MicroRNA: 线粒体功能调控的新机制

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摘要 线粒体是真核生物进行能量代谢的主要场所, 在自由基产生、细胞凋亡、衰老等生理病理活动中也起到重要作用。线粒体功能受核基因和线粒体基因共同调控, microRNA(miRNA)介导的基因转录后调控是重要机制之一。核基因编码的miRNA不仅可以通过调控核基因编码的线粒体相关蛋白的表达影响线粒体结构和功能, 而且可以进入线粒体并调控线粒体基因的表达。另一方面, 线粒体基因也可能编码miRNA, 直接调控线粒体基因表达或转运至胞质调控核基因的表达。

关键词 miRNA; 线粒体; mitomiR; 能量代谢; 细胞凋亡

MicroRNA: A New Mechanism for Regulation of Mitochondrial Function

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Abstract Mitochondria are the energy powerhouse of the cell, and they play an important role in other physiological and pathological process, such as free radical production, cell apoptosis and aging. MiRNA-mediated post-transcriptional regulation of gene expression is one of the important mechanisms that regulate mitochondria functions which rely on the crosstalk between nuclear genome and mitochondrial genome. The nuclear encoded miRNA not only regulates the structure and function of mitochondria through modulating mitochondrial-related proteins encoded by the nuclear genome, they can also translocate into the mitochondria and regulate mitochondrial genome expression. Besides, the mitochondrial genome may also encode miRNA that could be immediately active on the mitochondrial transcripts or exported in the cytosol in order to interfere with genomic mRNA.

Key words miRNA; mitochondrion; mitomiR; energy metabolism; apoptosis

前言

线粒体是真核细胞内重要的细胞器, 被誉为细胞的“发电站”。同时, 线粒体控制着细胞的生长、凋亡等生命活动, 其功能受核基因和线粒体基因(mtDNA)共同调控。mtDNA仅有37个基因, 编码13种线粒体氧化磷酸化(oxidative phosphorylation, OXPHOS)复合体亚基, 22种tRNA和2种rRNA[1]; 而其余的OXPHOS复合体亚基, 以及DNA聚合酶、转录因子、装配因子、装运蛋白、代谢酶等, 均由核基因编码并在细胞质核糖体上合成, 随后转运到线粒体[2]。由此可见, 细胞核与线粒体在DNA复制、转录和蛋白质等水平上存在密切的信息交流。最近研究表明, microRNA(miRNA)介导的基因转录后调控是线粒体功能调控的重要方式之一。

miRNA是一类真核生物中广泛存在的内源性非编码RNA, 由20-25个核苷酸组成。miRNA通过抑

收稿日期: 2012-08-27 接受日期: 2012-09-28

国家重大科学研究计划(批准号: 2012CB966800D), 国家自然科学基金(批准号: 30971599/C060503)和教育部新世纪优秀人才支持计划(批准号: NCET-06-0526)资助的课题

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Received: August 27, 2012 Accepted: September 28, 2012

This work was supported by the National Basic Research Program of China (Grant No.2012CB966800D), the National Natural Science Foundation of China (Grant No.30971599/C060503) and the Program for New Century Excellent Talents in University (Grant No.NCET-06-0526)

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制靶mRNA翻译或促进其降解调控生物体生理病理过程[3]。miRNA参与调控线粒体功能, 如能量代谢、细胞凋亡、分裂/融合等。早期研究认为, miRNA由核基因组编码, 细胞质是其发挥基因调控功能的唯一场所。随着研究的深入, 在细胞核[4]和胞质的P-小体[5]中均检测到成熟体miRNA, 线粒体等亚细胞器中是否含有miRNA也逐渐成为研究的新热点。最近, 研究者相继在大鼠[6]和小鼠[7]的肝脏、人骨骼肌[8]、Hela细胞[9]等细胞的线粒体中发现了pre-miRNA和miRNA, 并将这类定位于线粒体中的miRNA命名为mitochondrial miRNA(mitomiR)[9]。本文将综述线粒体相关miRNA的最新研究进展, 并着重介绍mitomiR及参与调控线粒体功能的核基因编码miRNA。

