LincRNAs serve as genetic air-traffic controllers

July 14 2009

Earlier this year, a scientific team from Beth Israel Deaconess Medical Center (BIDMC) and the Broad Institute identified a class of RNA genes known as large intervening non-coding RNAs or "lincRNAs," a discovery that has pushed the field forward in understanding the roles of these molecules in many biological processes, including stem cell pluripotency, cell cycle regulation, and the innate immune response.

But even as one question was being answered, another was close on its heels: What, exactly, were these mysterious molecules doing?

They now appear to have found an important clue. Described in the July 14 issue of the Proceedings of the National Academy of Sciences (PNAS) the scientific team from BIDMC and the Broad Institute shows that lincRNAs - once dismissed as "genomic junk" - have a global role in genome regulation, ferrying proteins to assist their regulation at specific regions of the genome.

"I like to think of them as genetic air traffic controllers," explains co-senior author John Rinn, PhD, a Harvard Medical School Assistant Professor of Pathology at BIDMC and Associate Member of the Broad Institute. "It has long been a mystery as to how widely expressed proteins shape the fate of cells. How does the same protein know to regulate one genomic location in a brain cell and regulate a different genomic region in a liver cell? Our study suggests that in the same way that air traffic controllers organize planes in the air, lincRNAs may be organizing key chromatin complexes in the cell."

Inspired by a lincRNA called HOTAIR -- which is known to bind key chromatin modifier proteins and to assist in getting these proteins to the proper location in the genome - the researchers hypothesized that other lincRNA molecules might be playing similar roles.

"DNA wraps around partner proteins to form a structure called chromatin, which affects which genes are 'turned on' and which are 'turned off'," explains first author Ahmad Khalil, PhD, a scientist in the Department of Pathology at BIDMC and the Broad Institute. "Chromatin does this through a process of compaction; by determining which areas to compact and which to leave open, chromatin successfully determines which genes are accessible for transcription."

But he adds, it has been a mystery as to how this chromatin structure is so precisely targeted by specific enzymes - and not others.

"By utilizing a technology known as RIP-Chip we were able to examine RNA-protein interaction on a large scale and determine which lincRNAs are associated with each enzyme we examined," he adds. To analyze this tremendous amount of data, coauthor Mitchell Guttman, PhD, a bioinformatician at BIDMC and the Broad Institute, used a mathematical algorithm that identified which lincRNAs are bound by chromatin-modifying enzymes and which are not.

"This analysis revealed that 20 to 30 percent of lincRNAs are bound by three distinct chromatin-modifying complexes," adds Khalil. "By depleting several of these lincRNAs from cells, we were able to show a significant overlap between the genes which become affected by the depletion of lincRNAs and the depletion of the enzymes. This provided us with the evidence that these proteins work together with lincRNAs to target specific regions of the genome."

Standard "textbook" genes encode RNAs that are translated into

proteins, and mammalian genomes contain about 20,000 such protein-coding genes. Some genes, however, encode functional RNAs that are never translated into proteins. These include a handful of classical examples known for decades and some recently discovered classes of tiny RNAs, such as microRNAs. By contrast, lincRNAs are thousands of bases long. Because only about 10 examples of functional RNAs were previously identified, they seemed more like genomic oddities than key players. With these latest findings, which also uncovered an additional 1,500 lincRNAs, it's clear these RNA molecules are no mere messengers - they have demonstrated that they can and do play a leading role.

"Much work still remains to be done but we could one day envision utilizing RNA to guide personalized stem cells to specific cell fates to restore diseased and degenerative disease tissues," notes Rinn.

Source: Beth Israel Deaconess Medical Center