Letter to the Editor

Non-coding RNAs in cellular response to ionizing radiation

Andrea Borghini, Maria Grazia Andreassi

CNR Institute of Clinical Physiology, Pisa, Italy

Correspondence to: Dr. Maria Grazia Andreassi. CNR Institute of Clinical Physiology, Via Moruzzi 1, 56124 Pisa, Italy.

Email: mariagrazia.andreassi@ifc.cnr.it.

Response to: Jimenez-Mateos EM, Henshall DC. Could miR-134 be a marker of ionizing radiation toxicity? Non-coding RNA Investig 2018;2:24.

Received: 14 June 2018; Accepted: 26 June 2018; Published: 06 July 2018.

doi: 10.21037/ncri.2018.06.10

View this article at: http://dx.doi.org/10.21037/ncri.2018.06.10

The evaluation of the health effects of low-dose ionizing radiation (IR) has always been a fundamental topic of scientific research. Health effects involve not only cancer, but also other common diseases (including cardiovascular diseases and neurocognitive impairment) and heritable mutations that can be transmitted to offspring, increasing the risk of diseases in future generations. Therefore, continued research is needed to better improve our understanding of the biological and, consequently, health effects of low levels of IR.

With the development and application of high-throughput technologies, there is a growing interest in non-coding RNAs (ncRNA) as key new players in the regulation of disease-relevant genes (1). Consequently, ncRNAs represent crucial and attractive biological markers for elucidating the molecular mechanisms underlying the onset of disease from low-level IR exposure (*Figure 1*).

ncRNAs include small non-coding RNAs (e.g., microRNA), long non-coding RNAs (lncRNA) and circular RNAs (circRNA), a specific subtype of lncRNAs that form circular structures. Of the small ncRNA, miRNAs are the most extensively studied in radiobiological response (2).

Generally, most miRNA-related research has been conducted on cellular and animal models, especially after exposure to high doses of IR (2).

Recently, our group also revealed the dysregulation of specific circulating miRNA profiles in interventional cardiologists, who accumulate significant lifetime IR exposure as a result of procedures they undertake (3).

As detailed in the elegant editorial by Jimenez-Mateos and Henshall (4), the altered expression of the brain-specific miRNA-134 in interventional cardiologists supports a direct effect of radiation on the molecular regulatory mechanisms modulating key functions in the brain, which might contribute to the development of radiation-induced late cognitive impairment.

These results also underline the importance of further exploration about the role of ncRNAs in cellular response to IR. Recently, important regulatory functions have been described for lncRNAs and circRNAs, which can influence gene expression through many ways, including epigenetic regulation, transcriptional activation and posttranscriptional modification of mRNA.

LncRNAs are non-protein coding transcripts that are longer than 200 nucleotides and account for a large proportion of the non-coding transcriptome (5).

CircRNAs are instead a novel type of RNA that is generated from exonic or intronic sequences and shows tissue-specific expression. Because circRNAs form a covalently closed continuous loop, they are free of exonuclease-mediated degradation and, in turn, more stable than linear RNAs (6).

Additionally, both lncRNAs and circRNAs can serve as miRNA sponges and regulate mRNA expression in a complicated and intertwined network.

However, whether and how exposure to low-dose IR affects lncRNA and circRNA expression is still poorly investigated.

Until now, few studies explored the role of lncRNAs in the response to low-dose radiation in human cell lines (7,8). Interestingly, dysregulated lncRNAs were predicted to target genes associated with fundamental cellular processes (e.g., cell signaling, programmed cell death) as well as to directly affect locus-specific methylation associated with silencing of gene expression (7,8). More recently, the increased levels of lncRNA particle following low-dose

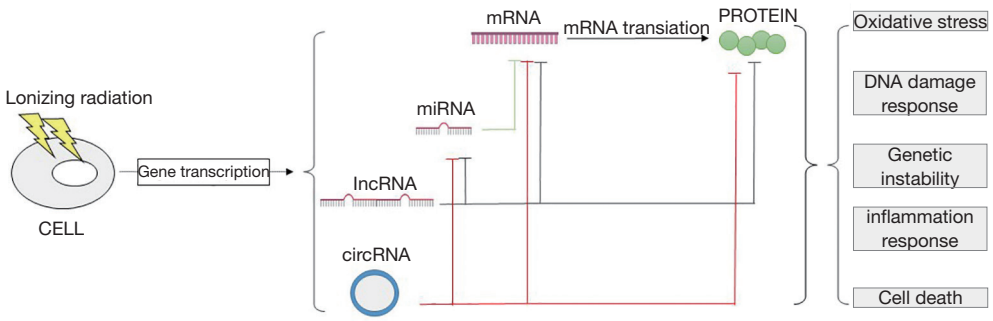

Figure 1 Schematic simplified representation of transcripted RNAs and their potential influence in cellular response to ionizing radiation.

irradiation has been shown to regulate transcription of its neighboring genes (9).

To date, only one study identified circRNAs as potential responders to IR in HUVEC cells (10). Microarray circRNA profiling and next-generation sequencing technology revealed that circRNA expression was altered by low and medium dose exposure and sourced predominantly from genes influencing the p53 pathway. In particular, two specific circRNAs (circRNA *KIRKOS-71* and *KIRKOS-73)* transcribed from the *WWOX* tumor suppressor gene (a p53 regulator) resulted dysregulated after irradiation (10).

Despite these preliminary evidences, however, the association between IR exposure and ncRNAs dysregulation remain largely uncharacterized.

Understanding the functions and regulatory mechanisms of these RNA molecules in the cellular radiation response is a priority research field to be intensively explored in next years.

Acknowledgments

Funding: None.

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.2018.06.10). 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. Esteller M.Non-coding RNAs in human disease. Nat Rev Genet 2011;12:861-74.
2. Chaudhry MA. Radiation-induced microRNA: discovery, functional analysis, and cancer radiotherapy. J Cell Biochem 2014;115:436-49.
3. Borghini A, Vecoli C, Mercuri A, et al. Low-dose exposure to ionizing radiation deregulates the brain-specific miR-134 in interventional cardiologists. Circulation 2017;136:2516-8.
4. Jimenez-Mateos EM, Henshall DC. Could miR-134 be a marker of ionizing radiation toxicity? Non-coding RNA Investig 2018;2:24.
5. KungJTY, Colognori D,Lee JT. Long Noncoding RNAs: Past, Present, and Future. Genetics 2013;193:651-69.
6. Qu S, Zhong Y, Shang R, et al. The emerging landscape of circular RNA in life processes. RNA Biol 2017;14:992-9.
7. Terradas M, Martín M, Repullès J, et al. Distinct

Sets of lncRNAs are Differentially Modulated after Exposure to High and Low Doses of X Rays. Radiat Res 2016;186:549-58.
8. O'Leary VB, Ovsepian SV, Carrascosa LG, et al. PARTICLE, a Triplex-Forming Long ncRNA, Regulates Locus-Specific Methylation in Response to Low-Dose Irradiation. Cell Rep 2015;11:474-85.
9. O'Leary VB, Smida J, Buske FA, et al. PARTICLE triplexes cluster in the tumor suppressor WWOX and may extend throughout the human genome. Sci Rep 2017;7:7163.
10. O'Leary VB, Smida J, Matjanovski M, et al. The circRNA interactome–innovative hallmarks of the intra- and extracellular radiation response. Oncotarget 2017;8:78397-409.

doi: 10.21037/ncri.2018.06.10
Cite this article as: Borghini A, Andreassi MG. Non-coding RNAs in cellular response to ionizing radiation. Non-coding RNA Investig 2018;2:42.

