Enhancer RNAs Alter Gene Expression

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New class of molecules may be key emerging "enhancer therapy"

In a pair of distinct but complementary papers, researchers at the University of California, San Diego School of Medicine and colleagues illuminate the functional importance of a relatively new class of RNA molecules. The work, published online this week in the journal *Nature*, suggests modulation of "enhancer-directed RNAs" or "eRNAs" could provide a new way to alter gene expression in living cells, perhaps affecting the development or pathology of many diseases.

Enhancers are sequences in the genome that act to boost or "enhance" the activity or expression of nearby genes. They "often behave in a cell-specific manner and play an important role in establishing a cell's identity and functional potential," said Christopher Glass, MD, PhD, a professor in the department of Medicine and Cellular and Molecular Medicine at UC San Diego and principal investigator of one of the papers.

Although enhancers have been recognized for more than 25 years, scientists have labored to fully flesh out the breadth and complexity of what enhancers do and how they do it. In 2010, it was discovered that enhancers directed expression of RNA on a broad scale in neurons and macrophages, a type of immune system cell. Dubbed eRNAs, they were different from other classes of nuclear non-coding RNAs, and raised new questions about their potential roles in the functions of enhancers. The two Nature papers attempt to answer some of these questions.

In the first, principal investigator Glass and colleagues investigated a pair of related transcriptional repressors called Rev-Erb-alpha and Rev-Erb-beta (proteins with important roles in regulating the circadian rhythm in many cell types) in mouse macrophages. Using genome-wide approaches, they found that the Rev-Erb proteins repressed gene expression in macrophages primarily by binding to enhancers. Collaboration with researchers at the Salk Institute for Biological Studies revealed that the repressive function of Rev-Erbs was highly correlated with their ability to repress the production of eRNAs.

In the second paper, principal investigator Michael G. Rosenfeld, MD, a professor in the UC San Diego Department of Medicine and Howard Hughes Medical Institute investigator, and colleagues

looked at estrogen receptor binding in human breast cancer cells – and its impact on enhancer transcription. In contrast to the repressive functions of Rev-Erbs, estrogen receptors (ERs) activate gene expression; but, like Rev-Erbs, they primarily function by also binding to enhancers. ER binding was shown to be associated with increases in enhancer-directed eRNAs in the vicinity of estrogen-induced genes, and to exert roles on activation of coding target genes.

Both papers offer new evidence that eRNAs significantly contribute to enhancer activity, and therefore to expression of nearby genes. "Because many broadly expressed genes that play key roles in essential cellular functions are under the control of cell-specific enhancers, the ability to affect enhancer function by knocking down eRNAs could potentially provide a new strategy for altering gene expression *in vivo* in a cell-specific manner," said Glass, noting that in his research, anti-sense oligonucleotides were developed in conjunction with Isis Pharmaceuticals, which suppressed enhancer activity and reduced expression in nearby genes.

Co-authors of the Glass paper are Michael T. Y. Lam, Hanna P. Lesch, David Gosselin, Sven Heinz, Yumiko Tanaka-Oishi, Christopher Benner, Minna U. Kaikkonen, Mika Kosaka and Cindy Y. Lee, Department of Cellular and Molecular Medicine, UCSD; Han Cho, Salk Institute for Biological Studies; Aneeza S. Kim, Andy Watt and Tamar R. Grossman, Isis Pharmaceuticals, Inc.; and Ronald M. Evans, Salk Institute for Biological Studies and Howard Hughes Medical Institute; and Michael G. Rosenfeld.

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Co-authors of the Rosenfeld paper are Wenbo Li, Dimple Notani, Esperanza Nunez, Aaron Yun Chen, Jie Zhang, Kenneth Ohgi, Xiaoyuan Song and Hong-Sook Kim, Howard Hughes Medical Institute, Department of Medicine, UCSD; Qi Ma and Daria Merkurjev, Howard Hughes Medical Institute, Department of Medicine, UCSD and Graduate Program in Bioinformatics, UCSD; Bogdan Tanasa, Howard Hughes Medical Institute, and The Scripps Research Institute; and Soohwan Oh, Howard Hughes Medical Institute, School of Biology, UCSD; and Christopher Glass.

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