Non-coding RNA relocates genes when it's time to go to work

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Cells develop and thrive by turning genes on and off as needed in a precise pattern, a process known as regulated gene transcription. In a paper published in the Nov. 9 issue of the *Journal of Neuroscience*, researchers at the University of California, San Diego School of Medicine say this process is even more complex than previously thought, with regulated genes actually relocated to other, more conducive places in the cell nucleus.

"When regulated gene transcription goes awry, many human diseases result, such as diabetes, atherosclerosis, cancer and growth defects in children," said Michael G. Rosenfeld, MD, a professor in the UC San Diego Department of Medicine, Howard Hughes Medical Institute investigator and senior author of the study. "We've shown that rather than being activated at certain, random locations within the cell nucleus, regulated genes can dynamically relocate. The discovery provides a more comprehensive picture of the interaction between regulated genes and human disease."

Specifically, Rosenfeld and colleagues found that genes regulating cell proliferation responded to growth signals by moving targeted genes from a "silencing environment" in the nucleus called Polycomb bodies to another nuclear compartment called interchromatin granules, which is enriched with activating transcription factors. The movement was precisely guided by two non-coding RNA (ncRNA) molecules called TUG1 and NEAT2.

NcRNA are molecules that are not translated into proteins. In recent years, researchers have ascribed a growing list of duties to them. In this case, Rosenfeld said, TUG1 and NEAT2 move genes to a location in the cell nucleus where they can be more effectively activated and accomplish their function. Cells contain many ncRNAs and it's likely that others play roles similar to TUG1 and NEAT2 in association with various human diseases.

"A big finding here is the uncovering of a general ncRNA-dependent sensor strategy that relocates a large subset of regulated transcription unit cohorts," said Liquing Yang, a postdoctoral member of the Rosenfeld lab and co-first author of the study. "Our data suggests that ncRNAs act as regulators and perhaps as modifiers of 'readers' and 'writers' of the histone code, which implies they have a critical 'switching' role in gene transcription regulation."

"The ability to have signal-dependent relocation of genes in the subnuclear architecture has intriguing implications both in normal regulation and in cancer," added the other co-first author, Chunru Lin.

The deeper, more detailed understanding of ncRNAs and proteins active in controlling gene relocation may reveal new targets for future chemical compounds or inhibitors against diseases that involve mis-regulated gene expression.

"The global roles of ncRNAs and regulated dynamic alterations in nuclear architecture that we have identified connect regulated gene activation programs to other cellular processes, including DNA damage/repair, proliferation, and inflammation," said Rosenfeld. "This discovery will hopefully provide the backdrop for new approaches to several diseases, including prevalent forms of cancer, neurodegeneration, growth defects and diabetes."