Un-junking Junk DNA

November 12, 2013 |

A study led by researchers at the University of California, San Diego School of Medicine shines a new light on molecular tools our cells use to govern regulated gene expression. The study will be published online in advance of print November 10 in the journal *Nature Structural and Molecular Biology*.

"We uncovered a novel mechanism that allows proteins that direct pre-mRNA splicing – RNA-binding proteins – to induce a regulatory effect from greater distances than was thought possible," said first author Michael T. Lovci, a biomedical sciences graduate student working in the Department of Cellular and Molecular Medicine, the Stem Cell Research Program and Institute for Genomic Medicine at UC San Diego.

Researchers from California, Oregon, Singapore and Brazil made this finding while working toward an understanding of the most basic signals that direct cell function. According to Lovci, the work broadens the scope that future studies on the topic must consider. More importantly, it expands potential targets of rationally designed therapies which could correct molecular defects through antisense RNA oligonucleotides – small pieces of DNA or RNA that can bind to specific RNA targets to either block interactions with RNA-binding proteins and/or initiate degradation of the target RNA.

"This study provides answers for a decade-old question in biology," explained principal investigator Gene W. Yeo, PhD, assistant professor of Cellular and Molecular Medicine, member of the Stem Cell Research Program and Institute for Genomic Medicine at UC San Diego, as well as with National University of Singapore. "When the sequence of the human genome just over a decade ago, we learned that less than 3 percent of the entire genome contains information that encodes for proteins. This posed a difficult problem for genome scientists – what is the other 97 percent doing?"

The role of the rest of the genome was largely a mystery and was thus referred to as "junk DNA." Since then sequencing of other, non-human, genomes has allowed scientists to delineate the sequences in the genome that are remarkably preserved across hundreds of millions of years of evolution. It is widely accepted that this evidence of evolutionary constraint implies that, even without coding for protein, certain segments of the genome are vital for life and development.

Using this evolutionary conservation as a benchmark, scientists have described varied ways cells use these non-protein-coding regions. For instance, some exist to serve as DNA docking sites for proteins which activate or repress RNA transcription. Others, which were the focus of this study, regulate alternative mRNA splicing.

Eukaryotic cells use alternative pre-mRNA splicing to generate protein diversity in development and in response to the environment. By selectively including or excluding regions of pre-mRNAs, cells make on average ten versions of each of the more than 20,000 genes in the genome. RNA-binding proteins are the class of proteins most closely linked to these decisions, but very little is known about how they actually perform their roles in cells.

"For most genes, protein-coding space is distributed in segments on the scale of islands in an ocean," said John G. Conboy, PhD, of the Lawrence Berkeley National Laboratory, co-lead investigator on the study. "RNA processing machinery, including RNA-binding proteins, must pick out these small portions and accurately splice them together to make functional proteins. Our work shows that not only is the sequence space nearby these 'islands' important for gene regulation, but that evolutionarily conserved sequences very far away from these islands are important for coordinating splicing decisions."

Since this premise defies existing models for alternative splicing regulation, whereby regulation is enacted very close to protein-coding segments, the authors sought to define the mechanism by which long-range splicing regulation can occur. They identified RNA structures – RNA that is folded and base-paired upon itself – that exist between regulatory sites and far-away protein-coding "islands." Dubbing these types of interactions "RNA-bridges" for their capacity to link distant regulators to their targets, the authors show that this is likely a common and under-appreciated mechanism for regulation of alternative splicing.

These findings have foreseeable implications in the study of biomedicine, the researchers said, as the RNA-binding proteins on which they focused – RBFOX1 and RBFOX2 – show strong associations with neurodevelopmental disorders such as autism and also certain cancers. Since these two proteins act upstream of a cascade of effects, understanding how they guide alternative splicing decisions may lead to advancements in targeted therapies which correct the inappropriate splicing decisions that underlie many diseases.

Additional contributors to the paper include Justin Arnold, Tiffany Y. Liang, Thomas J. Stark, Katlin B. Massirer and Gabriel A. Pratt, UC San Diego; Sherry Gee, Marilyn Parra, Dana Ghanem, and Henry Marr, Life Sciences Division, Lawrence Berkeley National Laboratory, Berkeley; Lauren T. Gehman and Douglas Black, UCLA Department of Microbiology, Immunology and Molecular Genetics and Howard Hughes Medical Institute, UCLA; Shawn Hoon, Nanyang Technological University, Singapore; and Joe W. Gray, Oregon Health and Science University.

Support was provided in part by the National Institutes of Health, (U54 HG007005, R01 HG004659, R01 GM084317 and R01 NS075449,HL045182,DK094699,CA112970, CA126551 and DK032094); and by the Director, Office of Science, and Office of Biological & Environmental Research of the US Department of Energy.

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Media Contact: Debra Kain, 619-543-6163, ddkain@ucsd.edu

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