·综　　述·

miRNA与蛛网膜下腔出血关系的研究进展

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【关键词】蛛网膜下腔出血；微小核糖核酸；MicroRNA；miRNA
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蛛网膜下腔出血(subarachnoid hemorrhage, SAH)是临床上常见的脑血管病，具有高病死率和高致残率的特点[1]。从分子角度研究SAH的发病机制是近年来SAH研究的热点。研究表明，微小RNA(microRNA，miRNA)作为重要的调节因子，与SAH的发病密切相关。本文就miRNA在SAH中的研究进展做一综述。

1 miRNA与SAH的关系

miRNA是内源性非编码RNA，长度在18~25 bp，可通过结合mRNA的3′-UTR，调节基因的表达[2]。miRNA依赖序列互补性的两个原理负调控靶基因表达：①miRNA与靶基因mRNA完全互补，导致其降解；②miRNA与靶基因mRNA不完全互补，在蛋白质翻译水平抑制靶基因的表达。目前，已发现1 000个以上的miRNA，它们可调节30%以上的基因表达，并形成复杂的调控网络。

研究证实miRNA与SAH的发病存在着紧密联系。miRNA不但参与SAH后神经细胞凋亡、炎症发生、神经突触重塑和其它细胞功能，而且SAH病人血液、脑脊液及大鼠SAH模型大脑中动脉均检测到miRNA的差异性表达。研究表明，miR-15a升高可能导致血管表型的改变，从而导致脑血管痉挛(cerebral vasospasm, CVS)。持续高水平的miR-502-5p与动脉瘤性蛛网膜下腔出血(aneurysmal subarachnoid hemorrhage, aSAH)病人的预后不良有关[3]。上调miRNA-24能够抑制内皮型一氧化氮合酶的表达，可导致SAH后CVS[4]。

2 SAH后miRNA的差异性表达

研究发现，SAH病人或动物模型存在差异性表达的miRNA，与SAH发生相关的信号通路受miRNA的调节[5]。

2.1 SAH动物模型异常表达的miRNA　目前，SAH大鼠模型大脑中动脉miR-30a和miR-143显著上调[6]。Yang等[7]在小鼠SAH模型中发现褪黑素通过调控H19/miR-675/p53/细胞凋亡和H19/let-7a/神经生长因子/细胞凋亡信号通路，对SAH后早期脑损伤(early brain injury, EBI)有保护作用。Yu等[8]在SAH小鼠模型中发现p53/miR-22的神经保护作用可能调节SAH后炎症反应和细胞凋亡。

2.2 SAH病人异常表达的miRNA　Su等[9]发现SAH病人外周血miR-132和miR-324上调。研究发现SAH病人脑脊液66个miRNA表达增加，含miR-21和miR-221[10]。还有研究发现，动脉瘤性SAH病人脑脊液miR-92a和let-7b表达随着时间延长明显降低，而miR-491随着时间延长明显增加[11]。最近，Stylli等[2]发现13个miRNA与SAH后CVS有关，包括miR-27a-3p、miR-516a-5p、miR-566和miR-1197。

3 与SAH相关的几种主要miRNA的作用机制

3.1 miR-24　属于miR-23~27~24家族，在血管内皮细胞(vascularendothelialcells，VECs)中高表达，调控VECs特异性基因的表达。研究发现，miR-24与内皮型一氧化氮合酶(nitric oxide synthase 3，NOS3)mRNA 3′-UTR结合，抑制NOS3的表达；SAH病人血miR-24和NOS3的表达水平呈负相关；而且，CVS病人miR-24表达水平升高，而NOS3则相反[12]。在线miRNA数据库分析显示，NOS3为miR-24的靶点。

3.2 miR-206　研究显示，卡英酸(kainic acid，KA)诱导的癫痫大鼠模型海马组织miR-206的表达明显降低；过表达miR-206，可作用于靶基因CCL2，降低癫

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痫发作活性，减少神经元丢失[13]。研究表明，脑源性神经营养因子是miR-206的靶基因，调控焦虑相关行为和慢性收缩损伤引起的神经性疼痛[14]。Zhao等[15]研究发现，应用SAH大鼠模型，敲低miR-206，通过靶向作用脑源性神经营养因子，显著改善神经功能缺损、脑水肿和抑制神经元凋亡，从而减轻EBI。

3.3 miR-502-5p 研究显示，miR-502-5p能够促进肿瘤细胞的凋亡，抑制肿瘤细胞的增殖。Lai等[16]研究表明，miR-502-5p可能是SAH的一个潜在的标志物。miR-502-5p作为SAH潜在有价值的诊断指标的机制尚不清楚，有待进一步研究。

3.4 miR-15a 研究表明，miR-15a参与缺血诱导的脑血管内皮损伤或后肢缺血中内皮细胞（endothelial cells，ECs）和VSMCs的血管生成或增殖。此外，miR-15a还与缺血后的脑血管保护密切相关。Zheng等[17]研究发现，miR-15a通过诱导KLF4上调，抑制ECs和VSMCs的增殖和血管生成。最近，Kikkawa等[18]研究显示，SAH后3~5 d脑脊液和血浆miR-15a显著升高，而KLF4表达显著降低。

4 miRNA在治疗应用方面的局限性

尽管，miRNA及其相关的信号通路在SAH发病过程中具有重要作用，但能否用于临床并发症的治疗靶点还需很长路要走。一个特定的miRNA可以有数百个靶基因，而一个单独的基因通常有多个靶向miRNA。但多个靶基因具体到哪一个才是被miRNA所影响并参与SAH发病，仍未有效解决。从治疗方面讲，miRNA可以同时调控多种蛋白质的表达，但是这既有利亦有弊：一方面，miRNA能够调控同SAH相关的蛋白质表达；另一方面，与疾病无关的mRNA可能也同时受到影响，产生不可预知的副作用。除此之外，对于miRNA抑制剂的应用，抑制剂是否能够作用除miRNA外的其它靶点，这也是一个问题。因此，miRNA做为应用于SAH的诊治，仍需要解决以下几个问题：①精确下游的靶mRNA；②如何有效避免miRNA治疗所带来的副作用；③促进剂与抑制剂作用的具体靶点；④抑制剂通过血脑屏障率低；⑤抑制剂与已进入临床药物药理学相互影响的问题；⑥miRNA的脱靶问题。

综上所述，miRNA在SAH发病过程中具有重要的作用。但是，从技术角度来说，因组织含量少，特异性要求高等，使miRNA的检测并不十分容易。目前，miRNA的检测方法主要是Northern blot、PCR和芯片检测。随着技术的发展和研究的深入，会有更多的miRNA被证实参与SAH的发生、发展过程。

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