管内皮生长因子和 CD31 表达减少，脑梗死面积和脑组织中细胞凋亡明显增加，从上述研究结果中可以假设 miR-384-5p 降低了实验小鼠模型内的核固缩和坏死脑神经细胞的数量，帮助增强小鼠模型的血管发生并减少细胞凋亡[39]。此外有研究揭示 miR-874-3p 的表达与缺血性卒中发生呈负相关[40]，CF 等人研究也表明 miR-451 对缺血性脑卒中患者和脑缺血及缺血后再灌注损伤的小鼠模型具有潜在的神经保护作用[41]。更有大量研究证据表明，BBB 是缺血性卒中的新治疗靶点，而微小核糖核酸在抑制 BBB 受损、维持 BBB 完整及中枢神经系统稳态中起着重要作用，因此 miRNA 在缺血性脑卒中的治疗和改善预后中具有重要的临床价值。

6. 半乳糖凝集素-3 (Gal-3)

半乳糖凝集素-3 (Gal-3)是凝集素家族中的一种碳水化合物结合蛋白[42] [43]，在细胞内外促进增殖并

参与多种生理过程。在胞外，Gal-3 与细胞外基质(ECM)化合物结合，控制细胞－细胞粘附，并与质膜受体相互作用，并触发细胞内事件；在胞内，Gal-3 存在于胞浆和细胞核中；在胞质，Gal-3 可发挥延缓细胞凋亡的作用，并通过信号通路调控细胞的繁殖和分化[44] [45]；在胞核，Gal-3 在前体 mRNA 剪接和转录调控[43]中起重要作用，且研究发现，神经细胞如小胶质细胞、神经元细胞、星形胶质细胞、内皮细胞和少突胶质细胞都能产生 Gal-3 [45]。Rahimian R 等人最近对 Gal 在神经炎症、神经退行性变、创伤性脑损伤和缺血性脑损伤中的作用进行了综述，表明Gal-3则可能因疾病情况而有害或有益[46]。缺血发生后，Gal-3 在受损脑组织中由小胶质细胞释放，释放的 Gal-3 通过与 Toll 样受体-4 结合而促进小胶质细胞的激活，导致炎性反应加剧[47]。既往研究表明，Gal-3 与高密度脂蛋白(HDL-C)呈负相关，提示 Gal-3 介导的急性缺血性卒中调节可能与血脂异常和炎症有关[48]。在一项纳入 2970 名急性缺血性卒中患者的前瞻性队列研究中，观察到血清中 Gal-3 水平升高，导致高密度脂蛋白水平降低，因此加重神经炎症反应和氧化应激。Wang A 等研究人员证实，高水平的血清 Gal-3 与卒中后死亡或严重残疾风险增加独立相关，提示 Gal-3 可能在缺血性卒中预后不良中具有预后价值[49]，细胞受到炎症刺激后可分泌大量的 Gal-3 影响疾病进展[50]，Gal-3 也参与急性炎症反应过程，包括单核/巨噬细胞的化学吸引[51]、中性粒细胞清除[52]等。上述研究表明，Gal-3 在急性缺血性卒中发病进展及预后中发挥重要影响，可通过检测该因子水平并加以控制。

7. 核苷酸结合寡聚化结构域样受体蛋白 3 (NLRP3)

