Institute of Radiation Biology

Highlight / Publication:
Gonzalez-Vasconcellos I, Schneider R, Anastasov N, et al. The *Rb1* tumour suppressor gene modifies telomeric chromatin architecture by regulating TERRA expression. *Scientific Reports*. 2017;7:42056. doi:10.1038/srep42056.

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Keywords:
Radiation, epigenetics, long non-coding RNA, genomic instability

Central statement of the highlight in one sentence:
Discovery of a new action of the Rb1 tumour suppressor, which regulates telomeric stability epigenetically by driving transcription of the TERRA long non-coding RNA

Text of the highlight:
Radiation therapy is used to kill malignant tissue, but is unselective and can damage surrounding non-cancerous cells. Modern image-guided approaches are designed to apply the radiation directly to the tumour. Whilst this strategy spares as much of the surrounding tissue as possible, some radiation exposure to the adjacent organs is unavoidable. As cancer survivorship improves there is an increase in chronic diseases affecting previously irradiated tissue.

Our goal is to lessen the impact of chronic diseases in long-term cancer survivors. Our strategy is to improve the effectiveness of cancer cell killing by radiation. This will lower the overall dose of radiation needed to treat the cancer and reduce damage to surrounding tissues.

We have recently shown that long non-coding RNAs activate a survival response in irradiated cells through epigenetic reprogramming of the cell phenotype (O'Leary et al Cell Reports 11(3) 474-485 2016). This process offers a new therapeutic target for increasing effectiveness of radiation therapy.
We now show that the product of the Rb1 tumour suppressor gene, responsible for triggering the decision of a cell to divide, also activates transcription of the TERRA long non-coding RNA genes. These genes are located at the terminal regions of chromosomes (sub-telomeric regions). The Rb1-induced TERRA RNA winds itself into the telomere DNA and stabilise the chromosomal ends, in part by changing the distribution of epigenetic marks on the DNA. Mutation of the Rb1 gene, common in many tumours, prevents synthesis of the TERRA RNA. This leads to the loss of the epigenetic markings and eventually to loss of the telomere DNA. Over time this results in the accumulation of sticky chromosome ends that fail to separate correctly when the cell divides. This process results in genomic instability, leading to the rapid accumulation of further gene mutations.

Armed with this new understanding of how radiation modifies the epigenetic environment of a cell via the production of different long non-coding RNAs, we can start to identify drug treatments that prevent these changes.

Taking account of the HMGU mission:
Translational research towards reducing the chronic health problems associated with long-term cancer survivorship (cardiovascular disease, lung fibrosis, neurodegeneration, cancer, diabetes and inflammatory responses).

The internal HMGU co-operation partners with whom the highlight was compiled, if appropriate:
Ralf Schneider, IEG