Editorial

Expression of miR-630 associated with tyrosine kinase inhibitor therapeutic response in lung adenocarcinoma cases

Srijit Das

Department of Anatomy, Universiti Kebangsaan Malaysia Medical Centre, Kuala Lumpur, Malaysia

Correspondence to: Srijit Das. Professor, Department of Anatomy, Universiti Kebangsaan Malaysia Medical Centre, 56000 Cheras, Kuala Lumpur, Malaysia. Email: drsrijit@gmail.com.

Provenance: This is an invited Editorial commissioned by the Section Editor Chunlin Ou (Cancer Research Institute of Central South University, Changsha, China).

Comment on: Wu DW, Wang YC, Wang L, *et al.* A low microRNA-630 expression confers resistance to tyrosine kinase inhibitors in EGFR-mutated lung adenocarcinomas via miR-630/YAP1/ERK feedback loop. Theranostics 2018;8:1256-69.

Submitted Dec 12, 2018. Accepted for publication Jan 23, 2019.

doi: 10.21037/jtd.2019.01.92

View this article at: http://dx.doi.org/10.21037/jtd.2019.01.92

The published manuscript entitled "*A low microRNA-630 expression confers resistance to tyrosine kinase inhibitors in EGFR-mutated lung adenocarcinomas via miR-630/YAP1/ERK feedback loop*" by Wu *et al.*, may be beneficial for all clinicians treating lung adenocarcinomas (1). There is paucity of reports on the role of miR-630 expression in lung cancers.

MicroRNA-630 (miR-630) was reported to play an important role in the development, progression and prognosis of various cancers. The miR-630 can affect different signaling pathways and cellular processes which include proliferation, differentiation or apoptosis. There are research reports on the role of miR-630 being involved in the regulation of apoptosis but again, this role is being widely debated by researchers.

It would be more interesting if Wu *et al.* (1) had discussed the multiple activators of apoptosis under genotoxic stress. The control of gene expression in any apoptosis is very important. The study by Wu *et al.* (1) also could also have highlighted the acetylcholinesterase gene regulation which is also related to any tumour development. An important question raised is whether acetylcholinesterase could be a tumour suppressor and whether it could be modulated by miR-630 or not. Many other unidentified miRNA targets which influence different cellular phenotypes, may need to be ascertained. It is pertinent to mention epithelial to mesenchymal transition (EMT). The EMT is important for better understanding of chemoresistance to any drug used for treatment of tumors.

One of the strong evidences observed by the researchers was the overexpression of apoptosis related proteins in few carcinomas (2). According to research reports, adamantly-substituted retinoid related (ARR) molecules were observed to induce apoptosis in many malignant cells and this was observed both *in vitro* and *in vivo* (3). ARR molecules were considered to be potent inducers of apoptosis. The ARRs were reported to modulate microRNAs expression and the enhancement of miR-630 resulted in the down regulation of IGF-1R protein. The IGF-1R protein is considered to be an important mediator of cell growth and apoptosis (3). Researchers observed such an effect in pancreatic carcinomas (3).

It was reported that miR-630 promoted apoptosis by targeting cell-cycle kinase 7 (CDC7) kinase and interestingly at the same time, it reduced apoptosis by downregulating other apoptotic modulators which included PARP3, DDIT4, EP300 and EP300 downstream effector p53 (4). It is important to mention that miR-630 may arrest the A549 cells in the G0-G1 phase of the cell cycle (5). These facts correlated with increased levels of the cell cycle inhibitor p27(Kip1) (5). The miR-630 may control the levels of multiple cell cycle regulators and hence control cell proliferation. If there is deregulation of any miRNA, then it may also lead to proliferative conditions similar to those seen in carcinomas. This may be due to the change in the protein levels of critical oncogenes or tumor suppressor genes (6). The expression of miRNA is essentially controlled by different cell cycle pathways and such cannot be undermined.

© Journal of Thoracic Disease. All rights reserved.

