Advances in Clinical Medicine 临床医学进展, 2021, 11(11), 5245-5251
Published Online November 2021 in Hans. http://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2021.1111774

Hans汉斯

炎症细胞释放物质对脑出血后血脑屏障的影响

郭　鑫[1]，张越林[2]

[1]西安医学院，陕西　西安
[2]陕西省人民医院，陕西　西安

收稿日期：2021年10月17日；录用日期：2021年11月7日；发布日期：2021年11月23日

摘　要

脑出血(Intracerebral hemorrhage, ICH)在脑卒中中是最严重的疾病之一，近年来发病率呈日益上升的趋势，且预后常常表现为严重的残疾或死亡，给人们的生活质量和社会发展带来了巨大的经济负担。常见的脑出血有高血压性脑出血、外伤性脑出血以及动脉瘤性脑出血三类。有研究表明，炎症可被视为脑出血总体预后的最重要指标之一。明确炎症细胞释放物质对脑出血预后的影响，采取一定的预防措施，改善预后，为临床治疗提供理论基础。

关键词

脑出血，血脑屏障，炎症细胞，预后

Effects of Substances Released from Inflammatory Cells on the Blood-Brain Barrier after Cerebral Hemorrhage

Xin Guo[1], Yuelin Zhang[2]

[1]Xi'an Medical University, Xi'an Shaanxi
[2]Shaanxi Provincial People's Hospital, Xi'an Shaanxi

Received: Oct. 17th, 2021; accepted: Nov. 7th, 2021; published: Nov. 23rd, 2021

Abstract

Intracerebral hemorrhage (ICH) is one of the most serious diseases of stroke. The incidence of which has been increasing in recent years, with a prognosis of severe disability or death and a huge economic burden on people's quality of life and social development. The three common types

文章引用: 郭鑫, 张越林. 炎症细胞释放物质对脑出血后血脑屏障的影响[J]. 临床医学进展, 2021, 11(11): 5245-5251.
DOI: 10.12677/acm.2021.1111774

of intracerebral hemorrhage are hypertensive cerebral hemorrhage, traumatic cerebral hemorrhage, and aneurysmal cerebral hemorrhage. It has been shown that inflammation can be considered one of the most important indicators of the overall prognosis of cerebral hemorrhage. Elucidating the effects of inflammatory cell-releasing substances on the prognosis of cerebral hemorrhage, and taking certain preventive measures to improve the prognosis, provide a theoretical basis for clinical treatment.

Keywords

Intracerebral Hemorrhage, Blood-Brain Barrier, Inflammatory Cells, Prognosis

1. 引言

ICH 作为最常见的脑血管疾病之一，每年在全球发病人数可达 200 万[1]，其发病率在我国为每年(60~80)/10 万，约占全部脑卒中的 20%~30%，其发病率在近年来呈现上升趋势。脑出血常常起病急，进展快，且常常伴有严重的后遗症。通过研究表明，脑出血继发性损伤(Secondary brain injury, SBI)较之原发性损伤对脑功能的影响更大且更为严重[2]，这也是人们认为影响脑出血预后最重要因素之一。继发性的损伤包括了炎症以及细胞死亡，且参与整个出血后的病理过程[3]。有人认为，氧化应激是调节 SBI 的一个重要因素[4]，特别是活性氧自由基(Reactive oxygen species, ROS)会导致氧化应激水平的增加，且可以明显破坏血脑屏障，进而影响脑损伤的严重程度与其病程进展[5]，此外，组织在氧化应激的作用下与原发性损伤都会引起炎症，且互为影响，引起炎症细胞释放物质，因此，出血后治疗炎症反应所带来的问题在病程中及预后中至关重要[6]。本研究对炎症细胞释放物(着重介绍基质金属蛋白酶、活性氧自由基、肿瘤坏死因子 α 与白细胞介素)对脑出血后血脑屏障的影响进行综述，为临床治疗提供相应的理论基础。

2. 炎症细胞释放物质对血脑屏障的影响

2.1. 基质金属蛋白酶(Matrix Metalloproteinases, MMPs)

