Editorial

Cancer therapy by targeting the Warburg effect with miR-143 and response monitoring with ^{18}F-FDG PET

Kyung-Ho Jung[1,2], Kyung-Han Lee[1,2]

[1]Department of Nuclear Medicine, Samsung Medical Center, Seoul, Korea; [2]Samsung Advanced Institute for Health Sciences & Technology, Sungkyunkwan University School of Medicine, Seoul, Korea

Correspondence to: Kyung-Han Lee, M.D. Department of Nuclear Medicine, Samsung Medical Center, 50 Ilwon-dong, Gangnam-gu, Seoul, Korea. Email: khnm.lee@samsung.com.

Comment on: Miao Y, Zhang LF, Guo R, *et al.* (18)F-FDG PET/CT for Monitoring the Response of Breast Cancer to miR-143-Based Therapeutics by Targeting Tumor Glycolysis. Mol Ther Nucleic Acids 2016;5:e357.

Submitted Mar 24, 2017. Accepted for publication Mar 31, 2017.
doi: 10.21037/tcr.2017.04.13
View this article at: http://dx.doi.org/10.21037/tcr.2017.04.13

MicroRNAs (miRNAs) and their role in cancer

miRNAs are non-coding short endogenous RNAs that act as negative regulators of gene expression by targeting mRNA (1). After its first discovery in C. elegans, a key paper confirmed the existence of many miRNAs in vertebrates, including humans (2). In subsequent years, miRNAs have emerged as critical players in modulating such key biological processes as cell proliferation and apoptotic death (1). More recently, several miRNAs are drawing attention for their roles in regulating glucose and energy metabolism (3,4).

miRNA dysregulation may lead to abnormal post-transcriptional regulation of tumor suppressor gene and oncogene expression, and thereby play a role in tumor pathogenesis and progression. Furthermore, several miRNAs themselves function as tumor suppressor or oncogenes (5). An example is miR-143, a tumor suppressor miRNA that is frequently downregulated in several types of cancers including colorectal, nasopharyngeal, prostate and gastric cancer. The effects of miR-143 are mediated in part by down-regulated expression of major signaling molecules including KRAS, Toll-like receptor 2, phosphatidylinositol 3-kinase and mitogen-activated protein kinase. Recent studies show that miR-143 can induce cancer cell apoptosis and that rescuing of miR-143 expression can abrogate tumor growth in mice.

miR-143 in cancer metabolism

In a recent study, Miao *et al.* treated triple negative breast cancer cells with a miR-143 mimic, and observed reductions in glucose consumption, uptake of the glucose tracer ^{18}F-fluorodeoxyglucose (^{18}F-FDG), and lactate formation. This metabolic effect, which is consistent with suppression of glycolytic flux, was accompanied by reductions of hexokinase-2 (HK2) mRNA and protein (6). Cancer cells have a characteristic shift of glucose metabolism from mitochondrial respiration toward increased aerobic glycolysis, even in the presence of sufficient oxygen. This phenomenon, called the Warburg effect, offers malignant cells survival advantage and is therefore recently emerging as target for anticancer therapy (7). Several miRNAs participate in cancer cell metabolism by regulating the expression of genes whose protein products either directly regulate metabolic machinery or indirectly modulate the expression of transporters or key metabolic enzymes (8). As the first rate-limiting enzyme of glycolysis, HK2 is among the top list of genes regulated by multiple miRNAs including miR-143 (9). Loss of miR-143 has been shown to repress HK2 activity, thus committing glucose metabolism toward glycolytic flux. The role of miR-143 as a regulator of cancer glycolysis has previous been observed in human lung cancer samples, where its expression was inversely associated with HK2 protein level (10).

