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HIF-1α表达与创伤性颅脑损伤预后关系的研究

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摘 要

创伤性颅脑损伤(traumatic brain injury, TBI)是世界范围内死亡和残疾的主要原因之一。在过去的几十年里，人们对TBI后组织损伤发展的相关机制进行了广泛的研究，越来越明显的是，脑水肿(cerebral edema, CE)的形成是导致TBI患者高死亡率和发病率的主要因素之一。出血灶脑组织缺血缺氧，造成细胞凋亡，并且周围脑组织受压，导致脑水肿形成并在发病后第3天达高峰，最终严重影响患者预后。有研究表明氧感知通路的缺氧诱导因子-1α (hypoxia inducible factor-1, HIF-1α)通过一种放大作用促进HIF-1α下游miR-21通路激活，最终miR-2通过抑制PTEN的表达和促进Tie-2表达，促进血管重建，继而加快血肿吸收，阻止水肿进展，最终改善TBI患者的神经功能预后。因此，我们就TBI后引起CE的氧感知通路作一综述，研究HIF-1α的表达对TBI患者预后具有重要意义。

关键词

脑水肿，创伤性颅脑损伤，缺氧诱导因子-1α

Study on the Relationship between the Expression of HIF-1α and the Prognosis of Traumatic Brain Injury

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Abstract

Traumatic brain injury (TBI) is one of the major causes of death and disability worldwide. In the past decades, people have conducted extensive research on the mechanism of tissue damage de-

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velopment after TBI. It is increasingly obvious that the formation of cerebral edema (CE) is one of the main factors leading to the high mortality and incidence rate of TBI patients. Ischemia and hypoxia in the brain tissue of the hemorrhage focus lead to apoptosis, and the surrounding brain tissue is compressed, leading to the formation of cerebral edema and reaching the peak on the third day after the onset, which ultimately seriously affects the prognosis of patients. Studies have shown that oxygen sensitive pathway HIF-1α promotes HIF-1 through amplification effect α. The downstream miR-21 pathway is activated, and finally miR-2 promotes vascular reconstruction by inhibiting PTEN expression and promoting Tie-2 expression, and then accelerate the absorption of hematoma, prevent the progress of edema, and finally improve the neurological prognosis of TBI patients. Therefore, we describe the oxygen sensing pathway that induces CE after TBI in summary, it is important to study the expression of HIF-1α for the prognosis of patients with TBI.

Keywords

Cerebral Edema, Traumatic Brain Injury, Hypoxia Inducible Factor-1α

1. 介绍

脑水肿(cerebral edema, CE)可定义为脑组织水的增加，包括单个细胞及其周围的间质空间，是中枢神经系统(central nervous system, CNS)损伤的严重并发症，是创伤性颅脑损伤(traumatic brain injury, TBI)在发病第一周内死亡的主要原因[1]。TBI 后 CE 的生成是一个复杂的异质过程。CE 的潜在机制可能因原发性损伤的不可改变性质(病因、速度、力量、严重程度、出血模式)、患者特征(年龄、性别、遗传、共病)和其他临床损害(缺氧、低血压、高热、癫痫)而不同。对 TBI 中 CE 基础的复杂网络的全面分子理解虽然发展迅速，但仍处于初级阶段。研究进展已经涉及到导致水肿发展的几种基本病理生理过程，包括血脑屏障完整性的破坏、各种离子泵对细胞体积的调节、肿瘤梯度和炎症反应[2]-[13]。

高原缺氧环境对机体的影响是广泛的，高原具有低氧、低气压、寒冷、干燥等环境特点，进入高原后，机体会发生急性缺氧反应，处于缺氧应激状态，引起一系列脏器功能、代谢、内分泌等方面的代偿性调节，当机体对缺氧环境的适应能力不全或失调时，会引发一系列高原疾病[14]。近年越来越多的平原居民前往高海拔地区工作、旅游，急进高原发生脑损伤的风险明显增加。因此，高原缺氧脑损伤为目前的研究热点之一。急性高原缺氧导致脑血管扩张、脑血流增加、颅内压升高、脑组织无氧代谢加强、ATP 生成减少，进而导致血脑屏障(blood brain barrier, BBB)破坏、脑水肿发生。缺氧诱导因子-1α (hypoxia inducible factor-1, HIF-1α)在高原缺氧脑损伤的机制中发挥着重要的作用，在缺氧条件下 HIF-1α 触发多种基因的表达，这些基因启动缺血缺氧损伤后的红细胞生成、血管生成、糖代谢及转运、细胞存活等，激活的 HIF-1α 可在脑缺血缺氧时起到保护作用[15]。因此，HIF-1α 是影响 TBI 患者预后的重要原因。因此，探索能够促进 TBI 病灶恢复，加快血肿吸收，继而抑制周围水肿发展的新策略对于改善 TBI 患者预后具有重要意义。

