微RNA在肿瘤细胞糖代谢中的功能

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摘要 大多数癌细胞产生能量是通过高速率糖酵解, 然后在胞液中进行乳酸发酵。而在大多数正常细胞中, 糖酵解速率相对较低, 丙酮酸主要在线粒体中进行有氧氧化。即使在氧充足的条件下, 快速生长的恶性肿瘤细胞进行糖酵解的速率通常要比其正常组织来源的细胞高二百多倍。微RNA(microRNA, miRNA)是一类具有转录后调控功能的非编码RNA。近年来, 越来越多的研究表明, miRNA主要通过诱导缺氧环境、影响葡萄糖摄入、调节糖酵解过程中的关键酶以及乳酸去路等诸多方面参与糖代谢过程, 从而在肿瘤细胞糖代谢中发挥重要作用。

关键词 微RNA; 糖酵解; 三羧酸循环; 葡萄糖代谢; 肿瘤细胞

Role of MicroRNA in Tumor Cell Glycometabolism

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Abstract Most cancer cells predominantly produce energy by a high rate of glycolysis followed by lactic acid fermentation in the cytosol, rather than by a comparatively low rate of glycolysis followed by oxidation of pyruvate in mitochondria as in most normal cells. Malignant, rapidly growing tumor cells typically have glycolytic rates up to 200 times higher than those of their normal tissues of origin even if oxygen is plentiful. MicroRNAs (miRNAs) are a class of non-coding RNAs that perform their function at the post-transcriptional level. In recent years, the increasing evidences demonstrate that miRNAs are mainly involved in glycometabolism by inducing hypoxia, affecting glucose uptake, regulating key enzymes and lactate production in the glycometabolism process. Consequently, miRNAs play a crucial role in tumor cell glycometabolism.

Key words microRNA; glycolysis; tricarboxylic acid cycle; glucose metabolism; tumor cell

肿瘤细胞主要通过糖酵解过程获得生命活动所需要的能量[1]。与正常细胞通过线粒体进行氧化磷酸化不同的是, 癌细胞通过有氧糖酵解产生大量乳酸和少量ATP, 这种现象被称作瓦博格效应(Warburg effect)[2]。肿瘤糖代谢方式的转变, 为癌细胞的生长带来诸多优势, 比如充足的能量供应、大量乳酸导致细胞侵袭力的增强、提供肿瘤细胞生物合成所需的小分子以及保护癌细胞免受细胞凋亡刺激等[3]。微RNA(microRNA, miRNA)是一类内源性的、在进化上非常保守的、其长度约为22个

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核苷酸的非编码小RNA[4]。经过一系列加工成熟的miRNA能够完全或不完全地与mRNA的3′端非翻译区结合, 通过抑制翻译或靶mRNA降解来调节基因表达[5]。大量研究表明, 肿瘤细胞细胞由于染色体异常、表观遗传修饰、基因转录调控等引起的miRNA表达异常在能量代谢中发挥着重要作用。本文将主要就miRNA在肿瘤细胞葡萄糖代谢中的调控方式作一简要综述。

1 miRNA调节缺氧诱导因子1α(HIF1α)

组织缺氧是肿瘤和正常组织之间的一个最主要的生理区别[6], 大量的研究表明, 在低氧或者缺氧条件下, 哺乳动物细胞能够启动一系列的细胞程序来进行糖酵解以维持细胞存活。缺氧诱导的转录响应机制非常复杂, 但主要是通过缺氧诱导因子1α(hypoxia inducible factor 1α, HIF1α)来实现[7]。HIF1α是对氨基水杨酸家族的一个碱性螺旋环状类转录因子, 在肿瘤细胞中, HIF1α调控的一个关键程序就是诱导细胞进行糖酵解, 这个过程由HIF1α依赖的基因表达上调引起, 进而调控包括葡萄糖摄取、糖酵解、乳酸生成、乳酸分泌以及阻碍葡萄糖进入三羧酸循环等在内的生理过程[8]。在由缺氧条件诱导的通路中, miR-199a是主要的调节子, 下调miR-199a能够增强HIF1α的表达[9]。在人卵巢癌细胞中, miR-199a和miR-138都能够显著地下调HIF1α在蛋白水平的表达, 其中miR-138直接靶向HIF1α分子[10-11]。在人乳腺癌细胞中, 缺氧诱导的miR-210的表达调控是由HIF1α介导[12]; 而在肾细胞癌中miR-210显著高表达, 同时它还是HIF1α的下游靶点[13]。这表明, 在肿瘤细胞中, miRNA通过调节HIF1α间接影响有氧糖酵解。