核苷酸结合寡聚化结构域样受体蛋白 3(NLRP3)是由三种蛋白组成的一种炎症小体，包括 NLR 受体蛋白、ASC 接头蛋白和 caspase-1 效应蛋白。在 J L 等人的研究中表明，NLRP3 炎症体成分的基因/蛋白质的变化可以调节 NLRP3 炎症体介导的炎症反应，可影响缺血性卒中的发病率和预后，该实验研究发现携带 NLRP3 杂合子的男性更易患缺血性脑卒中[53]。既往 Lammerding L 等人研究表明，NLRP3 主要在神经元中表达[54]，引发神经元细胞损伤、脑水肿和神经功能障碍[55]。NLRP3 的激活被认为是两阶段的过程，第一个阶段被称为启动阶段，第二阶段是激活阶段。如钾离子与氯离子流出、钠离子流入、Ca2+动员、溶酶体损伤、活性氧产生和线粒体功能障碍均可导致 NLRP3 炎症体的组装[56]，引起白介素-23/白介素-17 轴的损伤，从而加重脑组织的缺血再灌注损伤[57]。因此得知，NLRP3 炎症小体是炎症反应的关键炎性介质。另有研究表明，NLRP3 减少可改善局灶性缺血性卒中后小鼠的神经血管损伤，并减轻血脑屏障损伤和梗死体积[58]。Lammerding L 等人研究表明也发现，在短暂性局灶性缺血大鼠模型中，脑缺血后降低NLRP3的表达，可抑制炎症反应，减少梗死体积[54]。此外，牛角苷元预处理可通过抑制NLRP3的水平，激活信号传导通路，从而降低神经评分、梗死体积和脑含水量[59]，XF H 等人的一篇文章提到，既往的缺血性卒中的实验模型中，NLRP3 缺乏已被证明可以改善神经血管损害[60]。结合上述大量研究可知，多种药物通过抑制 NLRP3 通路对缺血性脑卒中模型的神经功能障碍、梗死体积和脑水肿有积极作用。一方面，NLRP3 炎症小体的发现为研究缺血性脑卒中提供了新的途径；另一方面，调控 NLRP3 的组装、表达和激活等多种水平的炎症反应，可能为保护半暗带组织和预防卒中后神经功能恶化提供新的想法[58]。故此，认为 NLRP3 炎症小体在缺血性卒中的作用较为重要，值得进一步深入研究。

8. 结语

缺血性脑卒中是目前全球第一大致死性疾病，其发病率和死亡率均呈逐年上升趋势，由于缺血性脑卒中的疾病特征，多数患者经过临床抢救及治疗后，仍遗留较为严重的卒中后遗症，现阶段缺血性脑卒中的治疗手段又存在很大的局限性，溶栓治疗的窗口期、溶栓药物的禁忌症及溶栓后的缺血再灌注损伤使疾病的治疗在各方面均受到制约。所以近年来，通过检验生物标记物来预防和监测疾病发生的方法受

到重视。本综述中描述的生物标记物可以为将来的缺血性卒中疾病预测新的预防和治疗靶点，为疾病的诊治奠定基础，在一定程度上减少缺血性脑卒中的发生，减轻患者痛苦。

参考文献

[1] GBD 2019 Diseases and Injuries Collaborators (2020) Global Burden of 369 Diseases and Injuries in 204 Countries and Territories, 1990-2019: A Systematic Analysis for the Global Burden of Disease Study 2019. *Lancet*, **396**, 1204-1222. https://doi.org/10.1016/S0140-6736(20)30925-9

[2] Krishnamurthi, R.V., Ikeda, T. and Feigin, V.L. (2020) Global, Regional and Country-Specific Burden of Ischaemic Stroke, Intracerebral Haemorrhage and Subarachnoid Haemorrhage: A Systematic Analysis of the Global Burden of Disease Study 2017. *Neuroepidemiology*, **54**, 171-179. https://doi.org/10.1159/000506396

[3] Kilic, U., Caglayan, A.B., Beker, M.C., Gunal, M.Y., Caglayan, B., Yalcin, E., *et al*. (2017) Particular Phosphorylation of PI3K/Akt on Thr308 via PDK-1 and PTEN Mediates Melatonin's Neuroprotective Activity after Focal Cerebral Ischemia in Mice. *Redox Biology*, **12**, 657-665. https://doi.org/10.1016/j.redox.2017.04.006

[4] Yawoot, N., Govitrapong, P., Tocharus, C. and Tocharus, J. (2020) Ischemic Stroke, Obesity, and the Anti-Inflammatory Role of Melatonin. *BioFactors* (Oxford, England), **47**, 41-58. https://doi.org/10.1002/biof.1690

[5] Kılıç, E., Çağlayan, B. and Caglar Beker, M. (2020) Physiological and Pharmacological Roles of Melatonin in the Pathophysiological Components of Cellular Injury after Ischemic Stroke. *Turkish Journal of Medical Sciences*, **50**, 1655-1664. https://doi.org/10.3906/sag-2008-32