MMPs 是由巨噬细胞、中性粒细胞、平滑肌细胞以及内皮细胞产生的一类锌内肽酶，其作用可以通过破坏细胞外的基质与其膜结构之间的联系，来破坏营养不良聚糖(Dystroglycan, DG)中的跨膜 β 亚基(β-DG) [7] [8]。从 Hawkins 等人的研究可以得出 DG 对于血脑屏障完整性起着重要的作用，随脑出血的发生会激活上述细胞，MMPs 合成会立即增加并分泌到细胞外基质中去，进而血脑屏障保护脑的功能遭到破坏[9]。在[10] [11]等人研究中也证实中风损伤与基质金属蛋白酶家族有联系，尤其在脑出血中。

本节重点介绍基质金属蛋白酶家族中的 MMP-9 对脑出血后血脑屏障的影响。相关研究[12]表明，在人类及动物中风的模型中，基质金属蛋白酶的激活，尤其对于 MMP-9，可能会导致 BBB 基底膜中的蛋白分解，进而破坏血脑屏障，并表示可以通过采用酶联免疫吸附法来测定血浆基质金属蛋白酶-9 的含量。这与[13]研究中基质金属蛋白酶-9 特异性地降解基底膜的主要成分，导致血脑屏障破坏的结果相一致。并且[14]研究表示，在急性原发性幕上脑出血后的前三天，机体中血清 MMP-9 水平与神经功能缺损程度成正相关。此外，较高的 MMP-9 在脑出血中还会促进神经元死亡以及 MMP-9 水平与缺血性卒中的严重程度、梗死面积及其不良预后有着密切的联系[15] [16]。[17]在实验中使用 MMPs 抑制剂证明，以此可以

减轻大鼠脑出血后血脑屏障完整性破坏的程度，使之脑功能障碍程度、血脑屏障的通透性以及炎症细胞浸润降低。

2.2. 活性氧自由基(Reactive Oxygen Species, ROS)

ROS 是由 NADPH 氧化酶 4/NOX 酶系统所产生的，而且是迄今为止人们所知道的唯一系统[18] [19]。虽然 ROS 在组织正常生理中维持在一个相对较低浓度，但在机体遭受破坏时即可快速转变为有害的生物及化学物质[20]。而脑出血的发生会引起 NOX4 系统的异常表达，导致细胞内 ROS 积聚增加，进而破坏其中 bcl-2 和 bax 的表达平衡，这里的 bcl-2 是一种抗凋亡分子，其作用可以减少氧自由基和过氧化脂质的产生[21]。而 Bax 是 bcl-2 的凋亡对应物，可以通过拮抗 bcl-2 而使破坏增加。有研究证实，bax 与 bcl-2 的相对比例是决定细胞凋亡程度的关键因素[22]。在 Xie 等[23]试验中证明，随着 NOX4 系统受到抑制时，其实验组内 Bax 明显增加，降低了脑出血后的神经元和血脑屏障损伤。这与[24]研究实验，通过口服西红花苷可减少 ROS 生成进而减轻脑出血早期的神经功能缺损结果相一致。且在[25]研究中证实，抑制了 NOX4 表达有利于降低氧化应激水平，并保持了有益的炎症反应。不仅如此，[26] [27] [28] [29]研究中表明，脑出血后随着产生过量的活性氧还可以导致 DNA 严重损伤、脂质过氧化和蛋白质氧化。Khan 在 2002 年[30]研究中证实，通过电子顺磁共振(electron paramagnetic resonance, EPR)中自旋捕获方法可以有效检测机体内活性氧自由基，这为临床工作提供有利保障。Mo [31]研究证实，ROS 在组织内的聚集还可以激活 MMPs，进一步导致血脑屏障的破坏。但其 NOX4 系统如何调控 MMPS 的机制还未明确，有待进一步的研究。

2.3. 肿瘤坏死因子 α (Tumor Necrosis Factor-α, TNF-α)

TNF-α 主要由神经系统中的单核、巨噬、T 淋巴细胞和小胶质细胞及其受体 1 分泌的促炎介质。在脑出血后，机体常出现缺血缺氧状态，由此产生大量的抗原物质，刺激单核细胞、巨噬细胞和 T 淋巴细胞产生大量的 TNF-α[32]，以及被激活的小胶质细胞随即转移导出血的部位，通过释放肿瘤坏死因子-α，刺激内皮细胞和巨噬细胞产生 IL-1 和其他粘附因子，引起连锁的炎症反应，进而使血脑屏障(Blood-brain barrier, BBB)通透性增加，且随着通透性的增加使有害物质更易通过血脑屏障，进而使脑正常组织水肿和加剧神经损伤[33] [34]。且有研究报告了在出血后促炎介质水平会立即增加[35] [36]，认为肿瘤坏死因子-(TNF-α)是该过程的主要成分之一[37]。