2. 低氧诱导因子的结构特征

HIF-1 是一种核转录因子，由 Semenza 博士于 1996 年发现[16]。它被认为是细胞氧稳态的主要调节因子。它通过诱导参与细胞代谢的葡萄糖转运蛋白(GLUT)、血管生成(VEGF、VEGFR1、血管生成素)

和清除自由基(血红素羟化酶-1；HO-1)等几种关键酶来激活组织存活途径。HIF 是由 α 亚基和 β 亚基组成的异源二聚体蛋白。HIF-α 有三种亚型：HIF-1α、HIF-2α 和 HIF-3α。β 类包括 HIF-1β。HIF1 是 HIF-1α (120 kDa)和 HIF-1β (91~94 kDa)亚基的结合体。HIF-1β 亚基是一种组成型表达蛋白，但 HIF-1α 亚基(一种胞质蛋白)的表达在很大程度上依赖于氧水平。HIF-1α 在缺氧时迅速上调，在复氧/再灌注时迅速降解。在常氧条件下，HIF-1α 与 von Hippel-Lindau 蛋白(pVHL)结合。pVHL 招募泛素连接酶，靶向 HIF-1α 进行 26S 蛋白酶体降解。pVHL 的结合依赖于 PHD 蛋白家族对 HIF-1α (pro402 和 pro564)中特定脯氨酸残基的羟基化(PHD)，特别是 HIF-1α 特异性 PHD，如 PHD3/PHD2 [17] [18]，这些 PHD 同工酶具有最大的同源性，它们与 HIF-1α 的降解有关。PHD 使用氧气作为底物，因此，它们的活性在缺氧条件下受到抑制。氧还可以激活抑制因子 HIF (FIH)，从而阻止共激活因子 p300/CBP 的结合，从而下调 HIF-1 诱导的转录活性。HIF-1α 基因敲除小鼠表现出血管发育受损和胚胎致死性，表明 HIF-1 在血管疾病中的保护作用[19]。

值得注意的是，HIF-1α 通路参与了创伤性脑损伤后的病理(缺氧)和神经修复(常氧)机制。HIF-1α 稳定剂/诱导剂，如去铁胺(一种被批准用于治疗血色病的铁螯合剂)，可以促进多种生存途径，包括神经保护、血管生成和神经营养素，并在卒中前或卒中后使用时减少脑梗死[20]。PHD 抑制剂，如 FG-4539，由于其通过阻止泛素蛋白酶体系统的降解来稳定 HIF-1α 的活性，目前正在进行 II 期贫血试验[18]。然而，在创伤性脑损伤的急性损伤期抑制 HIF-1α 也有神经保护作用[21] [22]。因此，开展该领域的研究至关重要。

3. 缺氧诱导因子的调控作用

HIF-1α 在细胞氧含量正常的情况下，通过脯氨酸羟化酶(prolylhydroxylase, PHD)使 HIF-1α 的氧依赖降解区域中脯氨酸残基发生羟基化作用后被泛素蛋白酶体识别而降解，导致 HIF-1α 失活[23]。尽管 HIF-1β 是组成性表达的，其 mRNA 和蛋白质保持在恒定水平，而与氧的利用率无关[24]，HIF-1 蛋白具有一个半衰期短(t1/25 分钟)，并受氧的高度调节[25]。HIF-1α 的转录和合成是组成型的，似乎不受氧的影响[24] [26] [27]。然而，在常氧条件下，HIF-1 蛋白迅速降解，导致基本上没有检测到 HIF-1α 蛋白[26]。在缺氧时，HIF-1α 变得稳定，并从细胞质进入细胞核，在那里与 HIF-1β 二聚，形成的 HIF 复合物在转录上成为活性[24] [28]。被激活的 HIF 复合物然后与靶基因的调控区域中的 HREs 结合，并结合转录辅因子来诱导基因表达[29]。HIF-1 的稳定性和随后的反式激活功能的调节主要受其后转录修饰的控制，如羟基化、泛素化、乙酰化和磷酸化[30]，HIF-1α 的修饰发生在几个域中。在常氧条件下，两个脯氨酸残基的羟基化和乙酰-ODDD 中赖氨酸残基的酰化促进 HIF-1α 与 von Hippel-Lindau (pVHL)泛素 E3 连接酶复合物[31] [32]。pVHL 复杂标记 HIF-1α 与泛素结合，从而标志着它被 26S 蛋白酶体降解。此外，C-TAD 中天冬酰胺残基的羟基化可抑制 HIF-1α 与 CBP/p300 的关联，从而抑制其转录活性[33]。

