microRNA-155 positively regulates glucose metabolism via PIK3R1-FOXO3a-cMYC axis in breast cancer

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Abstract
MicroRNA is an endogenous, small RNA controlling multiple target genes and playing roles in various biological processes including tumorigenesis. Here, we addressed the function of miR-155 using LC-MS/MS-based metabolic profiling of miR-155 deficient breast cancer cells. Our results revealed the loss of miR-155 hampers glucose uptake and glycolysis, via the down-regulation of glucose transporters and metabolic enzymes including HK2, PKM2, and LDHA. We showed this is due to the down-regulation of cMYC, controlled through phosphoinositide-3-kinase regulatory subunit alpha (PIK3R1)-PDK1/AKT-FOXO3a pathway. UTR analysis of the PIK3R1 and FOXO3a indicated miR-155 directly represses these genes. A stable expression of miR-155 in patient-derived cells (PDCs) showed activated glucose metabolism whereas a stable inhibition of miR-155 reduced in vivo tumor growth with retarded glucose metabolism. Furthermore, analysis of 50 triple-negative breast cancer (TNBC) specimens and specific uptake value (SUV) of PET images revealed a positive correlation between miR-155 level and glucose usage in human breast tumors via PIK3R1-PDK/AKT-FOXO3a-cMYC axis. Collectively, these data demonstrate the miR-155 is a key regulator of glucose metabolism in breast cancer.

Introduction

MicroRNA (miRNAs) is a class of non-coding, 20–25 nucleotide-long RNAs. Particularly, they can interact with 3’-untranslated regions (3’-UTRs) of target messenger RNAs (mRNAs) thereby regulate target gene expression by translation inhibition or mRNA degradation at post-transcriptional level. Among many miRNAs that have been linked to cancer, MicroRNA-155 is a well-known oncogenic microRNA with various functional targets [1–5]. However, because each microRNA can regulate the expression of hundreds of genes [6–8], understanding the functional consequence for the change in microRNA expression is challenging.

Abnormal metabolic shift by increased aerobic glycolysis (Warburg effect) is a common feature of cancer cells [9]. This metabolic shift is required for the rapid cell proliferation, rather than energy production. Understanding how cancer cells drive such metabolic shift is crucial to identify potential targets for cancer therapeutics. A recent study has demonstrated that miR-155 upregulates HK2 through the activation of STAT3 and suppression of miR-143 that can target HK2 [10].
Here, we report the miR-155 positively regulates energy metabolism through PIK3R1-PDK/ Akt-FOXO3a-cMYC axis in breast cancer. Using breast cancer model with miR-155\textsuperscript{ko/ko} or miR-155\textsuperscript{+\text/-\text/+} backgrounds, we investigated miR-155 dependent metabolic alterations. We found that miR-155\textsuperscript{+\text/-\text/+} tumor cells increase glucose uptake and lactate production compared to the miR-155\textsuperscript{ko/ko} tumor cells. We further showed that miR-155 directly repress the PIK3R1 or FOXO3a in breast cancer cells, and showed the PIK3R1-PDK1/AKT-FOXO3a pathway to be important in regulating glucose metabolism. Furthermore, we confirmed the regulation of glucose metabolism by miR155 in vivo, and revealed a positive correlation between miR-155 and standardized uptake values (SUV) in triple negative breast tumors.

Results

Retarded glucose metabolism in \textit{miR-155\textsuperscript{ko/ko}} mammary tumor cells

Our previous study suggested that the inhibition of miR-155 impedes breast tumor growth in mice [11, 12]. To understand the underlying mechanism of the oncogenic function of the miR-155, a miR-155 deficient-mouse breast cancer model was generated [12]. Phenotypic analysis of the miR-155 deficient tumor cells (miR-155\textsuperscript{ko/ko} cells hereafter) revealed a reduction in the mitochondrial oxygen consumption (Supplementary Fig 1a), suggesting a compromised energy metabolism. Based on this data, we challenged miR-155\textsuperscript{ko/+} and miR-155\textsuperscript{ko/ko} cells by culturing it in regular (with high glucose, HG) or low glucose (LG) media. Interestingly, we found fewer number of miR-155\textsuperscript{ko/ko} cells compared to miR-155\textsuperscript{ko/+} cells in both media but the difference was more evident in LG media, visualized by CellMask assay (Fig. 1a and Supplementary Fig 1b for phase contrast images). Proliferation assay (Fig. 1b and Supplementary Fig 1c for confirmation results), cell cycle analysis (Fig. 1c) and apoptosis assay (Fig. 1d) also indicated that the miR-155\textsuperscript{ko/ko} cells have enhanced proliferation defects in low glucose condition.

