New mechanisms describe how the genome regulates itself

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An organism's genome contains all of the information necessary for each of its cells and tissues to develop and function properly. Written in DNA, each individual gene encodes for something, whether it is a structural protein that helps define a tissue's shape, an enzyme that catalyzes the chemical reactions of life, or a signaling protein that cells use to communicate.

Like a dimmer light switch, each gene can be turned on (expressed) strongly or weakly, or turned off entirely. Individual cells have different gene expression profiles, which enables them to have the different functions that make them part of different tissues. For example, an immune cell expresses proteins that allow it to recognize harmful intruders, while a neuron expresses proteins that enable it to pass nerve signals to its neighbors.

The ability for a cell to repress genes, keeping them silent, is therefore critical. In the cell DNA is wound tightly around spools made of proteins, like thread wrapped around a bobbin, and this combined DNA-protein structure is called chromatin. Different genes have distinct chromatin structures, and these structures play an important role in regulating their expression. How genes that need to be silenced are identified and packaged in repressive chromatin structures is not well understood. Now, Caltech biologists have characterized molecular mechanisms that cells can use to silence their own genes.

The research is a collaboration between the laboratories of Professor of Biology Alexei Aravin and Research Professor Katalin Fejes Toth. It is described in two new papers appearing in the journal *Molecular Cell*.

The first paper looks at how cells silence transposons, parasitic genetic elements that, if not tightly controlled, are able to jump from one place to another in the genome and cause mutations in other genes while increasing their own numbers. It was known that nucleic acid molecules called piRNAs are able to recognize and suppress harmful transposons, but how they did so was unclear. In the new research, the authors report that piRNAs work together with a small protein called SUMO (small ubiquitin-like protein) that works as a tag that is attached to other proteins. piRNAs and SUMO cooperate to modify chromatin on these selfish transposons and repress them.

The second paper focuses on roles of SUMO and chromatin in control of normal cellular genes. There are, broadly, two main classes of chromatin: heterochromatin and euchromatin. Euchromatin comprises the most actively expressed genes in the genome, while the genes in heterochromatin, it was believed, tend to be silenced. This new research breaks the existing paradigm and suggests that genes residing in heterochromatin are expressed because of their chromatin environment and not despite it.

"We now know that SUMO acts as a silencing mark to suppress transposons that would otherwise interfere with the proper expression of heterochromatin genes. This is an unexpected function of SUMO," says postdoctoral scholar Maria Ninova, first author on the two new studies.

The Caltech researchers also found that heterochromatin restricts gene expression to specific tissues and identified a novel mechanism that allows cells to maintain the proper balance between heterochromatin and euchromatin.

More information: Maria Ninova et al. Su(var)2-10 and the SUMO Pathway Link piRNA-Guided Target Recognition to Chromatin Silencing, *Molecular Cell* (2019). DOI: 10.1016/j.molcel.2019.11.012

Maria Ninova et al. The SUMO Ligase Su(var)2-10 Controls Hetero- and Euchromatic Gene Expression via Establishing H3K9 Trimethylation and Negative Feedback Regulation, *Molecular Cell* (2019). DOI: 10.1016/j.molcel.2019.09.033

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