虽然对于激活的小胶质细胞对神经元死亡和卒中所产生的作用，目前仍然是一个有争议的观点。但随着时代的发展，有研究证实，褪黑素可以通过减少小胶质细胞的坏死来减少 TNF 分泌，达到保护 BBB 与细胞的正常脑功能[38]。与此相同的是，Chen 等人[34]通过实验证明，在使用抗 TNF-α (英夫利昔单抗，一种有效的临床用药)治疗后可明显保护血脑屏障功能，极大改善实验组的预后。此外，肿瘤坏死因子-α 本身也能够促进基质金属蛋白酶的产生，增加了血脑屏障的通透性[39]。基于大量的文献资料，可以得出 TNF-α 通过改变血脑屏障的通透性，大量的有害物质透过血脑屏障，进而破坏脑组织。

2.4. 白细胞介素

白细胞介素(Interleukin, IL)是一组由免疫细胞(淋巴、单核巨噬细胞)和其他非免疫细胞产生，介导白细胞和其他细胞间相互作用的细胞因子，主要参与调节组织细胞的生长分化与在免疫系统中介导炎症反应。随着脑出血的发生，血液中的白细胞进入大脑，使其机体的免疫细胞得以激活，进而释放出大量的有毒性化学物质，包括白细胞介素-1β (IL-1β)和白细胞介素-18 (IL-18) [40] [41]等，这里着重介绍以上两种。由于中枢神经系统有很多的神经细胞都会表达上述有毒物质的受体，使得脑组织对此类有毒物质信号极其敏感，这就会进一步加重 BBB 和脑组织的破坏[42] [43]。Shao 等人通过使用脂联素(Adiponectin,

APN)调节核苷酸结合寡聚化结构域(nucleotide-binding oligomerization domain, NOD)样受体蛋白 3 (NOD-like receptor protein 3, NLRP3)的表达，抑制了 IL-1β 和 IL-18 的活性，进而使 BBB 的损伤和脑含水量显著降低，有效的保护了脑功能[44]。值得一提的是，脑出血后水凝胶注射液还能减少炎性细胞因子(IL-1β 和 TNF-α)的释放[45]。此外，白细胞介素-1β 在神经炎、脑动脉瘤和主动脉瘤中起关键介质作用[46]。在[47] [48]研究中表明，IL-1β 水平的增加会增加心脏成纤维细胞中基质金属蛋白酶-9 的产生，进而促进细胞外基质的降解，使脆弱的瘤壁容易破裂。

综上所述，笔者认为，BBB 可以通过阻止大部分微生物和毒素、若干大分子和一些化合物从血液进入脑组织，从而维持大脑内环境的相对稳定，进而保护脑的正常功能，在一定程度上能够减少脑损伤发生的概率。当脑出血后，由于机体产生 MMPS、TNF-α、ROS 及白细胞介素等，上述指标对血脑屏障既独立影响，相互之间又存在一定的联系，进一步破坏血脑屏障及改变其通透性，以及脑出血本身就会损伤脑组织，使得 BBB 保护脑功能的作用降低，机体周围组织细胞水肿、死亡，严重影响了患者的预后。并且有实验证明，这些因子都会加重对血脑屏障和周围组织细胞的破坏，从而进一步加重脑损伤[43]。而随着医学技术的不断创新，在使用电子顺磁共振等相关技术，能够对脑出血后炎症释放物质精准检测，为临床治疗提供了理论依据，且通过一系列的干预措施，能减少炎症细胞释放的有害物质，极大改善患者预后，提升了患者的生活质量。

3. 展望

本文围绕影响脑出血后血脑屏障的炎症细胞释放物质展开分析，通过总结破坏血脑屏障因素以此提高临床医生的警惕，期望可以通过相关检查技术及采取相应干预措施，进而减轻脑出血后血脑屏障破坏，能够改善患者预后情况。

致　谢

首先，我要感谢我的导师张越林教授，在论文的选题阶段，张老师都对我倾注了极大的关怀及鼓励，在后期的无限次修稿中提出了诸多的中肯意见，使我在研究和写作过程中不致迷失方向。张老师对学术严谨的追求是我一生中学习的楷模，他对我的教诲更将永远铭记。借此机会，谨向张老师致以深深的谢意。