2 miRNA通过调控癌基因/抑癌基因影响糖代谢

作为肿瘤中最常见的突变基因, *p53*控制着包括细胞凋亡、细胞代谢、细胞分化等在内的进程[14]。TP-53诱导糖酵解和凋亡调节因子蛋白能够抑制糖酵解关键酶PFKFB2的活性[15]。另外, *p53*还能在转录水平上激活细胞色素C氧化酶2的表达[16], 从而实现对三羧酸循环的调控。一些miRNA已经被证实能够调节*p53*的活性。在人神经母细胞瘤细胞中, miR-125b能够负调节*p53*的活性[17]。除了miR-125b之外, miR-504、miR-25以及miR-30d都能特异性地结合在*p53*的3′端非翻译区, 从而实现对*p53*的负向调控[18]。c-Myc是一种能够调节基因表达的转录调节因子。研究表明, miRNA已经成为一种能调节c-Myc活性的新颖的调节因子[19]。线粒体谷氨酰胺酶(mitochondrial glutaminase, GLS)能够将谷氨酰胺转化为谷氨酸盐, 同时进入三羧酸循环后通过代谢产生ATP[20]。在前列腺癌细胞PC3中, c-Myc抑制miR-23的表达, 而miR-23能够靶向GLS, 通过增加GLS的表达来增强谷氨酸盐的代谢[21]。现已证实, 在Burkitt淋巴瘤细胞中let-7a能够在mRNA水平调节c-Myc表达[22]; 同时在裸鼠肺癌皮下瘤细胞中, 过表达let-7a能够通过抑制KRas和c-Myc使得肺癌细胞的生长受到抑制[23]。因此, 在肿瘤细胞中, miRNAs通过调控癌基因或抑癌基因的表达, 进而调控糖代谢过程。

3 miRNA调节葡萄糖摄入

葡萄糖转运子家族(glucose transporters, GLUTs)在绝大多数的哺乳动物中普遍存在, 是一种能够促进葡萄糖跨膜运输的膜蛋白。迄今为止, 已有14种葡萄糖转运子被确认[24], 其中GLUT1和GLUT3在大部分的肿瘤中表达上调[25]。在肾细胞癌中, GLUT1表达增加; 相反, GLUT4、GLUT9、GLUT12的表达却下调。同时, 高亲和性的GLUTs在增强肾脏肿瘤摄取葡萄糖这一功能方面起着主要的作用[26]。越来越多的研究表明, miRNA能够通过调节GLUTs的表达来调节肿瘤细胞糖代谢。在葡萄糖代谢的初始阶段, 葡萄糖通过GLUT3和GLUT4经过细胞膜进行运输。过表达miR-223使得GLUT4的表达增加, 从而促进细胞对葡萄糖的摄取[27]。另外, miR-133抑制GLUT4蛋白的表达, 从而导致胰岛素介导的葡萄糖摄入减少[28]。这表明miR-133能够通过作用于GLUT4负向调控葡萄糖的摄入。在人膀胱癌细胞系中, miR-195-5p通过直接靶向下调GLUT3表达, 抑制葡萄糖的摄取和细胞增殖[29]。因此, miRNA能够通过改变GLUTs的表达来调节葡萄糖的摄取, 进而影响肿瘤细胞中的糖代谢过程。

4 miRNA调控糖酵解过程中的关键酶

糖酵解是肿瘤细胞进行糖代谢的主要方式, 其调节主要由代谢途径中的关键酶完成。miRNA能够调节糖酵解中的关键酶, 从而实现对反应流量和细

胞能量需求的控制[30]。大量研究表明, miRNA能够调节糖酵解过程中的关键步骤, 尤其是调节其中的关键酶。己糖激酶2(hexokinase 2, HK2)是糖酵解中的第一个限速酶, 在人肺癌组织中, miR-143的表达与HK2的蛋白水平呈负相关, miR-143通过直接靶向作用于HK2, 从而降低葡萄糖代谢, 抑制癌细胞增殖及肿瘤形成[31]。同样, 在结肠癌[32]、乳腺癌[33]和头颈鳞状细胞癌[34]中, miR-143同样通过这一途径实现对糖酵解的调节。此外, 在乳腺癌细胞中, miR-155能够通过激活转录活化因子3, 从而增强HK2的活性[33]。