Table 1 Table showing mechanism of action of different types of miRNAs on anticancer drug resistance

Type of miRNA	Mechanism of action	Reference
miR-200b	Reverses chemoresistance of docetaxel-resistant human LA cells while targeting E2F3	(8)
miR-100	Resensitises docetaxel-resistant human LA cells to docetaxel while targeting plk1	(8)
miR-98	Resentises cisplatin-resistant human LA cells by upregulation of HMGA2	(9)
miR-513a-3p	Sensetises human lung adenocarcinoma cells to cisplatin while targeting GSTP1.	(10)
miR-451	Inhibits growth, promotes apoptosis and increases DDP sensitivity in non-small cell lung cancer cells while targeting RAB14	(7)

Admittedly, there are less reports on miR-630 associated with lung cancers. Tyrosine kinase inhibitors (TKIs), such as gefitinib and erlotinib are widely used for the treatment of adenocarcinomas. One of the most challenging situations faced by the clinician is the resistance to these drugs. Based on earlier published literature (7) several miRNAs have been highlighted for their action on anticancer drug resistance and these miRNAs were tabulated (*Table 1*).

One of the most mutated and amplified gene in lung adenocarcinoma are the *epidermal growth factor receptor* (*EGFR*) genes. The gene mutation may be an early event while the amplification may occur, later on. Mutations in lung adenocarcinoma cases can be detected by polymerase chain reaction (PCR). The mutation of EGFR and amplification of genes are the determining factors for any lung carcinoma which may respond to the treatment by TKIs. In few lung adenocarcinomas with EGFR mutation, the response rate to treatment may be better. Low level of miR-630 may be responsible for TKI resistance in lung adenocarcinomas. The EGFR amplification following mutation may also denote the aggressiveness of the lung adenocarcinomas. There is a need to identify overexpression or abnormal expression of EGFR in order to ascertain the proper response to any target therapies. It has to be kept in mind many lung adenocarcinomas with susceptible EGFR mutations may not respond effectively to treatment by TKIs.

It is concluded that new methods may be designed to study the mutation and gene amplification as these are important for knowing the efficacy of the proposed therapies.

Acknowledgements

None.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

References

1. Wu DW, Wang YC, Wang L, et al. A low microRNA-630 expression confers resistance to tyrosine kinase inhibitors in EGFR-mutated lung adenocarcinomas via miR-630/YAP1/ERK feedback loop. Theranostics 2018;8:1256-69.
2. Eoh KJ, Lee SH, Kim HJ, et al. MicroRNA-630 inhibitor sensitizes chemoresistant ovarian cancer to chemotherapy by enhancing apoptosis. Biochem Biophys Res Commun 2018;497:513-20.
3. Dawson MI, Fontana JA. The peptidomimetic, 1-adamantyl-substituted, and flex-het classes of retinoid-derived molecules: structure-activity relationships and retinoid receptor-independent anticancer activities. Mini Rev Med Chem 2010;10:455-91.
4. Cao JX, Lu Y, Qi JJ, et al. MiR-630 inhibits proliferation by targeting CDC7 kinase, but maintains the apoptotic balance by targeting multiple modulators in human lung cancer A549 cells. Cell Death Dis 2014;5:e1426.
5. Galluzzi L, Morselli E, Vitale I, et al. miR-181a and miR-630 regulate cisplatin-induced cancer cell death. Cancer Res 2010;70:1793-803.
6. Croce CM. Causes and consequences of microRNA dysregulation in cancer. Nat Rev Genet 2009;10:704-14.
7. Wang H, Zhu LJ, Yang YC, et al. MiR-224 promotes the chemoresistance of human lung adenocarcinoma cells to cisplatin via regulating G_1/S transition and apoptosis by targeting p21(WAF1/CIP1). Br J Cancer 2014;111:339-54.
8. Feng B, Wang R, Chen LB. MiR-100 resensitizes docetaxel-resistant human lung adenocarcinoma cells

© Journal of Thoracic Disease. All rights reserved.

(SPC-A1) to docetaxel by targeting Plk1. Cancer Lett 2012;317:184-91.
9. Xiang Q, Tang H, Yu J, et al. MicroRNA-98 sensitizes cisplatin-resistant human lung adenocarcinoma cells by up-regulation of HMGA2. Pharmazie 2013; 68:274-81.
10. Zhang X, Zhu J, Xing R, et al. miR-513a-3p sensitizes human lung adenocarcinoma cells to chemotherapy by targeting GSTP1. Lung Cancer 2012;77:488-94.

Cite this article as: Das S. Expression of miR-630 associated with tyrosine kinase inhibitor therapeutic response in lung adenocarcinoma cases. J Thorac Dis 2019;11(Suppl 3):S253-S255. doi: 10.21037/jtd.2019.01.92

© Journal of Thoracic Disease. All rights reserved.