其次，感谢我研究生学习生涯中的室友，始终营造一个良好的生活环境和一个积极向上的学习氛围，能在这样一个集体中度过研究生阶段是我莫大的荣幸。

感谢父母在近花甲之年，无怨无悔地支持我追求自己想要的生活，也是我十多年来求学路上的坚强后盾，在我面临人生选择的迷茫之际，为我排忧解难，对我无私的爱与照顾是我不断前进的动力。焉得谖草，言树之背，养育之恩，无以回报。同时，也感谢姐姐在家对父母生活中的帮衬，让我能够安心学习与进步。

最后，感谢参与我论文评审的各位老师，是你们给了我一个审视几年来学习成果的机会，让我能够明确今后的发展方向，你们对我的帮助是一笔无价的财富。

参考文献

[1] Hemphill, J.C., Greenberg, S.M., Anderson, C.S., Becker, K., Bendok, B.R., Cushman, M., *et al*. (2015) Guidelines for the Management of Spontaneous Intracerebral Hemorrhage: A Guideline for Healthcare Professionals from the American Heart Association/American Stroke Association. *Stroke*, **46**, 2032-2060. https://doi.org/10.1161/STR.0000000000000069

[2] Barzó, P., Marmarou, A., Fatouros, P., *et al*. (1996) Magnetic Resonance Imaging-Monitored Acute Blood-Brain Barrier Changes in Experimental Traumatic Brain Injury. *Journal of Neurosurgery*, **85**, 1113-1121.

https://doi.org/10.3171/jns.1996.85.6.1113

[3] Keep, R.F., Hua, Y. and Xi, G. (2012) Intracerebral Haemorrhage: Mechanisms of Injury and Therapeutic Targets. *The Lancet Neurology*, **11**, 720-731. https://doi.org/10.1016/S1474-4422(12)70104-7

[4] Ma, M.W., Wang, J., Dhandapani, K.M., *et al*. (2018) Deletion of NADPH Oxidase 4 Reduces Severity of Traumatic Brain Injury. *Free Radical Biology & Medicine*, **117**, 66-75. https://doi.org/10.1016/j.freeradbiomed.2018.01.031

[5] Rani, V., Deep, G., Singh, R.K., *et al*. (2016) Oxidative Stress and Metabolic Disorders: Pathogenesis and Therapeutic Strategies. *Life Sciences*, **148**, 183-193. https://doi.org/10.1016/j.lfs.2016.02.002

[6] Lin, X., Ye, H., Siaw-Debrah, F., *et al*. (2018) AC-YVAD-CMK Inhibits Pyroptosis and Improves Functional Outcome after Intracerebral Hemorrhage. *BioMed Research International*, **2018**, Article ID: 3706047. https://doi.org/10.1155/2018/3706047

[7] Li, H., Mittal, A., Makonchuk, D.Y., Bhatnagar, S. and Kumar, A. (2009) Matrix Metalloproteinase-9 Inhibition Ameliorates Pathogenesis and Improves Skeletal Muscle Regeneration in Muscular Dystrophy. *Human Molecular Genetics*, **18**, 2584-2598. https://doi.org/10.1093/hmg/ddp191

[8] Shang, Z.J., Ethunandan, M., Gorecki, D.C. and Brennan, P.A. (2008) Aberrant Expression of Beta-Dystroglycan May Be Due to Processing by Matrix Metalloproteinases-2 and -9 in Oral Squamous Cell Carcinoma. *Oral Oncology*, **44**, 1139-1146. https://doi.org/10.1016/j.oraloncology.2008.02.016

[9] Hawkins, B.T., Gu, Y.H., Izawa, Y. and Del Zoppo, G.J. (2013) Disruption of Dystroglycan-Laminin Interactions Modulates Water Uptake by Astrocytes. *Brain Research*, **1503**, 89-96. https://doi.org/10.1016/j.brainres.2013.01.049

[10] Wang, X. and Lo, E.H. (2003) Triggers and Mediators of Hemorrhagic Transformation in Cerebral Ischemia. *Molecular Neurobiology*, **28**, 229-244. https://doi.org/10.1385/MN:28:3:229