[6] Zhao, Y., Xiao, M., He, W., Cai, Z., Tang, Z. and Tian, F. (2015) Minocycline Upregulates Cyclic AMP Response Element Binding Protein and Brain-Derived Neurotrophic Factor in the Hippocampus of Cerebral Ischemia Rats and Improves Behavioral Deficits. *Neuropsychiatric Disease and Treatment*, **11**, 507-516. https://doi.org/10.2147/NDT.S73836

[7] Sadanandan, N., Cozene, B., Cho, J., Park, Y.J., Saft, M., Gonzales-Portillo, B., *et al*. (2020) Melatonin—A Potent Therapeutic for Stroke and Stroke-Related Dementia. *Antioxidants*, **9**, Article No. 672. https://doi.org/10.3390/antiox9080672

[8] Al Dera, H., Alassiri, M., Eleawa, S.M., AlKhateeb, M.A., Hussein, A.M., Dallak, M., *et al*. (2019) Melatonin Improves Memory Deficits in Rats with Cerebral Hypoperfusion, Possibly, Through Decreasing the Expression of Small-Conductance Ca^{2+}-Activated K^{+} Channels. *Neurochemical Research*, **44**, 1851-1868. https://doi.org/10.1007/s11064-019-02820-6

[9] Bin-Jaliah, I. and Sakr, H. (2018) Melatonin Ameliorates Brain Oxidative Stress and Upregulates Senescence Marker Protein-30 and Osteopontin in a Rat Model of Vascular Dementia. *Physiology International*, **105**, 38-52. https://doi.org/10.1556/2060.105.2018.1.1

[10] De Butte, M. and Gieseking, B. (2020) Efficacy of a Low-Dose Melatonin Pretreatment in Protecting against the Neurobehavioral Consequences of Chronic Hypoperfusion in Middle-Aged Female Rats. *Behavioural Brain Research*, **377**, Article ID: 112257. https://doi.org/10.1016/j.bbr.2019.112257

[11] Rancan, L., Paredes, S.D., García, C., González, P., Rodríguez-Bobada, C., Calvo-Soto, M., *et al*. (2018) Comparison of the Effect of Melatonin Treatment Before and after Brain Ischemic Injury in the Inflammatory and Apoptotic Response in Aged Rats. *International Journal of Molecular Sciences*, **19**, Article No. 2097. https://doi.org/10.3390/ijms19072097

[12] Azedi, F., Mehrpour, M., Talebi, S., Zendedel, A., Kazemnejad, S., Mousavizadeh, K., *et al*. (2019) Melatonin Regulates Neuroinflammation Ischemic Stroke Damage through Interactions with Microglia in Reperfusion Phase. *Brain Research*, **1723**, Article ID: 146401. https://doi.org/10.1016/j.brainres.2019.146401

[13] Muhammad, T., Ali, T., Ikram, M., Khan, A., Alam, S.I. and Kim, M.O. (2019) Melatonin Rescue Oxidative Stress-Mediated Neuroinflammation/Neurodegeneration and Memory Impairment in Scopolamine-Induced Amnesia Mice Model. *Journal of Neuroimmune Pharmacology*, **14**, 278-294. https://doi.org/10.1007/s11481-018-9824-3

[14] Zhang, E. and Liao, P. (2020) Brain-Derived Neurotrophic Factor and Post-Stroke Depression. *Journal of Neuroscience Research*, **98**, 537-548. https://doi.org/10.1002/jnr.24510

[15] Wang, X.M., Zhang, Y.G., Li, A.L., Long, Z.H., Wang, D., Li, X.X., *et al*. (2016) Expressions of Serum Inflammatory Cytokines and Their Relationship with Cerebral Edema in Patients with Acute Basal Ganglia Hemorrhage. *European Review for Medical and Pharmacological Sciences*, **20**, 2868-2871.