1 mitomiR

2009年, Kren等[6]通过改进线粒体富集纯化的方法, 率先在成年大鼠肝脏线粒体中发现了15种核基因编码的miRNAs, 首次证明线粒体中也含有miRNA。2010年, Bian等[7]在小鼠肝细胞线粒体中发现了一类独特的miRNA, 它们在线粒体总miRNA中的比例明显区别于在细胞总miRNA中的比例。2011年, Barrey等[8]在人线粒体基因组中发现25种pre-miRNA和33种miRNA的潜在编码序列, 并首次证实人类肌细胞线粒体中存在miRNA前体(pre-mir-302a、pre-let-7b)和成熟miRNA(mir-365)。同年, Bandiera等[9]在Hela细胞线粒体中发现13种含量丰富的miRNAs, 并将其命名为mitomiRs。2012年, Das等[10]证实核基因编码的miR-181c可以转运到线粒体, 通过调控线粒体蛋白COX-1影响线粒体的能量代谢, 第一次将mitomiR与线粒体基因进行功能联系。

生物信息学研究显示, 核基因组和线粒体基因组均存在mitomiR靶基因位点。其中, mtDNA中有169个miRNA靶位点, 38个位于*ND6*基因, 而*ND4L*、*ND4*、*COX-1*中的miRNA靶位点则相对较少(<10)[8]。线粒体基因组中存在miRNA靶位点, 说明miRNA可能参与调控线粒体基因的表达。此外, Bian等[7]和Bandiera等[9]均在线粒体中发现了miRNA功能依赖蛋白AGO2, 为miRNA调控线粒体基因表达增添了新的证据。

目前, mitomiR的来源有外转运和内合成两种假说[8]。外转运假说是指mitomiR由核基因编码并转运到线粒体中, 如参与肌肉细胞增殖和分化的"myo-miRNA(Muscle-specific miRNA)", 包括miR-133a、miR-1、miR-181a、miR-181b[11-13]等。这些miRNAs可能通过一种未知的转运系统转运至线粒体。内合成假说是指mitomiR由mtDNA编码并在线粒体中加工成熟, 如在线粒体中检测到miRNA前体(pre-mir-302a和pre-let-7b)。生物信息学研究显示, mtDNA含有pre-mir-302a和pre-let-7b等miRNA前体的编码序列, 表明mtDNA可能编码miRNA, 直接作用于线粒体内的mRNA或者运至胞质以干扰核基因组mRNA的表达, 调节细胞相关功能。

mitomiR的研究虽然取得了一定的进展, 但是仍存在一些技术难题。首先, 获取线粒体总RNA比细胞总RNA更加繁琐。在提取线粒体RNA过程中, 如何保证RNA的完整且不受胞质RNA污染, 是首要解决的问题; 其次, 虽然已知线粒体中存在miRNA功能依赖蛋白AGO2, 但是其他的辅助蛋白以及miRNA剪接体系蛋白是否也存在于线粒体中, 是证明线粒体miRNA在线粒体中加工而成或/并发挥功能的重要证据; 第三, 缺乏线粒体miRNA功能研究的有效方法。目前, 主要是通过转染miRNA模拟物或抑制剂以增加或降低胞质miRNA含量, 但这种方法是否能用于改变线粒体miRNA, 仍是未知。只有解决了上述困难, 才能对线粒体miRNA进行全面而深入的研究。

2 miRNA与能量代谢

线粒体是真核生物中糖类、脂肪和氨基酸等生物大分子氧化代谢的主要部位, 是ATP产生的主要场所。miRNA通过调控能量代谢过程的多个环节影响线粒体能量供应。目前, 已发现10种miRNAs参与调控线粒体能量代谢(表1)。

低氧在多种生理病理过程中发挥重要作用, 如癌症、心肌梗死、中风等。低氧环境下, 低氧诱导因子-1α(hypoxia-inducible factor-1α, HIF-1α)激活多种信号途径调控线粒体功能, 如低氧时细胞能量代谢由线粒体氧化磷酸化转变为糖酵解(巴斯德效应)。自2007年Kulshreshtha等[24]首次报道低氧能够影响miRNA的表达以来, 已发现一系列HIF-1α相关的miRNA。其中, miR-210是对低氧最敏感的miRNA之一。miR-210直接抑制Fe-S簇装配蛋白1/2(iron-sulfur cluster assembly protein 1/2, ISCU1/2)的合成, 而ISCU1/2对于三羧酸循环中柠檬酸向异柠檬酸