[11] Cunningham, L.A., Wetzel, M. and Rosenberg, G.A. (2005) Multiple Roles for MMPs and TIMPs in Cerebral Ischemia. *Glia*, **50**, 329-339. https://doi.org/10.1002/glia.20169

[12] Rosenberg, G.A. and Yang, Y. (2007) Vasogenic Edema Due to Tight Junction Disruption by Matrix Metalloproteinases in Cerebral Ischemia. *Neurosurgical Focus*, **22**, E4. https://doi.org/10.3171/foc.2007.22.5.5

[13] Rosenberg, G.A., Estrada, E. and Dencoff, J.E. (1998) Matrix Metalloproteinases and TIMPs Are Associated with Blood-Brain Barrier Opening after Reperfusion in Rat Brain. *Stroke*, **29**, 2189-2195. https://doi.org/10.1161/01.STR.29.10.2189

[14] Petrovska-Cvetkovska, D., Dolnenec-Baneva, N., Nikodijevik, D. and Cheprega nova-Changovska, T. (2014) Correlative Study between Serum Matrix Metalloproteinase-9 Values and Neurologic Deficit in Acute, Primary, Supratentorial, Intracerebral Haemorrhage. *Pril* (*Makedon Akad Nauk Umet Odd Med Nauki*), **35**, 39-44. https://doi.org/10.2478/prilozi-2014-0005

[15] Xue, M., Hollenberg, M.D. and Yong, V.W. (2006) Combination of Thrombin and Matrix Metallo Proteinase-9 Exacerbates Neurotoxicity in Cell Culture and Intracerebral Hemorrhage in Mice. *Journal of Neuroscience*, **26**, 10281-10291. https://doi.org/10.1523/JNEUROSCI.2806-06.2006

[16] Ramos-Fernandez, M., Bellolio, M.F. and Stead, L.G. (2011) Matrix Metalloproteinase-9 as a Marker for Acute Ischemic Stroke: A Systematic Review. *Journal of Stroke and Cerebrovascular Diseases*, **20**, 47-54. https://doi.org/10.1016/j.jstrokecerebrovasdis.2009.10.008

[17] Zhang, X., Gu, Y., Li, P., *et al*. (2019) Matrix Metalloproteases-Mediated Cleavage on *β*-Dystroglycan May Play a Key Role in the Blood-Brain Barrier after Intracerebral Hemorrhage in Rats. *Medical Science Monitor*, **25**, 794-800. https://doi.org/10.12659/MSM.908500

[18] Brown, G.C. and Borutaite, V. (2012) There Is No Evidence That Mitochondria Are the Main Source of Reactive Oxygen Species in Mammalian Cells. *Mitochondrion*, **12**, 1-4. https://doi.org/10.1016/j.mito.2011.02.001

[19] Haslund-Vinding, J., McBean, G., Jaquet, V., *et al*. (2017) NADPH Oxidases in Oxidant Production by Microglia: Activating Receptors, Pharmacology and Association with Disease. *British Journal of Pharmacology*, **174**, 1733-1749. https://doi.org/10.1111/bph.13425

[20] Sedeek, M., Nasrallah, R., Touyz, R.M., *et al*. (2013) NADPH Oxidases, Reactive Oxygen Species, and the Kidney: Friend and Foe. *Journal of the American Society of Nephrology*, **24**, 1512-1518. https://doi.org/10.1681/ASN.2012111112

[21] Chien, C.T., Lee, P.H., Chen, C.F., *et al*. (2001) De Novo Demonstration and Co-Localization of Free-Radical Production and Apoptosis Formation in Rat Kidney Subjected to Ischemia/Reperfusion. *Journal of the American Society of Nephrology*, **12**, 973-982. https://doi.org/10.1681/ASN.V125973

[22] Li, H., Zhuang, H.L., Lin, J.J., *et al.* (2018) Effect of Rosmarinic Acid from *Sarcandra glabra* in Inhibiting Proliferation and Migration and Inducing Apoptosis of MDA-MB-231 Cells via Regulation of Expressions of Bcl-2 and Bax. *China Journal of Chinese Materia Medica*, **43**, 3335-3340.

