·脑出血研究进展·

脑出血损伤相关分子模式研究进展

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【摘要】 脑出血后产生的免疫风暴可导致神经元及其支持细胞死亡，红细胞裂解释放的血红蛋白、血红素和铁离子等细胞毒性物质也具有促进神经细胞死亡的作用。神经细胞死亡后释放的损伤相关分子模式（DAMP）激活固有免疫反应，导致炎症反应-细胞死亡-DAMP释放-炎症反应的恶性循环，是脑出血后继发性脑损伤的重要机制。本文旨在对目前开展的一系列探讨DAMP在脑出血继发性脑损伤中作用的研究进展进行概述，以为进一步的基础研究与临床转化研究提供参考。

【关键词】 脑出血；　脑损伤；　血红素；　HMGB1蛋白质；　S100蛋白质类；　硫氧还原蛋白过氧化物酶类；　综述

Research progress on damage - associated molecular patterns in intracerebral hemorrhage

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【Abstract】 After the onset of intracerebral hemorrhage (ICH), the immune storm causes the massive death of neurons and their supporting cells. Cytotoxic substances such as hemoglobin, heme and iron ions released by red blood cells lysis also promote death of neurons. After neurons died, damage - associated molecular patterns (DAMP) are released to activate the innate immune response, leading to a vicious circle of "inflammatory response - cell death - DAMP release - inflammatory response", which is an important mechanism of secondary brain injury after ICH. A series of studies have explored the role of DAMP in secondary brain injury after ICH. This review summarizes the research progress and provides references for further basic research and clinical translational research.

【Key words】 Cerebral hemorrhage; Brain injuries; Heme; HMGB1 protein; S100 proteins; Peroxiredoxins; Review

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根据流行病学调查资料统计，脑出血占世界范围内全部脑卒中的10%～15%，我国这一比例则高达17%～55%[1-2]，脑出血患者发病后30天的病死率约为40%，发病后180天生活自理者仅占全部脑出血患者的20%[3-4]。脑出血的损伤机制包括原发性和继发性脑损伤，出血和占位效应对脑组织的直接破坏称之为原发性脑损伤[5]；出血后伴随的炎症反应、血-脑屏障（BBB）破坏，以及血肿周围水肿形成等造成的脑组织新发损伤为继发性脑损伤，与预后不良密切相关，被认为是脑出血治疗的潜在靶点[6]。脑出血后血液成分释放进入脑组织，首先活化小胶质细胞等中枢神经系统固有免疫细胞，引发炎症反应信号转导通路的级联反应，破坏血-脑屏障，导致外周血免疫细胞浸润活化，进而释放各类细胞因子、趋化因子、自由基，以及其他毒性物质，形成免疫风暴，导致神经元及其支持细胞大量死亡[7-8]。另外，脑出血后24小时，破入脑组织的红细胞发生裂解，由其释放的血红蛋白、血红素和铁离子等细胞毒性物质也在神经细胞死亡中发挥重要作用[9]。神经细胞死亡后释放的一系列内源性危险信号，称为损伤相关分子模式（DAMP），后者与模式识别受体相结合，激活固有免疫反应，诱发炎症反应-细胞死亡-DAMP释放-炎症反应之恶性循环，此为脑出血后继发性脑损伤的重要病理生理学机制[10]。常见

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的DAMP主要包括腺苷、热休克蛋白(HSP)、白细胞介素-33(IL-33)等，而近年文献报道的一系列研究更关注血红素、高迁移率族蛋白1(HMGB1)、S-100B蛋白(S-100B)和过氧化物还原酶(Peroxiredoxin)等重要的DAMP在脑出血继发性脑损伤中的作用，本文拟对此类内源性危险信号分子的研究进展进行概述，以为进一步的基础研究和临床转化研究提供参考。