Based on the results of Fig. 1a–c, we performed targeted metabolomics focused on the glycolysis and TCA cycle, and found the absence of miR-155 caused less level of intracellular glucose as well as downstream glycolytic metabolites (Supplementary Table 1 and Fig. 1e for flow diagram). Consistent with the cellular phenotype, the metabolic difference between miR-155\textsuperscript{ko/+} and miR-155\textsuperscript{ko/ko} cells became more evident under the low-glucose condition (Fig. 1e right side). To understand this observation further, we first measured the expression of major genes involved in the glucose transport and glycolysis. The miR-155\textsuperscript{ko/ko} cells showed reduced expression of Glut1,3,4 (Fig. 1f–h), Hk2, Pkm2, and Ldha RNAs (Fig. 1i–k) as well as proteins (Fig. 1l and Supplementary Fig. d–g). These data suggest that the loss of miR-155 causes a shift in glucose metabolism via altered regulation of multiple genes involved in glucose usage.

Upregulation of PIK3R1-FOXO3a-cMYC pathway by miR-155 augments glucose metabolism

To clarify the underlying mechanism of the miR-155 mediated shift in glucose metabolism, we searched for a miR-155 target gene responsible for the gene regulation shown above. Considering miRNA generally down-regulates its target genes, and the reduced gene expression shown in Fig. 1f–l was observed in miR-155 deficient cells, we speculated a mediator that is negatively controlled by miR-155 and deliver its signal to drive the expression change of metabolic genes. Among such mediator candidates, we first focused on FOXO3a-cMYC as the cMYC is a known master regulator of glycolysis [13, 14] and Foxo3a is a target of miR-155 in breast cancer [15]. Indeed, we found the Foxo3a expression to be dramatically up-regulated in miR-155\textsuperscript{ko/ko} cells (Fig. 2a, b). As the FOXO3a is known to destabilize cMYC [16], we also could detect repressed cMYC expression in miR-155\textsuperscript{ko/ko} cells (Fig. 2c and Supplementary Fig. c and d). Importantly, the siRNA mediated knock-down of Foxo3a (Supplementary Fig 2a) in miR-155\textsuperscript{ko/ko} cells dramatically increased the expression of glucose transporters (Fig. 2d–f) as well as glycolytic enzymes (Fig. 2g–i), demonstrating that FOXO3a is a key regulator of the miR-155 mediated metabolic shift. However, the Foxo3a does not have miR-155 binding site in its 3'UTR (in murine sequence), suggesting a presence of another upstream regulator targeted by miR-155 and initiate the signal for the metabolic shift.

PI3K pathway has been one of the known upstream regulator of the FOXO3a [17]. Specifically, the PI3K induces phosphorylation of FOXO3a via AKT that results in its degradation [18]. Interestingly, p85α (The protein from Pik3r1 gene) that negatively regulates the catalytic activity of PI3K [19, 20], was reported as a target of miR-155 in B-cell lymphoma [21]. Hence, we reasoned that the inhibition of Pik3r1 by miR-155 can result in PI3K-AKT activation and consequently cause a reduction in the Foxo3a level in breast cancer cell. Indeed, the Pik3r1 gene is upregulated in miR-155\textsuperscript{ko/ko} cells (Fig. 2j) and the absence of miR-155 increases Pik3r1-UTR reporter (Fig. 2k), suggesting it is negatively regulated by miR-155. Moreover, we found the loss of miR-155 inhibits PI3K-PDK1/AKT pathway via the up-regulation of p85α, as shown by western blotting (Fig. 2l and Supplementary Fig. e–f). The siRNA mediated knock-down of Pik3r1 in miR-155\textsuperscript{ko/ko} cells...
Supplementary Fig 2b) phenocopied the knock-down of Foxo3a in the metabolic gene regulation, as shown in Fig. 2m–r. This data suggests that these two genes are involved in the same regulatory pathway for the glucose usage. Furthermore, a stable knockdown of miR-155 (by miRZIP lentivirus; Supplementary Fig 1k) in five miR-155ko/ko cells caused a similar proliferation defect (Supplementary Fig 1l) in low glucose condition as well as a decreased glucose metabolism, consistent to the data from the miR-155ko/ko cells (Fig. 2s for flow diagram and Supplementary Table 2).