Overexpression of miR-143 was found in several cancer cell lines to suppress cellular glucose metabolism and proliferation, and promote apoptotic death. miR-143 has also been shown to inhibit HK2 expression in primary keratinocytes and head and neck squamous cell carcinoma-derived cell lines (11). Gain-of-function studies in human

prostate cancer cells showed that miR-143 decreased cell viability and increased apoptosis with HK2 as a metabolic target (12). In colon cancer cells, re-introduction of miR-143 down-regulated HK2 and decreased lactate secretion (13). MiR-143 was recently found to complementary pair to HK2, leading to the inhibition of glycolysis *in vitro* and *in vivo* (14). The study by Miao *et al*. also showed that suppression of glycolysis by treatment with miR-143 mimics was accompanied by inhibition of proliferation and promotion of apoptotic death of triple negative breast cancer cells (6). Taken together, these recent studies highlight the anti-tumor effect of miR-143 to involve inhibition of glucose metabolism through direct targeting of HK2 expression. This finding renders miR-143 a potential therapeutic agent for treating cancers that have high glycolytic activity.

miRNA-based cancer therapy and potential delivery strategies

The role of certain miRNAs as tumor suppressors suggests their potential utility for cancer therapy. Compared to DNA- and protein-based agents, these molecules have the added advantages of lower immune response and toxicity. Yet, there remain intrinsic challenges that hinder their clinical translation. This includes potential off-target effects, compromised tissue-specific delivery, poor cellular uptake and limited *in vivo* instability (15,16). *In vivo* miRNA delivery is particularly challenging because naked miRNAs that are administered systemically are quickly degraded by nucleases and cleared via renal excretion. The hydrophilic nature and charge of miRNAs further hinder entrance through cell membranes.

However, small size and low molecule weight make it feasible to formulate miRNA into delivery systems that help evade enzyme degradation and blood clearance (16). Among previous attempts, *in vivo* miRNA delivery via nanoparticles and liposomes has largely proved less than effective for clinical use. A novel approach to deliver miRNA for cancer therapy that is recently gaining interest is the use of exosomes (17), which are cell-derived nanometric small vesicles that routinely transfer large amounts of miRNA as cargo (18). In the study by Miao *et al*., the authors developed a therapeutic formulation using cholesterol-modified agomiR encapsulated in a neutral lipid-based delivery agent to deliver miR-143 *in vivo* (6). As a result, mice systemically administered with this formulation showed minimal toxic effects, and mice harboring triple negative breast cancer tumors displayed inhibition of tumor growth and increased apoptosis in a manner that was accompanied by reduced glucose metabolism and HK2 expression (6).

Monitoring of cancer therapy with FDG positron emission tomography (PET) imaging

Importantly, Miao et al. demonstrated that the anti-cancer effects of targeting tumor glycolysis could be efficiently monitored by ^{18}F-FDG PET/computed tomography (PET/CT) imaging. Hence, mice treated with five cycles of intravenous administration of miR-143 agomiR displayed significantly reduced tumor ^{18}F-FDG uptake (6). ^{18}F-FDG PET/CT is widely used in the clinics for the diagnosis of patients with cancer (19). Furthermore, reduction of tumor ^{18}F-FDG uptake on follow-up PET/CT studies is an indicator of response to anti-cancer therapies (20). For ^{18}F-FDG uptake to serve as a marker of response to newer therapeutic agents, in depth understanding is required on the molecular mechanisms through which cancer cell glucose metabolism is modulated. As an example, our group previously investigated the anticancer effect of resveratrol on colon cancer cells and observed suppression of proliferation and promotion of apoptosis via stimulation of reactive oxygen species (21). *In vivo* delivery of resveratrol encapsulated in polyethylene glycol-polylactic acid nanoparticles in mice allowed imaging of tumor response by reduced ^{18}F-FDG uptake. These findings indicate that the response of tumors to nanocarriers loaded with miRNA or small molecules that target the Warburg effect can be noninvasively assessed by monitoring ^{18}F-FDG uptake. The success of miRNA-based cancer therapy will require information on the potency and duration of target-gene silencing so that appropriate dosing schedules can be established. ^{18}F-FDG PET/CT imaging may have an important role in addressing this issue.

Acknowledgments

Funding: This work was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT & Future Planning (grants #2014050612 and #2015R1A2A2A01006419).

Footnote

Provenance and Peer Review: This article was commissioned

and reviewed by the Section Editor Long Chen (Department of PET-CT center at the Yunnan Tumor Hospital, The Third Affiliated Hospital of Kunming Medical University, Kunming, China; Department of Biochemistry and Molecular Biology of Kunming Medical University, Kunming, China).