[16] Eyileten, C., Sharif, L., Wicik, Z., Jakubik, D., Jarosz-Popek, J., Soplinska, A., *et al*. (2021) The Relation of the Brain-Derived Neurotrophic Factor with MicroRNAs in Neurodegenerative Diseases and Ischemic Stroke. *Molecular Neurobiology*, **58**, 329-347. https://doi.org/10.1007/s12035-020-02101-2

[17] Popova, N.K., Ilchibaeva, T.V. and Naumenko, V.S. (2017) Neurotrophic Factors (BDNF and GDNF) and the Serotonergic System of the Brain. *Biochemistry* (*Moscow*), **82**, 308-317. https://doi.org/10.1134/S0006297917030099

[18] Liu, W., Wang, X., O'Connor, M., Wang, G. and Han, F. (2020) Brain-Derived Neurotrophic Factor and Its Potential Therapeutic Role in Stroke Comorbidities. *Neural Plasticity*, **2020**, Article ID: 1969482. https://doi.org/10.1155/2020/1969482

[19] Zhang, X., Zhou, Y., Li, H., Wang, R., Yang, D., Li, B., *et al*. (2018) Intravenous Administration of DPSCs and BDNF Improves Neurological Performance in Rats with Focal Cerebral Ischemia. *International Journal of Molecular Medicine*, **41**, 3185-3194. https://doi.org/10.3892/ijmm.2018.3517

[20] Ramos-Cejudo, J., Gutiérrez-Fernández, M., Otero-Ortega, L., Rodríguez-Frutos, B., Fuentes, B., Vallejo-Cremades, M.T., *et al*. (2015) Brain-Derived Neurotrophic Factor Administration Mediated Oligodendrocyte Differentiation and Myelin Formation in Subcortical Ischemic Stroke. *Stroke*, **46**, 221-228. https://doi.org/10.1161/STROKEAHA.114.006692

[21] Kalinichenko, S.G., Matveeva, N.Y. and Korobtsov, A.V. (2020) Brain-Derived Neurotrophic Factor (BDNF) As a Regulator of Apoptosis under Conditions of Focal Experimental Stroke. *Bulletin of Experimental Biology and Medicine*, **169**, 701-706. https://doi.org/10.1007/s10517-020-04959-7

[22] Ishii, T., Warabi, E. and Mann, G.E. (2019) Circadian Control of BDNF-Mediated Nrf2 Activation in Astrocytes Protects Dopaminergic Neurons from Ferroptosis. *Free Radical Biology & Medicine*, **133**, 169-178. https://doi.org/10.1016/j.freeradbiomed.2018.09.002

[23] Zhao, H., Alam, A., San, C.Y., Eguchi, S., Chen, Q., Lian, Q., *et al*. (2017) Molecular Mechanisms of Brain-Derived Neurotrophic Factor in Neuro-Protection: Recent Developments. *Brain Research*, **1665**, 1-21. https://doi.org/10.1016/j.brainres.2017.03.029

[24] Han, F., Guan, X., Guo, W. and Lu, B. (2019) Therapeutic Potential of a TrkB Agonistic Antibody for Ischemic Brain Injury. *Neurobiology of Disease*, **127**, 570-581. https://doi.org/10.1016/j.nbd.2019.04.009

[25] Miranda, M., Morici, J.F., Zanoni, M.B. and Bekinschtein, P. (2019) Brain-Derived Neurotrophic Factor: A Key Molecule for Memory in the Healthy and the Pathological Brain. *Frontiers in Cellular Neuroscience*, **13**, Article No. 363. https://doi.org/10.3389/fncel.2019.00363

[26] Menzie-Suderam, J.M., Mohammad-Gharibani, P., Modi, J., Ma, Z., Tao, R., Prentice, H., *et al*. (2018) Granulocyte-Colony Stimulating Factor Protects against Endoplasmic Reticulum Stress in an Experimental Model of Stroke. *Brain Research*, **1682**, 1-13. https://doi.org/10.1016/j.brainres.2017.12.022

[27] Wu, M.Y., Yiang, G.T., Liao, W.T., Tsai, A.P., Cheng, Y.L., Cheng, P.W., *et al*. (2018) Current Mechanistic Concepts in Ischemia and Reperfusion Injury. *Cellular Physiology and Biochemistry*, **46**, 1650-1667. https://doi.org/10.1159/000489241

