A novel p53-responsive lncRNA GUARDIN is critical for genomic integrity

With support by the National Natural Science Foundation of China, the research group led by Professor Wu Mian (吴缅) at the Hefei National Laboratory for Physical Sciences at Microscale, the CAS Key Laboratory of Innate Immunity and Chronic Disease, University of Science and Technology of China, identified a particular long non-coding RNA molecule responsible for protecting the genome and keeping it intact, which was recently published in *Nature Cell Biology* (2018, 20: 492—502).

DNA damage response mediated by p53 to repair DNA lesions or to induce apoptosis is important for maintaining genomic integrity, which is a critical cellular mechanism, under steady-state conditions and after exposure to exogenous genotoxic stress. Named GUARDIN by Dr. Wu's laboratory, the long non-coding RNA molecule expression driven by p53 helps to stabilise particular proteins involved in DNA repair and telomere fusion processes, which can be altered to prevent the growth and spread of a gene mutation.

The protective mechanisms of GUARDIN were twofold. On one hand, it acts like a molecular 'sponge' to sequester the harmful molecules miRNA-23a, thus preventing chromosome end-to-end fusion through maintaining the expression of telomeric repeat-binding factor 2 (TRF2). On the other hand, it functions as a molecular scaffold that brings two proteins Breast Cancer 1 (BRCA1) and its binding partner BRCA1 associated RING domain protein 1 (BARD1) together, thus leading to formation of the protein complex fundamental in DNA repair.

A practical implication of this study is the potential application in cancer. By reducing the presence of GUARDIN in the genome, cells corrupted by cancer were made more vulnerable to common drug therapies that targeted the damaged DNA.

For cells to survive they must maintain the integrity of their genome, their DNA. Many cancer treatments actually work through DNA damage and the authors found that depleting GUARDIN in cancer cells significantly enhanced death caused by DNA damaging drugs. Of particular interests, targeted therapeutic drugs that interfere with DNA repair mechanisms are emerging as a class of cancer therapeutics. As a precedent, the poly (ADP-ribose) polymerase inhibitors are effective in the treatment of subsets of cancers that harbour mutant BRCA1. Identification of small molecules that block the interaction of GUARDIN with miR-23a and BRCA1 will be of great interest towards applications in the treatment of cancer.

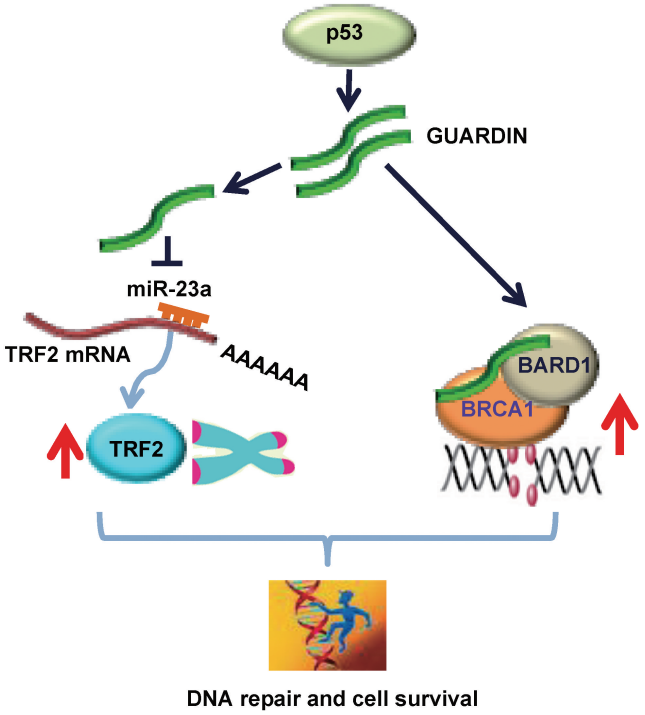

Figure Model depicting the GUARDIN-mediated pathway required to maintain genomic stability.