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◇综述◇

外泌体微RNA在高血压发病机制中的研究进展

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摘要: 外泌体微RNA(microRNA,miRNA)稳定存在于血浆、尿液及其他体液中。近期研究表明,外泌体miRNA在高血压发病机制、早期诊断、治疗等方面都具有良好的应用前景。因此,该研究总结了外泌体miRNA在高血压中的研究进展,以分析其潜在的应用价值。

关键词: 外泌体; 高血压; 内皮细胞; 肾素-血管紧张素-醛固酮系统; 外泌体微RNA

Research progress of exosomal miRNA in the pathogenesis of hypertension

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Abstract: Exosomal microRNA (miRNA) is stably present in plasma, urine and other body fluids. Recent studies have shown that secreted miRNA has a good application prospect in the pathogenesis, early diagnosis and treatment of hypertension. Therefore, this review summarizes the research progress of exosomal miRNA in hypertension in order to analyze its potential application value.

Key words: Exosomes; Hypertension; Endothelial cells; Renin-angiotensin-aldosterone system (RAAS); Exosomal miRNA

根据世界卫生组织2023年的一份报告,全世界范围内高血压病人约12亿[1]。高血压已经成为心血管系统疾病的主要危险因素。诊室血压测量目前仍然是确诊高血压的主要手段,但诊室血压测量受环境及精神因素影响极大,因此,新型分子生物标志物的开发对高血压的诊断具有重要的临床意义。据报道,微RNA(miRNA)可以调控大量信号通路,这些信号通路之间通过外泌体实现细胞间信息传递[2]。近些年有关于外泌体miRNA在心血管系统疾病中的研究越来越多,本研究总结了外泌体miRNA在高血压发病机制中的相关研究,希冀为高血压的基础实验研究及临床诊断、治疗提供思路。

1 外泌体

外泌体是通过内吞途径形成的直径约40~150 nm的细胞外囊泡[3],主要负责细胞间的信息传递和物质转运。几乎所有类型的细胞都能够分泌外泌体,特别是在淋巴细胞、内皮细胞、树突状细胞中。

外泌体形成始于细胞质膜向内出芽形成核内体。早期核内体与外泌体分泌的质膜蛋白内化到细胞质中,在细胞质结构域泛素化形成晚期核内体[4]。转运必需内体分选复合体-0(endosomal sorting complex required for transport 0,ESCRT-0)识别泛素化的胞质结构域并将该复合物导向ESCRT-Ⅰ。ESCRT-Ⅰ伴ESCRT-Ⅱ启动膜向内出芽,使晚期核内体吞噬蛋白质、mRNA、脂质和miRNA并形成腔内囊泡(intraluminal vesicles,ILVS)。随后,ESCRT-Ⅱ在ILVS开放位点招募ESCRT-Ⅱ来分离晚期核内体内的胞质生物分子。每个晚期核内体可以容纳一个以上的ILVS,并形成多泡体。多泡体要么与质膜再次融合释放出现在被称为"外泌体"的ILVS,要么与溶酶体融合降解[5]。

2 miRNA

miRNA是内源性、长度为22~26个核苷酸的非编码RNA。miRNA通过mRNA和miRNA的三个主要非翻译区(30UTR)序列之间的Watson-Crick碱基配对来抑制mRNA的转录、翻译,miRNA也可以直接剪切mRNA并促进其降解[6-7]。miRNA被认为在调控生物生长发育过程中具有重要作用。

转录起始,miRNA被核内RNA聚合酶Ⅱ转录为长度约为100~1 000 nt的转录初产物(pri-miRNA)。紧接着pri-miRNA被核酸酶Drosha在DGCR8作用下切割为一个60 nt核苷酸的短茎环结构,称为miRNA

前体(pre-miRNA)[8]。然后,pre-miRNA通过输出蛋白5被输送到细胞质中。在胞质中,pre-miRNA经过核酸酶Dicer的进一步处理,产生双链RNA分子[7]。双链中一条miRNA被选为成熟的miRNA调控基因表达,而另一条则被作为"客链"降解[7,9]。

据估计,人类基因组编码的miRNA已远远超过1 000个,它们调节约50%的基因组的活性[10]。miRNA是多种生物过程的非常重要的调节因子,包括细胞增殖、凋亡和分化。因此,它们表达的任何细微变化都可能引起细胞功能障碍,导致疾病的发展。miRNA不仅可以在细胞和组织中发现,而且还可以在体液中自由循环,如血清、血浆和尿液等。循环中的miRNA在体液中具有显著的稳定性[11],这使我们能够通过分析其浓度和成分来诊断各种疾病,包括高血压,甚至能被应用于临床指导各种治疗方案。

3 外泌体miRNA

外泌体是miRNA的细胞外载体。miRAN的载体并非外泌体一种,一些蛋白质和脂质载体在miRAN的转运中也起着重要作用。根据ExoCarta数据库数据,外泌体内容物包括9 769种蛋白质、3 408种mRNA、2 838种miRNA和1 116种脂质[12]。在外泌体的循环过程中,miRNA可以被邻近和/或远处的细胞吸收来调节受体细胞的活性。外泌体携带其成分(包括原始细胞的miRNA)与相邻或远处的细胞相互作用,在生理和病理生理条件下进行细胞间的信息交换[13]。外泌体miRNA能承受细胞外恶劣的环境,在体液循环中更加稳定,因此具有巨大的潜力成为非侵入性疾病生物标志。

