A new cellular response to radiation exposure

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Almost the entire human genome is transcribed into RNA, but only a fraction of this is actually used to produce protein. The function of the majority of the RNA, the so-called "non-coding transcriptome" remains an enigma. Some non-coding RNA families have been recognised through their shared structural features. Amongst these is the group of long non-coding RNAs (lncRNAs). Researchers at the Helmholtz Zentrum München now report the discovery of a very unexpected role for one such lncRNA, which they call PARTICLE, in regulating the response of cells to ionizing radiation

Biophysical studies have shown that the damage arising to cells from an exposure to ionizing radiation declines in a linearly manner with decreasing dose, with some damage still occurring even at the lowest doses. This linear no-threshold (LNT) dose-response relationship has been used to extrapolate the risks of low doses of radiation from epidemiological studies that were done following exposure to much higher doses of radiation (e.g. survivors of the atomic bombings). This strategy has been one of the tools of radiological protection for almost 50 years. However, at low doses some cellular phenomena (bystander, abscopal and hormetic effects) are inexplicably stronger than predicted by the LNT model. Until now there has been no plausible mechanism put forward to explain these non-linear effects, nor to question the established LNT model.

A new publication from the Institute of Radiation Biology of the Helmholtz Zentrum München in the April 16th edition of the journal *Cell Reports* sheds new light on this mystery. Dr. Valerie Brid O'Leary

and colleagues show that epigenetic DNA methylation is increased through the radiation-induced activation of MAT2A, a gene responsible for providing the S-Adenosyl Methionine essential for the methylation reaction. The team found that a non-coding RNA gene, PARTICLE, was located inside the MAT2A gene, and is itself overexpressed with a slight time delay following exposure to gamma radiation. PARTICLE acts in three different ways to prevent expression of the MAT2A gene: 1) by winding around the MAT2A gene to create a DNA : RNA triple helix structure locking down the MAT2A gene promoter, 2) by binding the messenger RNA product of the MAT2A gene and preventing it being used for MAT2A protein synthesis and 3) transferring MAT2A messenger RNA into intracellular vesicles that are subsequently ejected from the cell. The consequences of all of these actions of PARTICLE are that the radiation-induced activation of MAT2A is rapidly brought , back down to pre-irradiation levels, stopping the DNA methylation reaction.

Significantly, the effect of PARTICLE in limiting the time and extent of the radiation-induced increase in DNA methylation is more pronounced at lower radiation doses than at higher doses. Such an inverse dose-response effect contradicts the LNT understanding of radiation action, and is seen as the first mechanistic evidence to explain a non-linear effect. This challenge to the established LNT model and raises questions on some of the basic assumptions used to assess the risk of low dose radiation exposures. The team at the Institute of Radiation Biology led by Mike Atkinson and Natasa Anasasov have identified several more radiation regulated long non-coding RNA molecules, and are staring to unravel this exciting new aspect of the radiation response.

More information: "PARTICLE, a Triplex-Forming Long ncRNA, Regulates Locus-Specific Methylation in Response to Low-Dose Irradiation." *Cell Reports* 2015; Volume 11 , Issue 3 , 474-485. DOI: 10.1016/j.celrep.2015.03.043

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