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2017.04.13). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Zhou X, Yang PC. MicroRNA: a small molecule with a big biological impact. Microrna 2012;1:1.
2. Lagos-Quintana M, Rauhut R, Lendeckel W, et al. Identification of novel genes coding for small expressed RNAs. Science 2001;294:853-8.
3. Krützfeldt J, Stoffel M. MicroRAs: a new class of regulatory genes affecting metabolism. Cell Metab 2006:4:9-12.
4. Rottiers V, Naar AM. MicroRNAs in metabolism and metabolic disorders. Nat Rev Mol Cell Biol 2012:13:239-50.
5. Esquela-Kerscher A, Slack FJ. Oncomirs - microRNAs with a role in cancer, Nat Rev Cancer 2006;6:259-69.
6. Miao Y, Zhang LF, Guo R, et al. ^{18}F-FDG PET/CT for monitoring the response of breast cancer to miR-143-based therapeutics by targeting tumor glycolysis. Mol Ther Nucleic Acids 2016;5:e357.
7. Cairns RA, Harris IS, Mak TW. Regulation of cancer cell metabolism. Nat Rev Cancer 2011;11:85-95.
8. Chen B, Li H, Zeng X, et al. Roles of microRNA on cancer cell metabolism. J Transl Med 2012;10:228.
9. Singh PK, Singh PK, Hollingsworth MA, et al. Regulation of aerobic glycolysis by microRNAs in cancer. Mol Cell Pharmacol. 2011;3:125-34.
10. Fang R, Xiao T, Fang Z, et al. miR-143 regulates cancer glycolysis via targeting hexokinase 2. J Biol Chem. 2012;287:23227-35.
11. Peschiaroli A, Giacobbe A, Formosa A, et al. miR-143 regulates hexokinase 2 expression in cancer cells. Oncogene 2013;32:797-802.
12. Zhou P, Chen WG, Li XW. MicroRNA-143 acts as a tumor suppressor by targeting hexokinase 2 in human prostate cancer. Am J Cancer Res 2015;5:2056-63
13. Gregersen LH, Jacobsen A, Frankel LB, et al. MicroRNA-143 down-regulates Hexokinase 2 in colon cancer cells. BMC Cancer 2012;12:232.
14. Sun X, Zhang L. MicroRNA-143 suppresses oral squamous cell carcinoma (OSCC) cell growth, invasion and glucose metabolism through targeting Hexokinase2. Biosci Rep 2017. [Epub ahead of print].
15. Garzon R, Marcucci G, Croce CM. Targeting microRNAs in cancer: rationale, strategies and challenges. Nat Rev Drug Discov 2010;9:775-89.
16. Fernandez-Piñeiro I, Badiola I, Sanchez A. Nanocarriers for microRNA delivery in cancer medicine. Biotechnol Adv 2017;35:350-60.
17. Wang J, Zheng Y, Zhao M. Exosome-based cancer therapy: implication for targeting cancer stem cells. Front Pharmacol 2017;7:533.
18. Valadi H, Ekstrom K, Bossios A, et al. Exosome mediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells. Nat Cell Biol 2007;9:654-9.
19. Zhu A, Lee D, Shim H. Metabolic positron emission tomography imaging in cancer detection and therapy response. Semin Oncol 2011;38:55-69.
20. Contractor KB, Aboagye EO. Monitoring predominantly cytostatic treatment response with ^{18}F-FDG PET. J Nucl Med 2009;50:97S-105S.
21. Jung KH, Lee JH, Park JW, et al. Resveratrol-loaded polymeric nanoparticles suppress glucose metabolism and tumor growth in vitro and in vivo. Int J Pharm 2015:478;251-7.

Cite this article as: Jung KH, Lee KH. Cancer therapy by targeting the Warburg effect with miR-143 and response monitoring with ^{18}F-FDG PET. Transl Cancer Res 2017;6(Suppl 3):S519-S521. doi: 10.21037/tcr.2017.04.13