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How a critical enzyme keeps potentially dangerous genes in check

Meet OGT, your guardian enzyme on the dark side of the genome

LA JOLLA, CA—You may have heard of the fantastic-sounding "dark side of the genome." This poorly studied fraction of DNA, known as heterochromatin, makes up around half of your genetic material, and scientists are now starting to unravel its role in your cells.

For more than 50 years, scientists have puzzled over the genetic material contained in this “dark DNA." But there's a growing body of evidence showing that its proper functioning is critical for maintaining cells in a healthy state. Heterochromatin contains tens of thousands of units of dangerous DNA, known as "transposable elements" (or TEs). TEs remain silently “buried” in heterochromatin in normal cells—but under many pathological conditions they can “wake up” and occasionally even “jump” into our regular genetic code.

And if that change benefits a cell? How wonderful! Transposable elements have been co-opted for new purposes through evolutionary history — for instance the RAG genes in immune cells and the genes required for driving the development of the placenta and mammalian evolution have been derived from TEs.

But TEs may also wreak havoc on our health. In just the last few years, scientists have linked heterochromatin weakening to aging, premalignancy, cancer, and autoimmune disease.

“You can think of heterochromatin as a prison for transposable elements” says La Jolla Institute for Immunology (LJI) Professor Anjana Rao, Ph.D., the lead author of a new *Nature Structural & Molecular Biology* study, with key collaborators Professor Geoffrey J. Faulkner, Ph.D. of the University of Queensland, Robert Crawford, Ph.D., of biomodal (formerly Cambridge EpiGenetix), and Samuel Myers, Ph.D., Assistant Professor at LJI. “When heterochromatin loses its normal suppressive function, TEs escape and in parallel, the health of cells declines.”

The new study reveals a remarkable way that cells keep us safe from TEs gone wild. The researchers found that cells have taken advantage of an entire protein network to repress TE activity and keep themselves healthy.

"Reactivated transposable elements can create a lot of genomic instability," says Hugo Sepulveda, Ph.D., a Pew Latin American Postdoctoral Fellow, former Instructor at LJI, and one of the two co-first authors of the new study with LJI Instructor Xiang Li, Ph.D.

"Even just increased expression of these elements can affect the expression of nearby genes, as we show in our new paper," adds Sepulveda. "Abundant expression of transposable elements is a signature of many diseases, including cellular senescence, human aging, autoimmune disorders and many types of cancers."

How do cells keep transposable elements under control?

Meet O-GlcNAc transferase (OGT), an enzyme at the heart of many essential cellular functions. According to the new study, OGT is also a lead choreographer when it comes to suppressing TEs and keeping gene expression running smoothly.

For the new project, the researchers followed up on the fact that OGT interacts with important proteins called TET enzymes, discovered by the Rao Lab in 2009. TET proteins are part of the complex machinery that makes sure our DNA is correctly modified in our cells and that our cells activate the right transcriptional programs.

TET proteins are involved in the critical cycle of DNA modifications, where they play a role in a process that results in the removal of molecular markers that attach to DNA (an event called DNA demethylation). The most abundant DNA markers, called 5mC and 5hmC, are normally associated with transcriptional silencing and activation, respectively. Researchers have shown that 5mC is associated with genes turned "off" while 5hmC, mediated by TET proteins, is associated with gene expression turned "on."

This “on/off” epigenetic system gives our cells the flexibility to respond to environmental changes and health threats. DNA demethylation helps our immune cells spring into action if they detect a threat.

DNA demethylation is normal, but cells also need balance. You can't have TET proteins activating every gene at the same time. In normal cells, TET protein activity is restricted to the genes that need to be expressed in that particular cell type.

In the new study, the scientists harnessed Oxford Nanopore sequencing technology and other cutting-edge sequencing techniques to discover where OGT comes in. One especially important and new technique that they used is called duet evoC. This multiomics solution enabling the 6-base genome, developed by biomodal, was essential to establish that both 5mC and 5hmC were simultaneously changing at the same sites in the genome.

The researchers found that OGT protects cells by restraining TET activity. This is extremely important for controlling TE expression because it prevents the silencing modification 5mC from being converted to the activating modification 5hmC in heterochromatin.

Without OGT at the helm, TET proteins ramp up DNA demethylation in the wrong places, turning on too many genes at once, including intact TEs normally “buried” in our genetic material.

Next steps for understanding cancers, autoimmune disease, and more

This finding shows how the non-coding regions of our genome can turn active when TET functions are altered. The new understanding of the OGT-TET partnership shows that these proteins, their mediated marks, and TE expression can affect our cells in a big way.

"We think of these elements as totally 'silent,' and therefore completely inert, but the reality is that cells have to make a huge—and constant—investment to *keep* TEs silent," says Sepulveda.

This new research may also prove important for future drug development. Scientists have identified numerous genes linked to cancer, but controlling their expression remains a challenge. The new findings suggest we might stop cancer growth through interesting new avenues, such as by restraining TE activity in cancer cells.

"We want to control that activity, and we may now have an option through OGT and TETs," says Sepulveda.

Rao emphasizes that further studies are needed to investigate how OGT controls DNA modifications and TE expression—and how the dysregulation of this mechanism contributes to autoimmune disorders, cancers, and other diseases.

Additional authors of the study, "OGT prevents DNA demethylation and suppresses the expression of transposable elements in heterochromatin by restraining TET activity genome-wide," include Leo J. Arteaga-Vazquez, Isaac F. López-Moyado, Melina Brunelli, Lot Hernandez Espinosa, Xiaojing Yue, J. Carlos Angel, Caitlin Brown, Zhen Dong, Natasha Jansz, Fabio Puddu, Aurélie Modat, Jamie Scotcher, Páidí Creed, Patrick Kennedy, and Cindy Manriquez.

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