4 外泌体miRNA与高血压

外泌体miRNA反映了原始细胞的状态,其调控具有组织特异性[14]。外泌体miRNA通过调控基因转录来调节细胞通路,具体来说,与高血压相关的外泌体miRNA包括内皮外泌体miRNA、肾脏外泌体miRNA、血管平滑肌细胞的外泌体miRNA以及肾素-血管紧张素-醛固酮系统(RAAS)的外泌体miRNA[15]。Liu等[16]通过下一代测序技术分析了自发性高血压大鼠(SHR)和Wistar(Wistar-Kyoto,WKY)大鼠血浆外泌体的miRNA表达谱,发现WKY和SHR大鼠的血浆外泌体间有27个miRNA表达有显著差异,其中与WKY大鼠相比,SHR的外泌体中有23个miRNA上调。在23个上调的miRNA中有10个被证实参与了高血压特异性的信号通路,分别为miR-148a-3p、miR-122-5p、miR-143-3-3p、miR-192-7p-5p、miR-215、miR-1403p、miR-99a-5p、miR-378a-3p和miR-486,但关于外泌体miRNA调节细胞通路的具体机制,文中并未叙述,未来研究应关注外泌体miRNA调节高血压通路的具体分子机制。

4.1 高血压病人内皮细胞外泌体miRNA的研究

血管内皮多方面参与高血压的发生发展。血管内血压升高时,内皮细胞被激活,炎性因子和促凝介质释放,中性粒细胞和血小板黏附于血管壁,最终内皮细胞功能失调、血管舒张功能受损、血管内血栓形成[17]。内皮细胞功能障碍与高血压病人的靶器官损伤和预后密切相关。内皮细胞在血管网状结构的发育、维持和重塑中也起着重要作用。内皮细胞介导的高血压疾病发病的一个典型特征是功能微血管的丧失和靶器官水平上的血管生成障碍[18]。

越来越多的证据表明,外泌体miRNA在高血压内皮功能障碍和血管生成能力降低的发病机制中起重要作用。在内皮细胞中,Dicer具有组成性表达,并在血管生成中发挥重要作用。体外和体内Dicer的缺乏导致了血管生成和氧化还原信号通路的严重失调[19]。

内皮细胞特异性的miR-126在血管生成与维持血管完整性中起着关键作用。miR-126的缺失会导致血管渗漏、出血和胚胎死亡[20]。外泌体miR-126,通过转移内皮细胞凋亡小体、诱导基质细胞衍生因子-1(stromal cell-derived factor-1,SDF-1)的产生以防止细胞凋亡和内皮祖细胞的动员[21]。此外,间充质干细胞来源外泌体miR-126通过激活磷脂酰肌醇-3-激酶(phosphatidylinositol-3-kinase,PI3K)/蛋白激酶B(protein kinase B,Akt)通路发挥对内皮细胞保护作用[22]。最近的一项研究表明,来自脂肪干细胞的外泌体miR-21通过激活Akt、ERK以及诱导HIF-1α、SDF-1表达促进血管生成[23]。

许多其他外泌体miRNAs已被发现具有促血管生成作用(miR-135b、-130a、-23a、-155、-143、-26a、-27a、-221)[24-31]或具有抑制血管生成作用(miR-320、-224)[32-33]。

4.2 外泌体miRNA与RAAS 目前证据表明,外泌体miRNA可以调节RAAS系统的有害和有益途径,分别为血管紧张素转换酶(angiotensin-converting enzyme,ACE)/血管紧张素Ⅱ(angiotensinⅡ,ANGⅡ)通路和血管紧张素转换酶2(angiotensin converting enzyme 2,ACE2)/Mas通路。RAAS成分的调节不仅影响动脉血管和内皮细胞的结构和功能,还能减轻或放大炎症,而炎症是血管重塑和血压调控的关键因素。体外和体内研究表明,miR155-5p的过表达通过直接降低ACE基因水平来降低ANGⅡ肽,发挥减轻血管重塑、抑制血管增殖、降低血压的作用[34]。与正常血压WKY大鼠相比,SHR大鼠中miR-155-5p水平显著降低,表明miR-

155-5p可能通过RAAS在调节血压中发挥作用。外泌体miR-145、miR-143在高血压状态下的表达均下降,且与血压呈负相关[35-36]。Dahan等[37]研究表明,miR-143通过间接诱导miR-143/145基因敲除小鼠的ACE来调节血管平滑肌分化。外泌体miRNA还能够调节ACE2,ACE2通过降解ANGⅡ为Ang-(1-7)来抵消ACE的作用,Ang-(1-7)作用于Mas受体,产生与ACE/ANGⅡ通路相反的作用[38]。研究发现,高血压病人血浆中miR483-3p表达下调[39]。miR483-3p靶向作用于血管平滑肌细胞中ACE2,表明ACE2的表达增强可以抑制心肌肥厚。经脂多糖处理的人单核细胞外泌体miR-27a降低了内皮细胞中Mas受体的表达,在此过程中,内皮细胞性一氧化氮合酶(endothelial nitric oxide synthase,eNOS)磷酸化也随之降低,而eNOS磷酸化对维持血管张力至关重要[40]。

