'Linc-ing' a noncoding RNA to a central cellular pathway

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The recent discovery of more than a thousand genes known as large intergenic non-coding RNAs (or "lincRNAs") opened up a new approach to understanding the function and organization of the genome. That surprising breakthrough is now made even more compelling with the finding that dozens of these lincRNAs are induced by p53 (the most commonly mutated gene in cancer), suggesting that this class of genes plays a critical role in cell development and regulation.

Furthermore, the researchers identify one lincRNA in particular (lincRNA-p21), and demonstrate its critical role in suppressing the reading of many genes across the genome following p53 activation. Led by investigators at Beth Israel Deaconess Medical Center (BIDMC) and the Broad Institute, the results are published in the August 6 issue of the journal *Cell*, which appears on-line today.

"We think that lincRNA-p21 may represent a new class of 'tumor suppressor lincRNAs,'" said senior author John Rinn, PhD, Assistant Professor of Pathology at BIDMC and Harvard Medical School, and an Associate Member of the Broad Institute. "These findings may lead to the identification of novel biomarkers and targets for anti-cancer therapies, as well as add to our understanding of the mechanisms of gene regulation by lincRNAs."

Since the central role of the p53 gene in cancer was first described more than 30 years ago, literally thousands of scientific publications have been published describing various aspects of its "tumor suppressor" role in

regulating cell cycle and cell death (apoptosis) in response to DNA damage, by turning various relevant response genes on or off. However, the intermediary partners and mechanisms by which it carries out its function are still little understood. This current work demonstrates that several dozen lincRNAs are targeted directly by p53, and lincRNA-p21 in particular responds to p53 signaling by suppressing multiple genes across the genome to drive apoptosis.

"We were surprised to find that lincRNA-p21 appears to be functioning as a global repressor, regulating hundreds of genes in the p53 pathway," said Maite Huarte, PhD, first and co-corresponding author."This lincRNA is playing defense for p53 to block other pathways in their efforts to interfere with p53's critical job of tumor suppression by cell death."

lincRNA-p21 carries out this function by roping in other critical factors in the cell nucleus to assist in tamping down expression at specific genes. "In the same way that air traffic controllers organize planes in the air, lincRNAs organize key nuclear complexes in the cell," said Rinn. "lincRNA-p21 specifically binds to a protein called hnRNP-K and then guides hnRNP-K to its final destination to shut down any genes that interfere with p53."

As exciting as these findings are for understanding multiple forms of cancer, they have far broader implications for understanding basic genome biology and multiple diseases. "We know that so-called 'transcription factors' can turn genes on by recruiting transcriptional machinery, but it has been less clear how they turn genes off," says Rinn. "lincRNAs could be those elusive 'anti-factors' that serve to shut genes down by reshuffling proteins around the genome."

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