一、血红素

脑出血后红细胞随血液扩散至脑实质，小胶质细胞通过吞噬红细胞而在内源性血肿清除机制中发挥作用，该过程由CD36介导，受过氧化物酶体增殖物激活受体γ(PPARγ)调节，PPARγ活化可促进血肿清除并减轻脑出血后的继发性脑损伤[11]。然而，当大量红细胞进入脑实质后，内源性血肿清除机制则难以承受清除血肿的“重任”，加之脑实质的微环境不适宜红细胞生存，红细胞逐渐裂解、释放血红蛋白，后者进一步分解、释放游离血红素，最终经血红素加氧酶降解形成游离铁离子，游离血红素和铁离子均为重要的炎症反应诱因[12]。血红素是目前较为关注的血红蛋白衍生DAMP，可激活免疫细胞，上调细胞黏附分子(CAMs)和细胞因子的表达，引起急性神经炎症反应[13]。一方面，血红素以Toll样受体4(TLR4)依赖性方式激活巨噬细胞，诱导促炎性因子的分泌[14]；另一方面，显著上调小胶质细胞TLR4和肿瘤坏死因子-α(TNF-α)等促炎性因子的表达。敲除*TLR4*基因或应用TLR4抗体可抑制血红素诱导的小胶质细胞活化，动物实验显示，脑出血后小胶质细胞TLR4水平明显升高，游离血红素可使野生型小鼠促炎性因子水平和脑含水量显著升高，加重神经功能缺损，而*TLR4*基因敲除小鼠则不出现与之相同的炎症反应，表明脑出血后血红素可通过TLR4信号转导通路引起小胶质细胞活化并诱导核因子-κB(NF-κB)活化，继而诱发神经炎症反应，在脑出血继发性脑损伤机制中发挥重要作用[15]。血红素具有上调星形胶质细胞基质金属蛋白酶-9(MMP-9)、促炎性因子和趋化因子等炎性反应物质表达的作用，而敲除*TLR2*基因或应用TLR2抗体则可使血红素诱导的星形胶质细胞活化受到抑制；与野生型小鼠相比较，外源性血红素并未诱发*TLR2*基因敲除小鼠产生急性神经炎症反应，而且其血-脑屏障破坏和中性粒细胞浸润程度明显较轻，IL-1β、IL-6和TNF-α等促炎性因子水平显著降低，神经功能缺损程度轻微，提示脑出血后血红素所引起的继发性脑损伤需依赖TLR2蛋白的表达[16]。上述研究结果表明，血红素可根据不同细胞类型，采用不同模式识别受体，激活固有免疫反应，如通过TLR4蛋白激活小胶质细胞和巨噬细胞，通过TLR2蛋白激活星形胶质细胞。

二、高迁移率族蛋白1

HMGB1是一种普遍存在于哺乳动物且含量丰富的非组蛋白DNA结合蛋白，脑出血后血肿周围神经细胞受损，HMGB1自细胞核释放至细胞外，成为重要的DAMP[17-18]。Zhou等[19]的研究显示，脑出血患者血清HMGB1水平显著高于正常对照者；该作者于脑出血小鼠模型亦观察到同样的结果，即血肿周围组织HMGB1水平显著升高，并于出血后72小时达峰值，出血后5天表达水平逐渐下降。有研究显示，脑出血患者血清HMGB1表达变化与血肿量、美国国立卫生研究院卒中量表(NIHSS)评分、IL-6和TNF-α表达水平相关[19-20]，且为神经功能预后不良的重要影响因素，其受试者工作特征(ROC)曲线下面积(AUC)为0.718(95%CI：0.603～0.831，P=0.001)[20]。下调HMGB1表达可减轻脑出血继发性脑损伤，HMGB1抑制剂丙酮酸乙酯可减弱小胶质细胞活化、抑制神经元凋亡、缓解脑水肿和神经功能缺损程度[21]；HMGB1单克隆抗体具有抑制HMGB1释放、降低血清HMGB1表达水平、抑制小胶质细胞活化、缓解氧化应激反应和减轻脑水肿的作用[18]。动物实验结果亦提示，HMGB1抑制剂甘草甜素可逆转HMGB1激活固有免疫反应的作用，抑制神经元凋亡、减轻脑水肿和脑损伤程度、改善大鼠行为异常[22]；HMGB1抑制剂或晚期糖基化终末产物受体(RAGE)阻断剂可减少急性期脑出血大鼠模型血肿周围炎性细胞浸润、下调促炎性因子表达、缓解脑水肿、改善神经功能[23]；而上调脑出血大鼠模型微小RNA-129-5p(miRNA-129-5p)表达则能够有效抑制脑出血后HMGB1-RAGE信号转导通路相关蛋白的表达[24]。上述研究表明，HMGB1-RAGE信号转导通路可能参与脑出血急性期损伤机制。此外，亦有研究显示，HMGB1在脑出血恢复期具有促进血管生成和神经修复作用[25-27]，今后尚待进一步探究HMGB1在脑出血不同阶段的作用。