表1 参与调控线粒体代谢的miRNA

Table 1 miRNA associated with mitochondrial metabolism

miRNA miRNA	靶基因 Target gene	功能 Function	疾病 Disease	变化 Change
miR-696[14]	*PGC-1α*	Upregulates aerobic metabolism	Physical activity	Decrease
miR-743a[15]	*MDH*	Maintains the redox state of the neuron under oxidative stress	Alzheimer's disease	Decrease
miR-183[16]	*IDH2*	Decreases O_2 consumption and ATP production	Hypercapnia	Increase
miR-210[17]	*SDHD*	Leads to complex II dysfunction and HIF-1α stabilization	Non-small cell lung cancer	Increase
miR-210[18]	*ISCU*, *COX10*	Mediates cell metabolic switch to glycolysis to adapt to the hypoxia microenvironment	Colon cancer, breast cancer, esophageal adenocarcinoma	Increase
miR-338[19]	*COX IV*	Decreases axonal oxidative phosphorylation and function	Neurodegenerative diseases	Increase
miR-181c[10]	*COX-1*	Increases mitochondrial respiration	Cardiac myocytes	Overexpressed
miR-101[20]	*ATP5B*	Inhibits HSV-1 replication	HSV-1 infection	Increase
miR-15b[21]	*Arl2*	Decreases cellular ATP levels via inhibition the ADP/ATP exchange function of ANT	Heart failure	Increase
miR-15a[22]	*UCP-2*	Inhibits the synthesis of insulin	Type 2 diabetes	Decrease
miR-23a/b[23]	*GLS*	Enhances glutamine metabolism, provides energy and nitrogen for the growth of cancer cells	Prostate cancer	Decrease

的转变是不可或缺的[18]。此外, miR-210可以降低琥珀酸脱氢酶(succinate dehydrogenase, SDH)亚基D(SDHD)含量, 导致电子传递链复合体II功能障碍, 琥珀酸盐含量升高, 从而抑制脯氨酰羟化酶结构域蛋白(prolyl hydroxylase domain proteins, PHD)对HIF-1α的降解, 增强HIF-1α稳定性[17]。HIF-1α、miR-210、ISCU1/2及SDHD通过形成级联反应和反馈环, 下调线粒体的有氧呼吸, 增强细胞对低氧环境的适应。

miRNA还参与调控能量代谢的其他环节。(1) miRNA调控ATP合成酶活性。单纯疱疹病毒-1(herpes simplex virus-1, HSV-1)感染时, 宿主细胞编码的miR-101表达增加, 抑制ATP5B活性以减少细胞内ATP的产生, 从而影响病毒复制, 起到抗病毒作用[20]; (2)miRNA调控氧化与磷酸化的偶联。miR-15a抑制解偶联蛋白-2(uncoupling protein-2, UCP-2)的合成, 增加氧消耗和ATP合成[22]; (3)miRNA调控ADP/ATP转运。过表达miR-15b将降低ADP核糖基化样因子(ADP-ribosylation factor-like 2, Arl2)的表达, 影响ADP/ATP转运, 抑制细胞内ATP合成[21]; (4)miRNA调控谷氨酰胺代谢。癌细胞中, c-Myc的激活抑制miR-23a/b表达, 增加其靶蛋白线粒体谷氨酰胺酶(mitochondrial glutaminase, GLS)的含量, 从而促进谷氨酰胺转化成谷氨酸盐, 促进癌细胞生长[23]。

3 miRNA与细胞凋亡

线粒体起始的细胞凋亡过程中, 线粒体通透性转变孔开放, 线粒体跨膜电位降低, 细胞色素c(Cyt-c)、AIF等凋亡因子释放到胞质, 引发caspase级联活化反应或直接诱导细胞凋亡。此外, 死亡受体通路激活的caspase-8可切割Bid成为活化的tBid, 诱导促凋亡因子Bax和Bak寡聚化, 启动线粒体凋亡途径[25]。miRNA通过调节线粒体凋亡途径中多种蛋白参与调控细胞凋亡。目前, 已发现15种miRNAs参与调控细胞凋亡(表2)。

