Scientists discover new role for cell dark matter in genome integrity

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University of Montreal researchers have discovered how telomerase, a molecule essential for cancer development, is directed to structures on our genome called telomeres in order to maintain its integrity and in turn, the integrity of the genome. In an article published in the journal *Molecular Cell*, the scientists explain how they discovered that telomerase molecules are rallied together by a molecule called TERRA, a so-called "non-coding RNA" having no known function in the cell. The scientists used cutting edge microscopy techniques to visualize and track the telomerase molecules as they were ferried to telomeres by TERRA. "Non-coding RNAs constitute the "dark matter of the genome", as they are abundant but their function is largely unknown", explained Dr. Pascal Chartrand, senior investigator and professor of biochemistry.

Each time a cell divides, chromosomes, the long DNA molecules that encode our genes, must be duplicated. But the machinery that does this replication is imperfect, failing to perform duplication all the way to the ends of chromosomes. How living cells divide and how this process is accurately achieved are among the deepest questions scientists have been addressing for decades. It is also where this process goes wrong that aging occurs and cancers arise," Chartrand explained. "To protect the ends of our chromosomes, nature has evolved a simple workaround. Pieces of extra DNA called telomeres are sliced to the ends of the chromosomes and each time they divide, the replication machinery reads into the telomeres, assuring that all our genes remain intact. The telomeres get shorter, but a molecule called telomerase then splices a new piece of DNA to the shortened telomeres to bring them back to their original length. Telomerase is inactive in most of our cells, so repeated division of chromosomes shortens them to the point that cells no longer divide and eventually die. The opposite happens in cancer cells, where telomerase stays active and cells become immortal."

The gene for the non-coding RNA molecule TERRA is found in telomeres and it was suspected to play a role in telomere integrity. To figure out what TERRA might be doing to preserve telomeres, Dr. Chartrand's collaborators, lead author Emilio Cusanelli and Carmina Angelica Perez Romero, attached a fluorescent probe molecule to TERRA so that they could track what TERRA was doing in the cell under a microscope. They discovered that the production of TERRA is turned on when the telomere that its gene sits on gets shorter. They then found that TERRA molecules accumulated in a single spot and at the same time recruited telomerase molecules, which are subsequently directed to the short telomere from which TERRA originated.

This discovery reveals a whole other layer of regulation of telomerase activity, and a novel role for a non-coding RNA in the maintenance of the genome. TERRA could be a new target as well for anti-cancer therapeutic discovery.

More information: "Telomeric Noncoding RNA TERRA Is Induced by Telomere Shortening to Nucleate Telomerase Molecules at Short Telomeres" *Molecular Cell*, 2013.

Provided by University of Montreal