三、S-100B蛋白

S-100B蛋白是一种通过星形胶质细胞表达和释放的脑组织特异性钙结合蛋白(CaBP)，为RAGE

之配体，二者相互作用在脑出血损伤机制中发挥重要作用[28]。脑出血后S-100B自受损的细胞质快速释放进入血液[29]，活化星形胶质细胞和小胶质细胞，产生促炎性因子和活性氧（ROS），可进一步加重脑出血的继发性脑损伤[30]。对Ⅳ型胶原酶构建的脑出血大鼠模型观察发现，脑出血后6小时大鼠血清S-100B水平即达峰值[31]。临床研究显示，脑出血患者发病6小时内血清S-100B水平升高，24小时内达峰值，第2天进入平台期，此后逐渐下降[32]；脑出血患者血清S-100B水平不仅高于正常对照者且可持续至发病后第7天[32-33]，且血清与脑脊液S-100B水平呈显著正相关，均高于正常对照者[34]。研究显示，脑出血患者血清S-100B水平明显高于缺血性卒中患者，据此可对二者进行鉴别[29,35]。动物实验结果显示，脑出血大鼠模型血清S-100B水平与血肿量（$r = 0.37$，$P < 0.05$）和血肿周围水肿程度（$r = 0.48$，$P < 0.01$）呈正相关[31]；临床研究显示，脑出血患者血清S-100B水平与Glasgow昏迷量表（GCS）评分呈负相关（$r = -0.45$，$P = 0.004$），与血肿量（$r = 0.45$，$P < 0.0001$）和血肿周围水肿程度（$r = 0.27$，$P = 0.033$）呈正相关[32-33,35]。通过血清S-100B变化，尚可判断脑出血患者预后：血清S-100B水平升高为发病后1周病死率上升的预测因素（$OR = 1.046$，95%CI：1.014～1.078；$P = 0.004$）[32]；血清S-100B水平较高者大多预示早期神经功能恶化（$P = 0.001$）和预后不良（$P = 0.003$）[33]；另外，脑出血24小时内的血清S-100B水平被认为是出院时神经功能预后的预测因素（$OR = 1.02$，95%CI：1.003～1.039；$P = 0.02$）[36]；经研究表明，S-100B水平预测神经功能预后不良的灵敏度可达100%、特异度为76.2%[35]。Ferrete-Araujo等[37]对36例脑出血患者进行前瞻性观察发现，最终死亡13例、生存23例，而死亡患者入院时、发病后24和48小时血清S-100B水平均高于生存患者；生存患者神经功能预后良好者11例、预后不良12例，预后不良患者发病后24、48和72小时血清S-100B水平均高于预后良好患者，提示血清S-100B是脑出血患者病死和神经功能预后不良的早期预测指标。因此Ferrete-Araujo认为，血清S-100B可以成为脑出血治疗的可行靶点，目前此类研究尚处于动物实验阶段。动物实验显示，应用Arundic acid抑制星形胶质细胞合成S-100B，可降低脑出血大鼠模型中枢和周围神经系统S-100B的表达，以及抑制星形胶质细胞和小胶质细胞活化，减少促炎性因子释放和活性氧生成，减少神经元凋亡，缓解脑出血引起的神经功能缺损和脑损伤[30,38]；电针和凉血通瘀方剂等中药治疗亦可降低血清S-100B水平[39-40]。S-100B在脑出血中的作用和相关机制尚待进一步研究。

四、过氧化物还原酶

Peroxiredoxin是一类氧化应激诱导型过氧化物酶，在哺乳动物细胞中可分为Peroxiredoxin1～6（Prx1～6）共6种亚型，具有氧化还原活性，可以调节氧化应激相关细胞凋亡，发挥神经保护作用[41]。（1）Prx1：是Peroxiredoxin中的主要出血应激诱导型亚型[42]。其主要表达于脑出血大鼠模型的星形胶质细胞和小胶质细胞，于纹状体注射腺病毒使其过表达，可使炎症反应减轻并抑制细胞凋亡[43]；注射丹红注射液可上调脑出血大鼠模型星形胶质细胞Prx1的表达，下调TNF-α和IL-1β等促炎性因子的表达水平，以减轻脑出血后神经炎症反应[44]。亦有研究显示，Peroxiredoxin释放至细胞外即失去抗氧化能力，其可激活TLR2/4信号转导通路，从而加重神经炎症反应[45-46]。外源性Prx1具有激活RAW264.7细胞TLR4/NF-κB信号转导通路的作用，并分泌TNF-α和IL-6等促炎性因子。脑出血72小时内Prx1表达水平升高，并由凋亡细胞释放至细胞外，激活TLR4/NF-κB信号转导通路，使神经炎症损伤进一步加重[47]；而蒿本内酯及其衍生物则可降低脑出血后Prx1的表达和释放，抑制TLR4/NF-κB信号转导通路的激活，减少免疫细胞活化和促炎性因子的分泌，从而改善脑出血后的神经功能缺损[48]。上述研究表明，脑出血后细胞内Prx1产生正向有益作用，而细胞外Prx1介导的TLR4/NF-κB信号转导通路激活可在继发性脑损伤机制中发挥重要作用。（2）Prx2：在红细胞内表达丰富。于脑出血大鼠模型尾状核注射裂解红细胞可使其脑组织Prx2表达升高，引起脑水肿、血-脑屏障破坏、中性粒细胞浸润、小胶质细胞活化、神经元死亡和神经功能缺损，而Prx2抑制剂Conoidin A则可缓解上述损伤[49]。脑出血后，注射Lipocalin-2可促进脑出血小鼠模型Prx2相关中性粒细胞浸润、小胶质细胞/巨噬细胞活化、神经元凋亡，进而继发脑水肿和神经功能缺损，而敲除或敲低*Lipocalin-2*则Prx2相关性脑损伤程度明显减轻[50]。目前，尚无Prx3～6在脑出血后继发性脑损伤机制中作用的报道，因此，Peroxiredoxin在脑出血后继发性脑损伤中的作用及机制尚待进一步研究。