葡糖磷酸异构酶(phosphoglucose isomerase, PGI)在糖酵解和糖异生途径中具有重要作用, 它除了能够催化葡糖-6-磷酸生成果糖-6-磷酸之外, 还与癌细胞的浸润和转移有关。在人乳腺癌细胞中, 包括miR-200a、miR-200b以及miR-200c在内的miR-200家族能够调节PGI的活性[35], 从而调控糖酵解进程。果糖-1,6-二磷酸(fructose 1,6-diphosphate, FDP)是糖酵解过程中的重要产物, 醛缩酶A(aldolase A, ALDOA)能催化FDP生成二羟丙酮磷酸和3-磷酸甘油醛。miR-15a/miR-16-1簇在慢性淋巴细胞性白血病中的表达显著下调或缺失, 显著下调ALDOA的活性[36]。在人肝细胞癌细胞Huh7中, 内源性miR-122通过调节ALDOA的mRNA表达水平, 从而负向调节ALDOA的活性[37]。在肺癌细胞中, miR-17-92簇调节磷酸丙糖异构酶1(triosephosphate isomerase 1, TPI1)、烯醇化酶1(enolase 1, ENO1)以及磷酸甘油酸激酶1(phosphoglycerate kinase 1, PGK1)的活性[38]。另外, TPI1不仅是miR-15a/miR-16-1簇的直接作用靶点[36], 而且还是miR-195的预测靶点之一, 在膀胱癌中其表达显著下调[39]。经过蛋白组学分析发现, 在肺癌细胞DLKP-A中, miR-29a靶向调节ENO1、葡糖磷酸变位酶1以及PGK1的表达, 通过抑制糖酵解降低癌细胞的浸润和增殖[40]。

丙酮酸激酶是糖酵解途径中的另外一个重要限速酶, 其中丙酮酸激酶M2(pyruvate kinase M2, PKM2)能促进细胞的自我更新及增殖。研究发现, 肝细胞癌通常富含PKM2, miR-122在肝细胞癌中表达减少或缺失, 并通过靶向PKM2负向调控糖酵解[41]。miR-326亦能直接靶向PKM2, 并在神经胶质瘤细胞中显著地过表达[42]。在舌鳞状细胞癌细胞中PKM2的异常

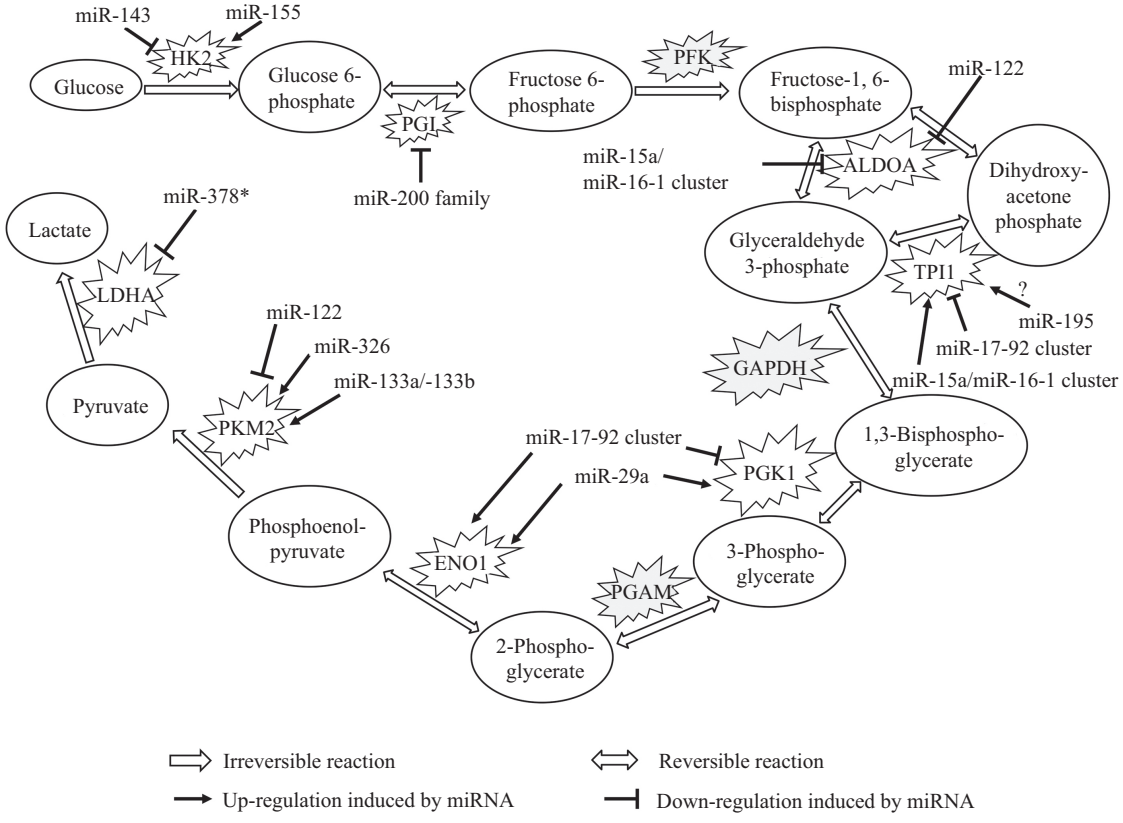

图1 miRNA调节糖酵解过程中的关键酶

Fig.1 miRNA regulates key enzymes involved in glycolysis

表达与miR-133a和miR-133b减少密切相关[43]。因此, miRNA可通过调节糖酵解途径中的关键酶的活性, 进而影响肿瘤细胞中能量的代谢过程(图1)。