4. 缺氧诱导因子-1α 表达在颅脑损伤预后的研究

HIF-1α 是 HIF-1 的主要亚基，在缺氧组织中过度表达，并能促进适应低氧气条件[34]。显然，HIF-1α 存在于神经元细胞中和星形胶质细胞[35] [36]。诚然，其表达上调已被脑出血动物脑组织中发现[37]。毫无疑问，HIF-1α 参与神经细胞凋亡、脑水肿形成及血脑屏障破坏[38]。不过，目前还不清楚是否 HIF-1α 对脑损伤具有一定的毒性或保护作用[39]-[44]。尽管如此，据显示，提高血清 HIF-1α 水平表达与脑急性缺血性脑卒中后梗死面积[45]。有研究发现血中的 HIF-1α 浓度升高与创伤严重程度密切相关，血清 HIF-1α 浓度升高与脑外伤后 90 天预后不良和血清 HIF-1α 浓度升高高度相关，总之，血清 HIF-1α 的表达可能是 TBI 的一个有用的预后生物标志物[46]。

有研究发现 HIF-1α 参与细胞凋亡的调节机制，然而 TBI 后的效果也是双重的[47]。HIF-1α 作为细胞

凋亡的启动子，诱导肿瘤抑制蛋白 BNIP3 [44]和 p53 的转录激活，在急性期诱导细胞凋亡，此外，我们还发现连续表达 HIF-1α 的细胞可能比正常细胞更具有抗凋亡能力，其潜在的抗凋亡机制可能包括抗凋亡因子的增加[48] [49]。另外，HIF-1α 是目前发现唯一在特异性缺氧状态下发挥活性的转录因子。研究表明，TBI 的病理过程中，脑组织由于缺氧而产生较高水平 HIF-1，HIF-1 进一步与其亚单位结合，形成有活性的 HIF-1α 并分泌致血液中，使外周血 HIF-1α 水平增加，并激活相关靶基因的转录，使血管内皮生长因子(VEGF)及其他下游因子表达水平增加，从而修复损伤血管的内皮，促进新生血管形成，并刺激红细胞再生[50]。HIF-1 作为低氧应答时基因表达和恢复内环境稳定的调节中心，其对 TBI 表达水平的增加对机体起积极保护作用，以减轻缺血、缺氧后的不良反应[51] [52] [53]。根据相关研究，HIF-1α 还可以上调微小核糖核酸-21 (micro ribonucleic acid-21, miR-21)的表达[54]。作为一种肿瘤抑制因子，PTEN (phosphatase and tensin homolog deleted on chromosome 10)是一个重要的目标 miR-21 基因，参与细胞周期和细胞凋亡[55]。AKT，一种促存活蛋白的激活，据报道，它对各种脑损伤有神经保护作用包括 TBI [56]和磷酸化 TBI 后 Akt (p-Akt)显着下降[57]。在体外缺血损伤模型中，PTEN 抑制通过促进 Akt 磷酸化和 HIF-1α 上调来促进血管生成[58]。miR-21 通过抑制 PTEN 的表达，解除 PTEN 对 PI3K/Akt 通路的抑制作用，PI3K/Akt 通路可促进 HIF-1α 的表达，进一步提高 HIF-1α 水平[59]。有研究表明，在 TBI 后，miR-21 在脑中的表达增加，可以缓解 BBB 渗漏相关的脑水肿[60]，而血管内皮重建标志物酪氨酸激酶受体-2 (tyrosine kinase with immunoglobulin-like and epidermal growth factor homology domains-2, Tie-2)的激活已被证实缓解 BBB 渗漏，促进紧致表达脑损伤后的连接蛋白[61] [62]。miR-21 可以促进细胞 Tie-2 在脑外伤后的表达，促进颅脑损伤病灶的血管再生，并抑制 BBB 损伤，最终加速血肿吸收，继而减轻脑水肿，改善动物模型的神经功能预后[63]。由上述研究发现得出 HIF-1α 的表达对于颅脑损伤的预后有着重要的影响作用。

5. 总结及展望

缺氧是影响 TBI 患者病灶吸收和神经功能恢复的重要因素，氧感知通路 HIF-1α 通过一种放大作用促进 HIF-1α 下游 miR-21 通路激活，最终 miR-2 通过抑制 PTEN 的表达和促进 Tie-2 表达，促进血管重建，继而加快血肿吸收，阻止水肿进展，最终改善 TBI 患者的神经功能预后。与此同时，TBI 病灶的局部微环境缺氧因血管重建而逐渐改善，整个放大环路终止。而目前针对该通路在低氧环境下的验证尚未提出，现阶段有多种研究都不同程度地评估了 HIF-1α 作为治疗靶点及 HIF-1α 抑制剂的有效性，但目前临床上尚无延缓或逆转颅脑疾病进展的 HIF-1α 抑制剂。那么我们在未来的研究中应该需要更多的动物及临床试验对 HIF-1α 靶点调控进行深一步的研究，将有助于改善临床患者的生活质量。

利益冲突

文章所有作者共同认可文章无相关利益冲突。

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