[28] Modi, J., Menzie-Suderam, J., Xu, H., Trujillo, P., Medley, K., Marshall, M.L., *et al*. (2020) Mode of Action of Granulocyte-Colony Stimulating Factor (G-CSF) as a Novel Therapy for Stroke in a Mouse Model. *Journal of Biomedical Science*, **27**, Article No. 19. https://doi.org/10.1186/s12929-019-0597-7

[29] Huang, X., Liu, Y., Bai, S., Peng, L., Zhang, B. and Lu, H. (2017) Granulocyte Colony Stimulating Factor Therapy for Stroke: A Pairwise Meta-Analysis of Randomized Controlled Trial. *PLoS ONE*, **12**, e175774. https://doi.org/10.1371/journal.pone.0175774

[30] Dumbuya, J.S., Chen, L., Shu, S.Y., Ma, L., Luo, W., Li, F., *et al*. (2020) G-CSF Attenuates Neuroinflammation and Neuronal Apoptosis via the mTOR/p70SK6 Signaling Pathway in Neonatal Hypoxia-Ischemia Rat Model. *Brain Research*, **1739**, Article ID: 146817. https://doi.org/10.1016/j.brainres.2020.146817

[31] Menzie-Suderam, J.M., Modi, J., Xu, H., Bent, A., Trujillo, P., Medley, K., *et al*. (2020) Granulocyte-Colony Stimulating Factor Gene Therapy as a Novel Therapeutics for Stroke in a Mouse Model. *Journal of Biomedical Science*, **27**, Article No. 99. https://doi.org/10.1186/s12929-020-00692-5

[32] Ping, S., Qiu, X., Gonzalez-Toledo, M.E., Liu, X. and Zhao, L.R. (2018) Stem Cell Factor in Combination with Granulocyte Colony-Stimulating Factor Reduces Cerebral Capillary Thrombosis in a Mouse Model of CADASIL. *Cell Transplantation*, **27**, 637-647. https://doi.org/10.1177%2F0963689718766460

[33] Wang, M.-L., Zhang, L.-X., Wei, J.-J., Li, L.-L., Zhong, W.-Z., Lin, X.-J., *et al*. (2020) Granulocyte Colony-Stimulating Factor and Stromal Cell-Derived Factor-1 Combination Therapy: A More Effective Treatment for Cerebral Ischemic Stroke. *International Journal of Stroke*, **15**, 743-754. https://doi.org/10.1177%2F1747493019879666

[34] Kabekkodu, S.P., Shukla, V., Varghese, V.K., D'Souza, J., Chakrabarty, S. and Satyamoorthy, K. (2018) Clustered miRNAs and Their Role in Biological Functions and Diseases. *Biological Reviews*, **93**, 1955-1986. https://doi.org/10.1111/brv.12428

[35] Li, P., Stetler, R.A., Leak, R.K., Shi, Y., Li, Y., Yu, W., *et al*. (2018) Oxidative Stress and DNA Damage after Cerebral Ischemia: Potential Therapeutic Targets to Repair the Genome and Improve Stroke Recovery. *Neuropharmacology*,

134, 208-217. https://doi.org/10.1016/j.neuropharm.2017.11.011

[36] Xi, T., Jin, F., Zhu, Y., Wang, J., Tang, L., Wang, Y., *et al*. (2017) MicroRNA-126-3p Attenuates Blood-Brain Barrier Disruption, Cerebral Edema and Neuronal Injury Following Intracerebral Hemorrhage by Regulating PIK3R2 and Akt. *Biochemical and Biophysical Research Communications*, **494**, 144-151. https://doi.org/10.1016/j.bbrc.2017.10.064

[37] Pan, J., Qu. M., Li, Y., Wang, L., Zhang, L., Wang, Y., *et al*. (2020) MicroRNA-126-3p/-5p Overexpression Attenuates Blood-Brain Barrier Disruption in a Mouse Model of Middle Cerebral Artery Occlusion. *Stroke*, **51**, 619-627. https://doi.org/10.1161/STROKEAHA.119.027531