These data indicate the miR-155 acts as a strong regulatory factor in glucose metabolism, overriding diverse mutation backgrounds of the primary cancer cells.

**miR-155, a modulator of PIK3R1 and FOXO3a expression, positively regulates glucose metabolism in human breast cancer cells**

We next examined if the miR-155 mediated metabolic shift is also valid in human cancer. In MCF7 breast cancer cells, UTR reporter assay of PIK3R1 and FOXO3a with miR-155 mimic indicated that miR-155 negatively regulates PIK3R1 (Fig. 3a) and FOXO3a (Fig. 3b) genes. Alternatively, we established a set of PDC (Patient Derived Cells) from TNBC specimen and stably expressed miR-155 in miR-155 low-PDCs (PDCL, Supplementary Fig. a and b). In these cells, we observed restoration of upregulated FOXO3a and...
PIK3R1 (Fig. 3c, d) as well as increased cMYC level (Fig. 3e), comparable to the miR-155 high cells (PDCH). Consequently, the stable expression of miR-155 boosted glucose metabolism via up-regulated GLUT1 and glycolytic enzymes at the protein level (Fig. 3f and Supplementary Fig. g–m). In the miR-155 low PDCs, the level of glucose metabolites was lower than miR-155 high cells (Supplementary Fig 3c–f and Supplementary Table 3). Upon the stable expression of miR-155, we observed up-regulated glucose metabolites and NAD level (Fig. 3g–j). Altogether, these data demonstrate that miR-155 controls p85α-AKT-FOXO3a axis and causes a shift in glucose metabolism via cMYC in human breast cancer cells.

miR-155 promotes glucose metabolism through the activation of p85α-FOXO3a-cMYC axis in vivo

Based on these results in cancer cells, we further examined the positive role of miR-155 in glucose metabolism in vivo. First, an allograft model using two primary murine cancer cells (Lav670 and Lav714) with stable miR-155 knockdown (by miRZIP, Supplementary Fig 4a) showed slower in vivo growth compared to their isogenic, paired clones (Fig. 4a–b and Supplementary Fig. EV4b–d). In these control/miRZIP allograft tumors, we found increased p85α and FOXO3a protein expression as well as decreased cMYC, GLUT1, HK2, PKM2, and LDHA expression (Fig. 4c–j). Consistent
with these expression regulations, metabolic profiling also revealed decreased glucose metabolites in both the xenograft pairs (Fig. 4k for flow diagram, Fig. 4l–o for graphs of each metabolite and Supplementary Table 4).

**miR-155 is positively correlated with the elevated glucose usage in human TNBC samples**

Next, we examined whether the miR-155 driven metabolic shift also occurs in human breast tumors (Clinical information summarized in Supplementary Table 6). Measurement of miR-155 (Fig. 5a) along with FOXO3a, PIK3R1, and cMYC mRNA expressions in 50 TNBC tumors revealed significant negative correlations between miR-155 and FOXO3a or PIK3R1 (Fig. 5b, c). In contrast, there was a positive correlation between miR-155 and cMYC expression (Fig. 5d), supporting the observations in cancer cells. These expression correlations are further confirmed by western blot analysis for a subset of breast tumors with miR-155 high or low, showing significant correlations for FOXO3a, cMYC and PKM2 (Fig. 5e, f, see discussion). In addition, the analysis of major metabolites in glucose metabolism including glucose, glucose-6-phosphate(G6P) and pyruvate also consistently showed a positive correlation to miR-155 levels (Fig. 5g–i, Supplementary 4e–g, Supplementary Table 5). Furthermore, we addressed whether miR-155 high tumors can uptake more glucose by checking the standard uptake value (SUV) score of the tumors (Fig. 5j), obtained from PET images (Fig. 5k as representative pictures). The results showed a significant, positive correlation between...
normalized SUV score (see methods) and miR-155 level (Fig. 5l) validating the results from cancer cells as well as in vivo models. Altogether, these data strongly demonstrate that miR-155 upregulation drives glucose metabolism in human breast tumors (Fig. 6).