[23] Xie, J., Hong, E., Ding, B., *et al*. (2020) Inhibition of NOX4/ROS Suppresses Neuronal and Blood-Brain Barrier Injury by Attenuating Oxidative Stress after Intracerebral Hemorrhage. *Frontiers in Cellular Neuroscience*, **14**, Article ID: 578060. https://doi.org/10.3389/fncel.2020.578060

[24] Duan, Z., Li, H., Qi, X., *et al*. (2019) Crocin Attenuation of Neurological Deficits in a Mouse Model of Intracerebral Hemorrhage. *Brain Research Bulletin*, **150**, 186-195.

[25] Matsushima, S., Tsutsui, H. and Sadoshima, J. (2014) Physiological and Pathological Functions of NADPH Oxidases during Myocardial Ischemia-Reperfusion. *Trends in Cardiovascular Medicine*, **24**, 202-205. https://doi.org/10.1016/j.tcm.2014.03.003

[26] Altermann, C.D.C., Souza, M.A., Schimidt, H.L., *et al*. (2017) Short-Term Green Tea Supplementation Prevents Recognition Memory Deficits and Ameliorates Hippocampal Oxidative Stress Induced by Different Stroke Models in Rats. *Brain Research Bulletin*, **131**, 78-84. https://doi.org/10.1016/j.brainresbull.2017.03.007

[27] Qu, J., Chen, W., Hu, R. and Feng, H. (2016) The Injury and Therapy of Reactive Oxygen Species in Intracerebral Hemorrhage Looking at Mitochondria. *Oxidative Medicine and Cellular Longevity*, **2016**, Article ID: 2592935. https://doi.org/10.1155/2016/2592935

[28] Zhou, F., Liu, Y., Yang, B. and Hu, Z. (2018) Neuroprotective Potential of Glibenclamide Is Mediated by Antioxidant and Anti-Apoptotic Pathways in Intracerebral Hemorrhage. *Brain Research Bulletin*, **142**, 18-24. https://doi.org/10.1016/j.brainresbull.2018.06.006

[29] Choi, K.S., Kim, H.J., Do, S.H., *et al*. (2018) Neuroprotective Effects of Hydrogen Inhalation in an Experimental Rat Intracerebral Hemorrhage Model. *Brain Research Bulletin*, **142**, 122-128. https://doi.org/10.1016/j.brainresbull.2018.07.006

[30] Khan, N. and Swartz, H. (2002) Measurements *in Vivo* of Parameters Pertinent to ROS/RNS Using EPR Spectroscopy. *Molecular and Cellular Biochemistry*, **234-235**, 341-357. https://doi.org/10.1007/978-1-4615-1087-1_39

[31] Mo, J., He, L., Ma, B., *et al*. (2016) Tailoring Particle Size of Mesoporous Silica Nanosystem to Antagonize Glioblastoma and Overcome Blood-Brain Barrier. *ACS Applied Materials & Interfaces*, **8**, 6811-6825. https://doi.org/10.1021/acsami.5b11730

[32] Peng, C., Duan, S. and Gang, L. (2018) Efficacy of Danhong Injection on Serum Concentration of TNF-α, IL-6 and NF-κB in Rats with Intracerebral Hemorrhage. *Open Life Science*, **13**, 77-81. https://doi.org/10.1515/biol-2018-0011

[33] Hong, S.-L., Dong, G., Ai, L.-G., *et al*. (2014) Human Amniotic Epithelial Stem Cells Inhibit Microglia Activation through Downregulation of Tumor Necrosis Factor-a, Interleukin-1b and Matrix Metalloproteinase-12 *in Vitro* and in a Rat Model of Intracerebral Hemorrhage. *Cytotherapy*, **16**, 523-534. https://doi.org/10.1016/j.jcyt.2013.11.007

[34] Chen, A.-Q., Fang, Z., Chen, X.-L., *et al*. (2019) Microglia-Derived TNF-α Mediates Endothelial Necroptosis Aggravating Blood Brain-Barrier Disruption after Ischemic Stroke. *Cell Death & Disease*, **10**, 487. https://doi.org/10.1038/s41419-019-1716-9

[35] Zhang, X.M., Li, X.L., Tang, S.H. and Liu, Q.C. (2006) Effect of Head Hypothermia on Serum Inflammatory Cytokines Levels Inpatients with Hypertensive Intracerebral Hemorrhage. *Chinese Critical Care Medicine*, **18**, 294-296.