4.3 高血压病人肾外泌体miRNAs的研究 肾脏在维持血压方面也起着不容忽视的作用,高血压是肾脏疾病的原因或结果。肾脏通过调节血管外周阻力和心输出量调节血压,其机制涉及钠稳态、血容量、动脉血管阻力。持续性高血压引起肾小球局部损伤,坏死性肾小球硬化是高血压肾损害的标志。另一方面,肾脏疾病、遗传性或发育性肾脏畸形也可导致高血压。实际上,出生时肾小球数量的下降通常是导致高血压的原因[41]。Dicer和特异性miRNA敲除动物的显著表型表明miRNA在肾脏发育和肾脏功能调节中起着重要作用[42]。miRNA在肾脏生理和疾病中的作用也得到了综述[43-44]。

肾间质纤维化见于各种肾小球疾病晚期,是肾脏衰老和慢性肾功能衰竭的重要病理特征。间充质干细胞来源外泌体miR-133b可抑制转化生长因子-β1诱导的肾小管上皮己糖激酶2(hexokinase2,HK2)-间质转化(epithelial-mesenchymal transition,EMT),缓解肾间质纤维化[45]。Jeon等[46]研究表明,来自肾小球足细胞的外泌体miR-424、149诱导HK2细胞的凋亡和p38磷酸化,说明外泌体miR-424、149加速肾小球疾病中肾小管损伤的发展。

高血压引起肾脏内固有细胞受损后释放的细胞因子会吸引血液中的一系列炎症细胞,这些细胞浸润到系膜区、血管区和肾间质区引起炎性反应,这反过来又促进了肾脏内固有细胞的表型转化。此时,肾脏固有细胞释放出一系列肾毒性细胞因子、生长因子,这些影响因子使肾间质中的成纤维细胞增生、分化并转化为肌成纤维细胞。外泌体介导的细胞间通信被认为参与各种疾病,包括肾纤维化。Zhao等[47]研究表明,来自肾小管上皮细胞的外泌体miR-21可通过阻断肾脏中的miR-21/磷酸酶及张力蛋白同源物(phosphatase and tensin homolog deleted on chromosome ten,PTEN)/Akt途径激活成纤维细胞加速肾纤维化的发展。miR-21已被证明有望成为心血管疾病中心肌梗死诊断的新靶点,但其在高血压中的价值尚有待进一步探究[48]。Wang等[49]发现儿童局灶性节段性肾小球硬化症病人尿液外泌体miR-193a水平与肾小球硬化的程度呈正相关。

4.4 高血压病人尿外泌体miRNAs的研究 尿液中存在一些“跨肾”的尿外泌体miRNA,它们来源于泌尿道之外的细胞,经血液循环通过肾小球滤过,最终以尿外泌体方式排出[50]。尿白蛋白排泄(urinary albumin excretion,UAE)是高血压心血管风险和肾损伤的标志。一项针对UAE升高的高血压病人的研究发现,在UAE高血压受试者中有29个异常的循环miRNA,这些miRNA调控21条通路。研究还发现4个外泌体miRNA水平的变化与蛋白尿相关。研究表明,外泌体miR-26a似乎在调节足细胞损伤相关效应因子中起关键作用[51]。这些发现支持使用外泌体miRNA作为心血管风险进展的生物标志物和早期肾损伤的治疗工具。

5 展望

尽管科学界不断努力了解原发性高血压的发病机制,但在分子水平上的尚未取得显著成果。外泌体miRNA在心血管领域的价值研究已经得到证实。阐明外泌体miRNA在高血压发病机制作用是有价值的,对高血压外泌体miRNA的研究可能会开发新的治疗方法来预防和逆转高血压的结果。但目前阶段,外泌体miRNA分离及纯化技术尚未成熟,有待进一步提高。

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◇综述◇

青春期男性乳房发育的病因及发病机制研究进展

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摘要: 青春期男性乳房发育症(pubertal gynecomastia,PG)是一种男性乳腺良性增生疾病,90%的发病者属于生理性,且具有自限性。雌激素与雄激素水平比值的短暂失衡被认为是男性乳房发育的主要原因,但这也可能是内分泌相关性腺疾病及遗传基因病的潜在征兆,引起生殖系统疾病及社会心理障碍。PG的病因及发病机制对认识及诊疗PG具有重要意义,故该研究就国内外PG的病因及发病机制相关研究作一综述,归纳其关键病理环节,如雄激素缺乏相关性男性乳房发育和高雌激素相关性男性乳房发育,以期为PG的早期筛查及诊断提供一定的参考依据。

关键词: 男子乳腺发育; 性腺发育不全; 性腺功能减退症; 青春期; 病因; 发病机制; 综述

Progress in the etiology and pathogenesis of pubertal gynecomastia

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