Discussion

Our study described here provides a mechanistic insight for how the oncogenic miR-155 promotes tumor growth by activating glucose metabolism (a graphical summary in Fig. 5m). A previous report showed miR-155/143 controls HK2 via STAT3 or C/EBP beta [10], and a recent report also showed that miR-155 control HK2 expression in NSCLC [22]. Another study using knockout mice showed that the loss of miR-155 confers insulin resistance [23]. Our group also reported that miR-155 controls thiamine, a critical cofactor for energy metabolic enzymes [24]. Considering the miR-155 controls the expression of approximately 250 genes [25, 26], we reason that analyzing its physiological output, i.e., metabolism in this study, will enable us to understand its function better. As shown here, we were able to identify multiple metabolic enzymes and upstream regulators as targets of miR-155. Moreover, we showed the miR-155 can promote glucose usage in multiple breast cancer cells as well as human breast cancer specimen. Collectively, we have demonstrated that a metabolic profiling followed by mechanistic study is an effective way to dissect the complex biological functions of microRNA that have the potential to regulate the expression of hundreds of genes.

Our data provided here demonstrates a pivotal role of miR-155 in multiple steps of glucose metabolism. Of note, our finding showed the genes involved in glucose uptake and metabolism was reduced in miR-155 deficient cells. This data suggested an indirect regulation by miR-155 onto the genes, considering a repressive nature of miRNA-target
Further study revealed that the regulation is primarily achieved by the cMYC, but the cMyc gene was not a direct target of miR-155 either because there was no miR-155 binding site in cMyc UTR. Therefore, we investigated how the cMYC is regulated by miR-155. As FOXO3a and PIK3R1 have been reported as targets of miR-155 in human breast cancer cells [15] or B-cell lymphoma [21], we examined the possible mechanism by which PIK3R1 and FOXO3a can regulate the cMYC level. Therefore, our study shown here presents a typical bottom-up approach that reveals multiple layers of regulation by miR-155. Even though we demonstrated here PIK3R1-FOXO3a-cMYC as critical axis regulated by miR-155, the functional interactions among these players can be more complicated than linear pathway. Further study will tackle more network-based approach to clarify these relations. Importantly, because the cMYC is not only a known master regulator of glucose metabolism [27, 28], but also a regulator of glutamine metabolism [28]. Therefore, future study will also focus on the effect of miR-155 on glutamine metabolism in cancer.

Finally, we have demonstrated that our findings are valid not only in mouse model but also in human TNBC. Some of the target genes we identified in cancer cell study did not show significant correlations with miR-155 in tumor protein level (Fig. 5f). We think this is due to the heterogeneity in...
the tumor cell content in each specimen and differences of the sampling history. Despite of that, we could detect significant correlations between the FOXO3a, cMYC, and HK2 proteins with miR-155 level, supporting cellular and in vivo model data. Although the oncogenic role of miR-155 in human breast cancer has been reported [4, 29, 30], our study provides a more precise and novel function of miR-155 in terms of glucose metabolism. We expect other unknown functions of the miR-155 will be uncovered via more studies on the miR-155-deficient tumor models. Such studies will help us to fully understand this multifunctional, oncogenic microRNA.

Materials and methods

Cell isolation and culture

miR-155-deficient, breast cancer mouse model was generated by mating, as described previously [31]. Isolation and culture of miR-155KO/ko and miR-155ko/ko cells was performed as described [11] with minor modification. Human primary breast cancer cells obtained from patients with triple negative breast cancer (TNBC) (ASAN medical center, IRB No. 2013-0939) were previously described [24]. Depending on the level of miR-155, six of the primary cells were grouped as patient-derived cells (PDC) H1-H3 or L1-L3. 293TN, MCF7 and HeLa cells were cultured in DMEM supplemented with 10% FBS and 1% PS (Penicillin Streptomycin).

CellMask plasma membrane stain

To check cell density and morphology of murine mammary tumor cells with or without glucose restriction, the cells were washed and incubated with CellMask Green (1/1000 diluted, Invitrogen) for 15 min at room temperature (RT). The cells were rinsed twice with distilled water and then stained with DAPI for 5 min. After staining, the cells were fixed with 3.75% formaldehyde for 15 min and imaged using an inverted fluorescence microscope (Carl Zeiss AG, Oberkochen, Germany).

alamarBlue® cell viability and BrdU cell proliferation assay

To measure the cell proliferation and viability, the cell alamarBlue assay was performed as previously described [24]. FITC-BrdU kit (BD Pharmingen, San Diego, CA, USA) was also used to analyze cell cycle progression as previously described [24].