[36] Rosell, A., Vilalta, A., García-Berrocoso, T., *et al*. (2011) Brain Perihematoma Genomic Profile Following Spontaneous Human Intracerebral Hemorrhage. *PLoS ONE*, **6**, e16750. https://doi.org/10.1371/journal.pone.0016750

[37] Behrouz, R. (2016) Re-Exploring Tumor Necrosis Factor Alpha as a Target for Therapy in Intracerebral Hemorrhage. *Translational Stroke Research*, **7**, 93-96. https://doi.org/10.1007/s12975-016-0446-x

[38] Lu, J., Sun, Z., Fang, Y., *et al*. (2019) Melatonin Suppresses Microglial Necroptosis by Regulating Deubiquitinating Enzyme A20 after Intracerebral Hemorrhage. *Frontiers in Immunology*, **10**, 1360. https://doi.org/10.3389/fimmu.2019.01360

[39] Ewen, T., *et al*. (2013) Neuroprotective Effect of Atorvastatin Involves Suppression of TNF-α and Upregulation of IL-10 in a Rat Model of Intracerebral Hemorrhage. *Cell Biochemistry and Biophysics*, **66**, 337-346. https://doi.org/10.1007/s12013-012-9453-z

[40] Li, M., Li, Z., Ren, H., *et al*. (2017) Colony Stimulating Factor 1 Receptor Inhibition Eliminates Microglia and Attenuates Brain Injury after Intracerebral Hemorrhage. *Journal of Cerebral Blood Flow and Metabolism*: *Official Journal of the International Society of Cerebral Blood Flow and Metabolism*, **37**, 2383-2395. https://doi.org/10.1177/0271678X16666551

[41] Feng, L., Chen, Y., Ding, R., Fu, Z., Yang, S., Deng, X., *et al*. (2015) P2X7R Blockade Prevents NLRP3 Inflammasome Activation and Brain Injury in a Rat Model of Intracerebral Hemorrhage: Involvement of Peroxynitrite. *Journal of Neuroinflammation*, **12**, 190. https://doi.org/10.1186/s12974-015-0409-2

[42] Walsh, J.G., Muruve, D.A. and Power, C. (2014) Inflammasomes in the CNS. *Nature Reviews Neuroscience*, **15**, 84-97. https://doi.org/10.1038/nrn3638

[43] Li, M., Ren, H., Sheth, K.N., Shi, F.D. and Liu, Q. (2017) A TSPO Ligand Attenuates Brain Injury after Intracerebral

Hemorrhage. *FASEB Journal*: *Official Publication of the Federation of American Societies for Experimental Biology*, **31**, 3278-3287. https://doi.org/10.1096/fj.201601377RR

[44] Wang, S.H., Yao, Q.H., Wan, Y., *et al*. (2019) Adiponectin Reduces Brain Injury after Intracerebral Hemorrhage by Reducing NLRP3 Inflammasome Expression. *International Journal of Neuroscience*, **130**, 301-308. https://doi.org/10.1080/00207454.2019.1679810

[45] Xu, J., Duan, Z., Qi, X., *et al*. (2020) Injectable Gelatin Hydrogel Suppresses Inflammation and Enhances Functional Recovery in a Mouse Model of Intracerebral Hemorrhage. *Frontiers in Bioengineering and Biotechnology*, **8**, 785. https://doi.org/10.3389/fbioe.2020.00785

[46] Ye, L., Gao, L. and Cheng, H. (2018) Inflammatory Profiles of the Interleukin Family and Network in Cerebral Hemorrhage. *Cell Molecular Neurobiology*, **38**, 1321-1333. https://doi.org/10.1007/s10571-018-0601-x

[47] Miyamoto, T., Kung, D.K., Kitazato, K.T., *et al*. (2017) Site-Specific Elevation of Interleukin-1β and Matrix Metalloproteinase-9 in the Willis Circle by Hemodynamic Changes Is Associated with Rupture in a Novel Rat Cerebral Aneurysm Model. *Journal of Cerebral Blood Flow & Metabolism*, **37**, 2795-2805. https://doi.org/10.1177/0271678X16675369

[48] Sozen, T., Tsuchiyama, R., Hasegawa, Y., *et al*. (2009) Role of Interleukin-1beta in Early Brain Injury after Subarachnoid Hemorrhage in Mice. *Stroke*, **40**, 2519-2525. https://doi.org/10.1161/STROKEAHA.109.549592