[38] Xie, K., Cai, Y., Yang, P., Du, F. and Wu, K. (2020) Upregulating MicroRNA-874-3p Inhibits CXCL12 Expression to Promote Angiogenesis and Suppress Inflammatory Response in Ischemic Stroke. *American Journal of Physiology-Cell physiology*, **319**, C579-C588. https://doi.org/10.1152/ajpcell.00001.2020

[39] Fan, J., Xu, W., Nan, S., Chang, M. and Zhang, Y. (2020) MicroRNA-384-5p Promotes Endothelial Progenitor Cell Proliferation and Angiogenesis in Cerebral Ischemic Stroke through the Delta-Likeligand 4-Mediated Notch Signaling Pathway. *Cerebrovascular Diseases*, **49**, 39-54. https://doi.org/10.1159/000503950

[40] Yan, Y., Song, X., Li, Z., Zhang, J., Ren, J., Wu, J., *et al*. (2017) Elevated Levels of Granzyme B Correlated with miR-874-3p Downregulation in Patients with Acute Myocardial Infarction. *Biomarkers in Medicine*, **11**, 761-767. https://doi.org/10.2217/bmm-2017-0144

[41] Fu, C., Chen, S., Cai, N., Liu, Z., Wang, P. and Zhao, J. (2019) Potential Neuroprotective Effect of miR-451 against Cerebral Ischemia/Reperfusion Injury in Stroke Patients and a Mouse Model. *World Neurosurgery*, **130**, e54-e61. https://doi.org/10.1016/j.wneu.2019.05.194

[42] Dong, R., Zhang, M., Hu, Q., Zheng, S., Soh, A., Zheng, Y., *et al*. (2018) Galectin-3 as a Novel Biomarker for Disease Diagnosis and a Target for Therapy (Review). *International Journal of Molecular Medicine*, **41**, 599-614. https://doi.org/10.3892/ijmm.2017.3311

[43] Thomas, L. and Pasquini, L.A. (2018) Galectin-3-Mediated Glial Crosstalk Drives Oligodendrocyte Differentiation and (Re)myelination. *Frontiers in Cellular Neuroscience*, **12**, Article No. 297. https://doi.org/10.3389/fncel.2018.00297

[44] Kariya, Y., Oyama, M., Hashimoto, Y., Gu, J. and Kariya, Y. (2018) β4-Integrin/PI3K Signaling Promotes Tumor Progression through the Galectin-3—*N*-Glycan Complex. *Molecular Cancer Research*, **16**, 1024-1034. https://doi.org/10.1158/1541-7786.MCR-17-0365

[45] Thomas, L. and Pasquini, L.A. (2019) Extracellular Galectin-3 Induces Accelerated Oligodendroglial Differentiation through Changes in Signaling Pathways and Cytoskeleton Dynamics. *Molecular Neurobiology*, **56**, 336-349. https://doi.org/10.1007/s12035-018-1089-6

[46] Rahimian, R., Béland, L.C. and Kriz, J. (2018) Galectin-3: Mediator of Microglia Responses in Injured Brain. *Drug Discovery Today*, **23** 375-381. https://doi.org/10.1016/j.drudis.2017.11.004

[47] Burguillos, M.A., Svensson, M., Schulte, T., Boza-Serrano, A., Garcia-Quintanilla, A., Kavanagh, E., *et al*. (2015) Microglia-Secreted Galectin-3 Acts as a Toll-like Receptor 4 Ligand and Contributes to Microglial Activation. *Cell Reports*, **10**, 1626-1638. https://doi.org/10.1016/j.celrep.2015.02.012

[48] Winter, M.P., Wiesbauer, F., Alimohammadi, A., Blessberger, H., Pavo, N., Schillinger, M., *et al*. (2016) Soluble Galectin-3 Is Associated with Premature Myocardial Infarction. *European Journal of Clinical Investigation*, **46**, 386-391. https://doi.org/10.1111/eci.12605

[49] Wang, A., Zhong, C., Zhu, Z., Xu, T., Peng, Y., Xu, T., *et al*. (2018) Serum Galectin-3 and Poor Outcomes among Patients with Acute Ischemic Stroke. *Stroke*, **49**, 211-214. https://doi.org/10.1161/STROKEAHA.117.019084