Annexin V assay

For apoptosis assay, mouse primary cancer cells were seeded onto a six-well plate and incubated overnight under high or low glucose condition. Apoptotic cells were measured by using FITC-Annexin V Apoptosis Detection Kit (BD Pharmingen) described by the manufacture. Briefly, cells were incubated with FITC-Annexin V in FACS staining buffer for 15 min. Stained cells were subjected to the CFlow software analyses using an AccuriFlow Cytometry (BD Biosciences).

LC-MS/MS analysis

A liquid chromatography-tandem mass spectrometry (LC-MS/MS) system was used to measure metabolites according to a previously described method [24].

OXPHOS measurements

Oxygen consumption rate (OCR) was detected using a Seahorse XF24 analyser (Seahorse Bioscience), per the manufacturer’s instructions. Briefly, miR-155+/Ko or miR-155Ko/Ko cells were cultured to approximately 70–80% confluence in DMEM medium. Cells were seeded at 50,000 cells per well in an XF24 cell culture microplate and then incubated at 37 °C with 5% CO₂ for 3 h. Before OCR detection, culture medium was changed, and the plate was incubated at 37 °C without CO₂ for 1 h. Finally, the plate was transferred to the XF24 analyser. OCR was measured by sequential additions of oligomycin A (Sigma), FCCP (Sigma) and antimycin A (Sigma).
**Quantitative RT-PCR (qRT-PCR)**

Total RNA extraction was performed using TRizol (Invitrogen), by the manufacturer’s instruction. The primer sequences are shown in Supplementary Table 7. The mRNA expression levels of major glucose transporters (*Glut1, 3, and 4*), glycolysis enzymes (*HK2, Pkm2, and LdhA*), as well as *PIK3R1* and *FOXO3a* genes were measured according to a previously described method [24]. Relative expression value was normalized to *RPL13a* and calculated by using the 2-\(\Delta\Delta Ct\) method as previously described [32]. Quantitative measurement of miR-155 were performed by a previously described method [12]. The expression was normalized with small nuclear RNA U6 (RNU6).

**Antibody and western blot analysis**

Preparation of total cell lysates and Western blot analysis were performed as described previously [33]. A total of 10–50 μg of protein was used per lane. The blot was probed with anti-GLUT1 (1:500; Santa Cruz Biotechnology, Santa Cruz, CA, USA), anti-HK2 (1:1000, Cell Signaling Technology, Danvers, MA, USA), anti-PKM2 (1:1000, Cell Signaling), anti-LDHA (1:1000, Cell Signaling), anti-p85α (1:1000, Cell Signaling), anti-p110α (1:1000, Cell Signaling), anti-p110β (1:1000, Cell Signaling), anti-phospho-AKT (Ser473) (1:1000, Cell Signaling), anti-AKT (1:1000, Cell Signaling), anti-PDK1 (1:1000, Cell Signaling), anti-FOXO3a (1:1000, Cell Signaling), and anti-cMYC (1:1000, Cell Signaling) antibodies. The relative densities of bands were analyzed with NIH image J 1.47v software.

**Knockdown of PIK3R1 and FOXO3a by siRNA**

Small-interfering RNAs (siRNAs) that effectively inhibit mouse *Pik3r1* and *Foxo3a* were purchased from Genolution Pharmaceuticals Inc (Genolution, Seoul, Republic of Korea). siRNA sequences of *Pik3r1* and *Foxo3a* were as follows; *Pik3r1*, 5′- UUGUUGGCUCACAGUGUGG-3′; *Foxo3a*, 5′-UGAUGAUCUCAGUCUCUGC-3′. Primary mouse cancer cells were transfected with either 200 nmol/L of target siRNAs (*Pik3r1* or *Foxo3a)* or scramble siRNA using lipofectamine 2000 (Invitrogen).

**miR-155 knockdown and overexpression**

Lentiviral vector system from SBI (Mountain View, CA, USA) was used for miR-155 inhibition, as previously described [12]. For the overexpression of miR-155, we performed two kinds of methods, using lentiviral vector encoding miR-155 (miRH155, SBI) and miR-155 mimic.
Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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