多种miRNAs参与人类恶性肿瘤的发生, 发挥抑癌或致癌作用。Cimmino等[29]发现慢性淋巴细胞白血病(chronic lymphocytic leukemia, CLL)中miR-15a/16-1表达下调, 导致抗凋亡因子Bcl-2活化, 抑制细胞凋亡。Gao等[40]发现, miR-15a/16-1和三氧化二砷(As_2O_3, ATO)在诱导白血病细胞凋亡中起到协同作用, 即miR-15a/16-1或ATO单独作用于白血病细胞, 线粒体跨膜位势仅轻微丧失; 但两者同时作用会导致线粒体膜势大幅度丧失、细胞色素c释放、caspase-3激活和PAPR降解, 引发细胞凋亡, 极大提升治疗效果。因此, miRNA有望成为疾病治疗的新思路。

miRNA还调控线粒体凋亡途径中的其他蛋白。(1)miRNA调控caspase依赖/非依赖凋亡。caspases的主要内源抑制物——X连锁凋亡抑制剂(X-linked inhibitor of apoptosis, XIAP)是miR-23a的靶蛋白。中风后, miR-23a的表达在男女中表现出显著差异, 最终导致男性脑细胞以caspase非依赖形式凋亡, 而女

表2 参与调控细胞凋亡的miRNA

Table 2 miRNA associated with apoptosis

miRNA miRNA	靶基因 Target gene	功能 Function	疾病 Disease	变化 Change
miR-101[26]	*Mcl-1*	Inhibits mitochondrial pathway of apoptosis	Hepatocellular carcinoma	Decrease
miR-128[27]	*Bax*	Induces mitochondrial pathway of apoptosis	Human embryonic kidney cells	Overexpressed
miR-148a[28]	*Bcl-2*	Inhibits mitochondrial pathway of apoptosis	Colorectal cancer	Decrease
miR-15a/16-1[29]	*Bcl-2*	Inhibits mitochondrial pathway of apoptosis	Chronic lymphocytic leukemia	Decrease
miR-15b/16[30]	*Bcl-2*	Inhibits mitochondrial pathway of apoptosis, actives hepatic stellate cells and liver fibrosis	Liver fibrosis	Decrease
miR-29[31]	*Bcl-2*, *Mcl-1*	Inhibits mitochondrial pathway of apoptosis	Hepatocellular carcinoma	Decrease
miR-497[32]	*Bcl-2*	Induces mitochondrial pathway of apoptosis	Chronic alcoholism	Increase
miR-885-3p[33]	*Bcl-2*	Induces the cisplatin-induced TP53-dependent mitochondrial apoptosis	Squamous cell carcinoma	Increase
miR-138[29]	*Caspase-9*	Inhibits mitochondrial pathway of apoptosis, actives hepatic stellate cells and liver fibrosis	Liver fibrosis	Increase
miR-23a[34]	*XIAP*	Leads to caspase-dependent cell death in females and caspase-independent cell death in males	Cerebral ischemia	Increase in females, Decrease in males
miR-221/ miR-222[35]	*PUMA*	Inhibits mitochondrial pathway of apoptosis	Lung cancer, breast cancer	Increase
miR-494[36]	*PTEN*, *ROCK1*, *FGFR2*, *LIF*, *CaMK*II*δ*	Inhibits Akt-mitochondrial signaling pathway	Ischemia/reperfusion-induced cardiac injury	Decrease
miR-23b*[37]	*POX*	Promotes the cell survival through increasing HIF signaling and decreasing the generation of ROS	Renal cancer	Increase
miR-1[38]	*IGF-1*	Induces mitochondrial pathway of apoptosis	Diabetes mellitus	Increase
miR-23a-27a-24-2 cluster[39]	*FADD*	Induces mitochondrial pathway of apoptosis	Human embryonic kidney cells	Overexpressed

性则以caspase依赖形式凋亡[34]; (2)miRNA调控Atk-线粒体途径细胞凋亡。miR-494调节Atk-线粒体途径中三种促凋亡蛋白(PTEN、ROCK1、CaMKIIδ)和两种抗凋亡蛋白(FGFR2、LIF), 从而保护心脏免受缺血/再灌注引发的损伤[36]。

4 miRNA与ROS的生成

线粒体在消耗氧为机体提供能量的同时, 也会产生活性氧自由基(reactive oxygen species, ROS)。正常生理状态下, 线粒体通过有效的抗氧化系统(包括超氧化物歧化酶和过氧化物酶等)清除ROS, 减少细胞或组织损伤。但随着年龄增加或病理条件下, 细胞抗氧化能力降低或ROS生成速度超过细胞清除速度, ROS在细胞中增多并积累, 最终造成细胞损伤。miRNA通过调节生理病理条件下ROS的生成, 影响机体正常代谢。目前, 已发现4种miRNAs参与调控ROS生成(表3)。