5 miRNA调节肿瘤细胞中乳酸的去路

葡萄糖转变为乳酸增加是许多癌细胞的典型特征, 它能够促进癌细胞的快速增长。同时, 在癌细胞中PKM2增加, 促进乳酸产量增加[44]。正常细胞中, 在缺氧条件下葡萄糖代谢从氧化磷酸化转入糖酵解过程, 并最终生成乳酸。然而, 在有氧条件下, 乳酸也被认为是肿瘤细胞的一种能量来源[32]。在肿瘤细胞中, 乳酸脱氢酶A(lactate dehydrogenase A, LDHA)水平增加能够导致细胞内乳酸产量增加[45]。在乳腺癌细胞BT-474中, 抑制miR-378*的表达, 使得细胞内乳酸产量减少, 细胞从有氧糖酵解向氧化磷酸化转化, 从而导致细胞内总呼吸量增加[46]。

在癌细胞的有氧糖酵解中, 产生的乳酸通过单羧酸转运蛋白(monocarboxylate transporter, MCTs)转运出细胞, 它们中的大部分能够被肝脏利用, 并在肝脏中异生成葡萄糖, 再次进入肿瘤细胞中进行代谢。miR-29a、miR-29b和miR-124能够选择性地靶向MCT1基因的3′端非翻译区, 进而调节肿瘤细胞分泌乳酸的能力[47]。细胞膜上一种广泛表达的糖蛋白CD147, 能够调节细胞膜水平上的MCT1和MCT4的活性[48], 同时CD147的表达受let-7b的调节。let-7b作为一种具有肿瘤抑制作用的miRNA能够抑制癌细胞的增殖、迁移以及转移[49]。由此可见, let-7b通过作用于CD147, 调节MCTs的活性, 从而间接调节葡萄糖的代谢。另外, 在体内外调节miR-320a的水平, 都能实现对乳酸水平的调控[50]。

6 miRNA调节三羧酸循环

尽管肿瘤细胞主要通过糖酵解获得所需要的能量, 但其在一定程度上也依赖于线粒体的代谢, 尤其是通过对谷氨酸盐的分解代谢而获得ATP[51]。乙酰辅酶A作为三大物质代谢的枢纽, 是能量代谢的重要中间产物。miR-103和miR-107已经被预测能够增加细胞内乙酰辅酶A的含量, 同时使乙酰辅酶A进入三羧酸循环(tricarboxylic acid cycle, TCA)进行有氧氧化[52]。柠檬酸合成酶是TCA中一种重要的酶[19], Tibiche等[53]已经证实, miR-152、miR-148a和miR-148b等miRNA能够通过调节控制柠檬酸合成酶的基因, 进而起着对TCA的调控作用。铁硫簇装配蛋白(iron-sulfur cluster assembly proteins, ISCU1/2)能够提高顺乌头酸酶的活性, miR-210通过抑制ISCU1/2表达, 调节自由基反应并使得TCA的速率降低[54-55]。同时, 缺氧诱导调节的miR-210靶向抑制线粒体电子传递链重要因子细胞色素氧化酶装配蛋白COX10的表达, 降低线粒体功能[56]。miR-210亦能够激活活性氧的产生, 这表明miRNA在肿瘤微环境、氧化磷酸化、活性氧类和铁稳态中发挥功能。由此可见, miRNA通过调节线粒体中TCA产生的能量从而与糖代谢密切相关。

7 小结与展望

miRNA不仅能在肿瘤细胞中调节与糖酵解相关的代谢途径, 而且还能通过其他途径调节体内葡萄糖的平衡。比如, 在胰岛内分泌细胞中过表达miR-375能够抑制葡萄糖诱导的胰岛素的分泌, miR-375通过控制胰岛素的分泌来调节体内葡萄糖平衡[57]。在胰岛β细胞中, 磷酸肌醇3激酶信号通路介导miR-375表达, 进而调节体内葡萄糖平衡[58]。尽管miRNA已经成为肿瘤细胞葡萄糖代谢中一种非常重要的调节因子, 然而大部分代谢途径中关键酶或蛋白的特异性miRNA还需进一步验证。随着对miRNA及肿瘤细胞糖代谢研究的进一步深入, 人们可以通过异常表达某些特异性miRNA, 改变肿瘤细胞的代谢途径, 从而为治疗恶性肿瘤开辟新的途径。

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