Could miR-134 be a marker of ionizing radiation toxicity?

Eva M. Jimenez-Mateos[1], David C. Henshall[1,2]

[1]Department of Physiology and Medical Physics, Royal College of Surgeons in Ireland, Dublin, Ireland; [2]FutureNeuro Research Centre, RCSI, Dublin, Ireland

Correspondence to: Eva M. Jimenez-Mateos. 123, St Stephen's Green, Royal College of Surgeons in Ireland, Dublin D02 YN77, Ireland. Email: evajimenez@rcsi.ie.

Comment on: Borghini A, Vecoli C, Mercuri A, *et al.* Low-Dose Exposure to Ionizing Radiation Deregulates the Brain-Specific MicroRNA-134 in Interventional Cardiologists. Circulation 2017;136:2516-8.

Received: 29 March 2018; Accepted: 11 April 2018.; Published: 26 April 2018.

doi: 10.21037/ncri.2018.04.04

View this article at: http://dx.doi.org/10.21037/ncri.2018.04.04

MicroRNAs (miRNAs) are a class of non-coding RNAs that play a crucial role in cell differentiation, proliferation and survival by binding to target mRNAs. The binding between the miRNA and the mRNA results in mRNA degradation or translational inhibition. Since the discovery in 1993 of the first miRNA in Caenorhabditis elegans (1), and 7 years later the first human miRNA, let-7 (2), miRNAs have been linked to multiple human diseases, including cancer, cardiovascular and brain diseases such as epilepsy, stroke, Alzheimer's and Huntington's disease (3).

The biogenesis of miRNAs occurs in sequential steps, beginning as a primary transcript in the nucleus, which is processed to a shorter precursor form (~70nt) followed by export to the cytoplasm for final processing to the mature form of the miRNA (19-24nt) (4). Mutation of the genes involved in the biogenesis pathway has been linked to numerous types of cancer and external stressors such as hypoxia can also mediate changes in biogenesis components resulting in dysregulation of miRNAs (5). Thus, normal expression and regulation of miRNA is necessary for health and is often perturbed in disease.

miR-134

The *miR-134* gene is expressed from the miRNA cluster 14q32 in humans. Mir-134 was originally described as a brain specific miRNA; however, several recent papers have shown that miR-134 is involved in tumours and cancer, including lung cancer and glioblastoma. In neurons, miR-134 regulates dendritic morphology and neuronal differentiation, regulates hippocampal memory and regulates neuronal homeostasis by targeting transcripts including *Limk1*, *Pumilo-2* and/or *NRIP1* (nuclear receptor interacting protein 1) (6). In the original study by Schratt and colleagues, miR-134 was demonstrated to negatively regulate dendritic spine volume, and hence might regulate brain excitability. This was later confirmed *in vivo* in mice (6). A recent study showed that miR-134 plays a key role in enhancing hippocampal memory and synaptic plasticity through *NRIP1* (6). Importantly, *in vivo* targeting of miR-134 was shown to interrupt epileptogenesis and decrease seizure susceptibility in murine models of epilepsy (6).

Recently, miR-134 has been also reported to regulate carcinomas and tumours. Changes in methylation of the 14q32 miRNA cluster have been strongly related with changes in miR-134 expression in cancer (7). Upregulation of miR-134 was observed in lung tumor, pancreatic cancer and prostate cancer, whereas, downregulation of miR-134 was found in glioblastomas, breast cancer, renal cancer and hepatocellular carcinoma among others. Consistent with its involvement in cancer, miR-134 was shown to play a crucial role in cell proliferation, apoptosis and metastasis (7).

Circulating miR-134 as biomarkers

The tissue specificity and stability of miRNAs in biofluids makes them attractive biomarkers of disease. Research on miRNAs as biomarkers first emerged in 2008, with studies showing miRNAs could be detected in blood, in particular in plasma, platelets, erythrocytes and nucleated blood cells. This subsequently

drove extensive efforts to explore the diagnostic and prognostic value of miRNAs as biomarkers (8). Over subsequent years, miRNAs were reported in a variety of extracellular fluids including saliva, tears, urine and breast milk among others. Importantly, the expression profile of miRNAs is unique to each of these different biofluid sources which necessitates careful consideration of the appropriate biofluid for a given study (8).

The stability of miRNAs in biofluids was attributed to their association with protein complexes (including Argonaute-2), lipoproteins [such as HDL (high density lipoprotein)], and their inclusion into micro-particles (such as exosomes) (8). The presence of miRNAs in micro-particles led to the idea that the excretion of miRNAs may be an active process which may be involved in cell-to-cell communication. For example, exosomes derived from leukaemia cells contain higher levels of miR-210 compared to control cells. These exosomes containing miR-210 could be taken up by endothelial cells and this enhanced the formation of new blood capillaries (8).

Supporting the role of miR-134 as a biomarker of pathological conditions, studies have shown altered levels of miR-134 in plasma from patients with epilepsy (9) and in adult-onset Still's syndrome (AOSS) patients. AOSS is a rare inflammatory disease which affects a young adults and its symptoms include fever, rash, arthritis and variable multi systemic response. Surprisingly, miR-134 was found elevated in AOSS patients compared to healthy volunteers (10).

miR-134 as biomarker of radiation toxicity in interventional cardiologists

In recent years, concern has grown about the health risk of low levels of ionizing radiation exposure, particularly in interventional cardiologists (11). This has led to calls for a biomarker of IR exposure and attention has turned to miRNAs. In the recent study by Borghini and colleagues, the authors performed microarray profiling of plasma from a cohort of interventional cardiologists exposed to IR and compared this to 10 non-IR exposed cardiologists. The authors found four downregulated miRNAs in plasma which included miR-134, miR-575, miR-127 and miR-2392 (11). A confirmation phase of the study in an expanded cohort of IR-exposed interventional cardiologists confirmed miR-134 downregulation compared to the unexposed controls (11). Importantly, the study found that the levels of miR-134 were lower in high-dose exposed individuals compared to lower-dose exposed groups. Other clinical variables such as age, gender, smoking and body mass index (BMI) did not display any association with plasma miR-134 levels (11). Based on the known role of miR-134 in neurons, the authors tentatively concluded there may be a link between IR exposure and brain injury.