[50] Gao, Z., Liu, Z., Wang, R., Zheng, Y., Li, H. and Yang, L. (2020) Galectin-3 Is a Potential Mediator for Atherosclerosis. *Journal of Immunology Research*, **2020**, Article ID: 5284728. https://doi.org/10.1155/2020/5284728

[51] Subhash, V.V., Ling, S.S.M. and Ho, B. (2016) Extracellular Galectin-3 Counteracts Adhesion and Exhibits Chemoattraction in Helicobacter *Pylori*-Infected Gastric Cancer Cells. *Microbiology* (Reading, England), **162**, 1360-1366. https://doi.org/10.1099/mic.0.000322

[52] Wright, R.D., Souza, P.R., Flak, M.B., Thedchanamoorthy, P., Norling, L.V. and Cooper, D. (2017) Galectin-3-Null Mice Display Defective Neutrophil Clearance during Acute Inflammation. *Journal of Leukocyte Biology*, **101**, 717-726. https://doi.org/10.1189/jlb.3A0116-026RR

[53] Schoultz, I., Verma, D., Halfvarsson, J., Törkvist, L., Fredrikson, M., Sjöqvist, U., *et al*. (2020) Combined Polymorphisms in Genes Encoding the Inflammasome Components NLRP3 and CARD8 Confer Risk of Ischemic Stroke in Men. *Journal of Stroke and Cerebrovascular Diseases*, **29**, Article ID: 104874. https://doi.org/10.1016/j.jstrokecerebrovasdis.2020.104874

[54] Lammerding, L, Slowik, A., Johann, S., Beyer, C. and Zendedel, A. (2016) Poststroke Inflammasome Expression and Regulation in the Peri-Infarct Area by Gonadal Steroids after Transient Focal Ischemia in the Rat Brain. *Neuroendocrinology*, **103**, 460-475. https://doi.org/10.1159/000439435

[55] Minutoli, L., Puzzolo, D., Rinaldi, M., Irrera, N., Marini, H., Arcoraci, V., *et al*. (2016) ROS-Mediated NLRP3 Inflammasome Activation in Brain, Heart, Kidney, and Testis Ischemia/Reperfusion Injury. *Oxidative Medicine and Cellular Longevity*, **2016**, Article ID: 2183026. https://doi.org/10.1155/2016/2183026

[56] Kelley, N., Jeltema, D., Duan, Y. and He, Y. (2019) The NLRP3 Inflammasome: An Overview of Mechanisms of Activation and Regulation. *International Journal of Molecular Sciences*, **20**, Article No. 3328. https://doi.org/10.3390/ijms20133328

[57] Wang, H., Zhong, D., Chen, H., Jin, J., Liu, Q. and Li, G. (2019) NLRP3 Inflammasome Activates Interleukin-23/Interleukin-17 Axis during Ischaemia-Reperfusion Injury in Cerebral Ischaemia in Mice. *Life sciences*, **227**, 101-113. https://doi.org/10.1016/j.lfs.2019.04.031

[58] Feng, Y.-S., Tan, Z.-X., Wang, M.-M., Xing, Y., Dong, F. and Zhang, F. (2020) Inhibition of NLRP3 Inflammasome: A Prospective Target for the Treatment of Ischemic Stroke. *Frontiers in Cellular Neuroscience*, **14**, Article No. 155. https://doi.org/10.3389/fncel.2020.00155

[59] Zhang, S., Jiang, L., Che, F., Lu, Y., Xie, Z. and Wang, H. (2017) Arctigenin Attenuates Ischemic Stroke via SIRT1-Dependent Inhibition of NLRP3 Inflammasome. *Biochemical and Biophysical Research Communications*, **493**, 821-826. https://doi.org/10.1016/j.bbrc.2017.08.062

[60] He, X.F., Zeng, Y.X., Li, G., Feng, Y.K., Wu, C., Liang, F.Y., *et al*. (2020) Extracellular ASC Exacerbated the Recurrent Ischemic Stroke in an NLRP3-Dependent Manner. *Journal of Cerebral Blood Flow and Metabolism*, **40**, 1048-1060. https://doi.org/10.1177%2F0271678X19856226