五、其他

除上述4种重要DAMP外，还有其他常见DAMP，如HSP、腺苷、IL-33等内源性危险信号分子，近年也有研究探讨其在脑出血后继发性脑损伤中的作用。(1)HSP：是一类进化上相对保守的分子伴侣家族，通过调节应激反应参与脑出血的病理生理学机制[51]。HSP70家族是常见的HSP，采用格尔德霉素上调HSP70表达可以减轻脑出血小鼠模型的神经炎症反应，降低血-脑屏障损伤，改善其神经功能[52]。葡萄糖调节蛋白75(GRP75)是HSP70家族成员，诱导脑出血大鼠模型过表达GRP75可以降低促炎性因子的分泌，抑制炎症反应，减少神经元凋亡，具有神经保护作用[53]。HSP32亦称为血红素加氧酶-1(HO-1)，其在脑出血继发性脑损伤中的作用仍存争议[54]。动物实验显示，通过miRNA-183-5p抑制HO-1表达可减轻脑出血小鼠模型氧化应激和神经炎症反应，从而改善其神经功能[55]。基于脑出血大鼠模型的研究发现，HO-1可通过调节磷脂酰肌醇3-激酶(PI3K)/丝氨酸/苏氨酸激酶(AKT)信号转导通路发挥神经保护作用[56]。在脑出血小鼠模型发病早期，HO-1可加重神经炎症反应和氧化应激反应，促进细胞死亡和脑白质损害；至疾病后期，HO-1则促进血肿吸收和血管生成，有利于神经功能的恢复[57]。上述结果提示，HO-1在脑出血病理生理学机制中的作用较为复杂，尚待更多研究深入探讨。(2)ATP：脑组织富含ATP，是一类常见的DAMP[58]。脑出血后受损伤的神经细胞释放ATP，激活嘌呤能P2X7受体并产生信号级联反应，最终导致促炎性因子释放和细胞死亡[59]。基于脑出血小鼠模型研究发现，P2X7受体水平于脑出血后24小时达到峰值，且主要表达于神经元，P2X7受体激活后可通过细胞外信号调节激酶1/2(ERK1/2)/NF-κB信号转导通路加重氧化应激反应[60]；抑制P2X7受体可通过丝裂原激活蛋白激酶(MAPK)信号转导通路限制脑出血大鼠模型继发性脑损伤的进展[61]；牛磺酸具有抑制P2X7受体作用，可缓解脑出血大鼠模型神经炎症反应，减少神经元凋亡和脑白质损伤[62]。上述研究结果表明，ATP相关信号转导通路有可能是脑出血的潜在治疗靶点。(3)IL-33：属于IL-1家族成员，可结合其膜受体肿瘤抑制素2(ST2)，激活免疫细胞[63]。基于脑出血小鼠模型的研究显示，IL-33可以减轻脑出血后炎症反应、细胞凋亡与自噬，缓解脑水肿，具有神经保护作用[64]。Chen等[65]发现，IL-33能够促进脑出血大鼠模型小胶质细胞由促炎症型向抑炎症型转变，减轻神经元损伤和脑白质损伤，改善神经功能。

综上所述，DAMP功能多样化，与细胞类型密切相关，在脑出血后不同阶段可能发挥不同作用。因此，未来研究有必要进一步深入探讨不同类型DAMP在不同阶段对不同细胞的作用，同时也有必要开发针对DAMP的治疗策略，以改善脑出血患者预后。

利益冲突 无

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下期内容预告 本刊2021年第3期报道专题为神经外科疾病大数据，重点内容包括：大数据在神经系统疾病中的应用；垂体腺瘤数据库研究现状；脑卒中大型医学数据库应用及研究进展；伴多内分泌腺瘤病的促肾上腺皮质激素依赖性库欣综合征临床研究；库欣综合征合并围手术期肺栓塞临床研究；脑转移瘤患者手术治疗与其联合放射治疗方案对比分析：基于北京协和医院脑转移瘤数据库的回顾性研究；基于美国SEER数据库的小儿胶质瘤临床特点和预后分析；基于卷积神经网络的硬膜下血肿与硬膜外血肿分割方法的一致性评价；中国颅内出血影像数据库中脑实质出血血肿体积变化的流行病学研究；贵州地区颅脑创伤临床特点分析：附1931例病例