The authors study has revealed an interesting biomarker of IR exposure in interventional cardiologists. The study has a number of important strengths. While this is not the first study to implicate plasma miR-134 as a biomarker of a disease, it is the first study to profile and validate a miRNA in this population. The authors used a genome-wide profiling platform initially to identify miRNAs affected by ionizing radiation and therefore assessed all potential miRNAs in an unbiased fashion before going on to validate those differentially expressed in a larger cohort. The findings could lead to a biomarker or IR exposure based on testing plasma levels of miR-134.

The mechanism underlying the down-regulation of miR-134 after exposure to ionizing radiation was not explored (11). However, the authors suggested the downregulation of miR-134 may be related to a subclinical brain damage. Whether this is the cause or not will require further investigation. It is perhaps counter-intuitive that a brain injury would lead to lower levels of miR-134 in plasma, although this was reported in a recent study in epilepsy (9). An alternative explanation is the change reflects other systemic disturbances caused by IR exposure. Notably, miR-134 is down-regulated in a number of cancers, although has not been strongly linked as a plasma biomarker. Future studies will be needed to mechanistically link the changes in plasma to tissue toxicity or injury.

A limitation of the present study was that the authors did not perform receiver operating characteristic (ROC) analysis of diagnostic performance. This would yield area under the curve (AUC) evidence of the sensitivity and specificity of low plasma miR-134 to discriminate from controls. This information would be valuable in deciding whether to take this biomarker further. Additionally, the authors did not explore whether a combination of plasma miR-134 with another miRNA or other variable might further enhance diagnostic accuracy. If plasma miR-134 is a biomarker of IR exposure in interventional cardiologists then a future step could be to develop a simple test. While the authors used standard PCR-based approaches, efforts are underway by a number of teams to develop rapid point-of-care detection of miRNAs in biofluids (12).

In summary, the study by Borghini and colleagues supports plasma levels of miR-134 as a biomarker of

health that is changed in response to long-term exposure to ionizing radiation in interventional cardiologists. This finding, if validated and extended, could form the basis of a diagnostic test for these clinical practitioners.

Acknowledgments

Funding: The authors wish to acknowledge support for microRNA diagnostic research from Science Foundation Ireland (13/SIRG/2114, 13/IA/1891, 16/RC/3948) and the European Union's 'Seventh Framework' Programme (FP7) under Grant Agreement no. 602130

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by the Section Editor Dr. Rongrong Gao (Department of Cardiology, the First Affiliated Hospital of Nanjing Medical University, Nanjing, China).

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/ncri.2018.04.04). 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.

doi: 10.21037/ncri.2018.04.04
Cite this article as: Jimenez-Mateos EM, Henshall DC. Could miR-134 be a marker of ionizing radiation toxicity? Non-coding RNA Investig 2018;2:24.

References

1. Lee RC, Feinbaum RL, Ambros V. The C. elegans heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. Cell 1993;75:843-54.
2. Pasquinelli AE, Reinhart BJ, Slack F, et al. Conservation of the sequence and temporal expression of let-7 heterochronic regulatory RNA. Nature 2000;408:86-9.
3. Quinlan S, Kenny A, Medina M, et al. MicroRNAs in Neurodegenerative Diseases. Int Rev Cell Mol Biol 2017;334:309-43.
4. Ambros V. microRNAs: tiny regulators with great potential. Cell 2001;107:823-6.
5. Daugaard I, Hansen TB. Biogenesis and Function of Ago-Associated RNAs. Trends Genet 2017;33:208-19.
6. Bicker S, Lackinger M, Weiss K, et al. MicroRNA-132, -134, and -138: a microRNA troika rules in neuronal dendrites. Cell Mol Life Sci 2014;71:3987-4005.
7. Sun CC, Li SJ, Li DJ. Hsa-miR-134 suppresses non-small cell lung cancer (NSCLC) development through down-regulation of CCND1. Oncotarget 2016;7:35960-78.
8. Pogribny IP. MicroRNAs as biomarkers for clinical studies. Exp Biol Med (Maywood) 2018;243:283-90.
9. Avansini SH, de Sousa Lima BP, Secolin R, et al. MicroRNA hsa-miR-134 is a circulating biomarker for mesial temporal lobe epilepsy. PLoS One 2017;12:e0173060.
10. Liao TL, Chen YM, Hsieh CW, et al. Upregulation of circulating microRNA-134 in adult-onset Still's disease and its use as potential biomarker. Sci Rep 2017;7:4214.
11. Borghini A, Vecoli C, Mercuri A, et al. Low-Dose Exposure to Ionizing Radiation Deregulates the Brain-Specific MicroRNA-134 in Interventional Cardiologists. Circulation 2017;136:2516-8.
12. McArdle H, Jimenez-Mateos EM, Raoof R, et al. "TORNADO" - Theranostic One-Step RNA Detector; microfluidic disc for the direct detection of microRNA-134 in plasma and cerebrospinal fluid. Sci Rep 2017;7:1750.