ROS引起的线粒体和mtDNA损伤累积是衰老发生的主要机制。研究发现, *Lin-4*突变的线虫寿命比野生型要短, 并认为*Lin-4*缺失引发的ROS生成增加及线粒体拷贝数减少是其发生的主要原因[44]。此外, 线粒体内清除ROS的两种抗氧化酶——超氧化物歧化酶2(superoxide dismutase 2, SOD2)和硫氧还蛋白还原酶2(thioredoxin reductase 2, Txnrd2)分别是miR-335和miR-34a的靶蛋白。在衰老肾细胞中, miR-335和miR-34a含量显著升高, 抑制SOD2和Txnrd2的合成, 导致细胞中ROS积累, 促进衰老发生[42]。而在前列腺癌细胞中, miR-17*抑制锰超氧化物歧化酶(manganese superoxide dismutase, MnSOD)、谷胱甘肽过氧化物酶2(glutathione peroxidase 2, GPX2)和Txnrd2的活性, 加重肿瘤细胞的氧化损伤, 达到抗肿瘤的目的[41]。

5 miRNA与线粒体动力学

线粒体是具有动态变化的细胞器, 其形成的网状结构可以通过动态的融合/分裂迅速重建以应答细胞的不同生理需求。若动态平衡被打破, 细胞功能受到严重影响, 从而导致疾病的发生。目前, 已发现2种miRNAs参与调控线粒体动力学(表4)。

表3 参与调控ROS生成的miRNA

Table 3 miRNA associated with the production of ROS

miRNA miRNA	靶基因 Target gene	功能 Function	疾病 Disease	变化 Change
miR-17*[41]	*MnSOD*, *GPX2*, *Txnrd2*	Clears up the high levers of ROS production	Prostate cancer	Decrease
miR-335[42]	*SOD2*	Induces premature senescence of young mesangial cells	Kidney aging	Increase
miR-34a[42]	*Txnrd2*	Induces premature senescence of young mesangial cells	Kidney aging	Increase
miR-382[43]	*SOD2*	Promotes the TGF-β induced epithelial—mesenchymal transition of human renal epithelial cells	Renal epithelial cells interstitial fibrosis	Increase

表4 参与调控线粒体动力学的miRNA

Table 4 miRNA associated with the dynamics of mitochondria

miRNA miRNA	靶基因 Target gene	功能 Function	疾病 Disease	变化 Change
miR-30[45]	*p53*	Promotes mitochondrial fission	Cardiac diseases	Decrease
miR-499[46]	*Calcineurin*	Promotes mitochondrial fission	Myocardial infarction	Decrease

在心肌梗死及缺血/再灌注引起的心功能障碍中, 缺氧激活p53, 抑制miR-499的转录, 解除对其靶蛋白——钙神经素的抑制, 促进发动蛋白相关蛋白1(dynamin-related protein 1, Drp1)去磷酸化, 导致Drp1在线粒体中积累并激活Drp1介导的线粒体裂解, 最终促进心肌细胞凋亡[46]。此外, p53是miR-30的靶蛋白, 受到凋亡信号(氧化性应激)的刺激, miR-30的表达量下调, 同样通过激活Drp1参与线粒体动态平衡调控[45]。

尽管目前已经发现一些miRNA参与调控线粒体动力学, 但大多数与线粒体的分裂相关, 而参与线粒体融合的较少。miRNA调节线粒体动力学的具体机制仍有待进一步研究。

6 小结与展望

线粒体作为真核生物重要的细胞器, 在维持细胞正常的生理活动中起到枢纽作用。线粒体功能障碍会影响细胞功能, 从而导致病变。线粒体功能的正常发挥离不开核基因组和线粒体基因组的相互作用。然而, 目前关于核基因组与线粒体基因组间的相互调控机制所知甚少。miRNA介导基因转录后调控, 在调节生理病理条件下线粒体结构和功能中具有重要作用。mitomiR的发现, 表明miRNA可能参与了细胞核和线粒体间的信息交流, 有助于核基因和线粒体基因互作机制的研究。此外, 研究miRNA与线粒体功能障碍的关系, 有利于阐明线粒体疾病的致病机制, 为线粒体相关疾病的医学治疗方案提供新的思路。

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