Scientists discover a new mechanism that prevents the proliferation of cancer cells

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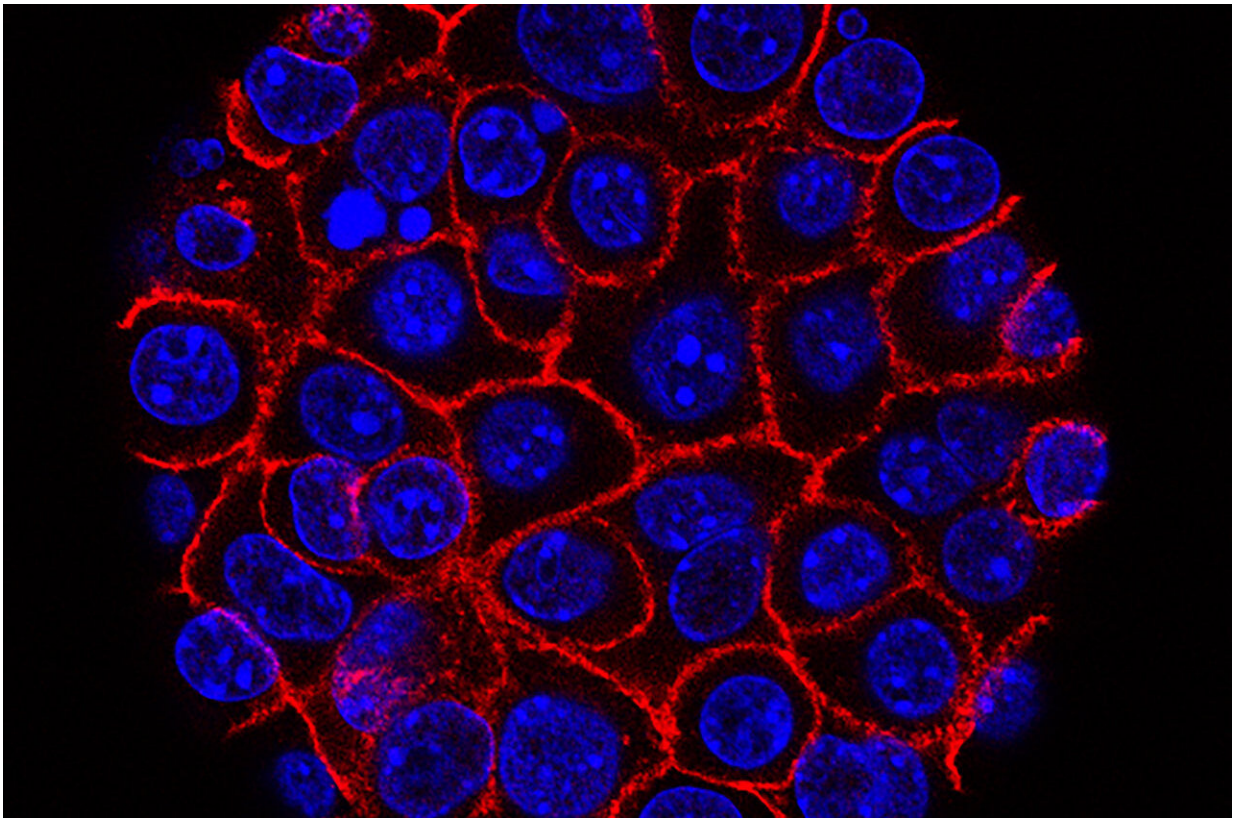

Credit: Min Yu (Eli and Edythe Broad Center for Regenerative Medicine and Stem Cell Research at USC),USC Norris Comprehensive Cancer Center

Canadian researchers have discovered a new and direct molecular mechanism to stop cancer cells from proliferating. In the prestigious

journal Nature Cell Biology, scientists from Université de Montréal show that a disruption of a fine balance in the composition of ribosomes (huge molecules that translate the genetic code into proteins) results in a shutdown of cancer cell proliferation, triggering a process called senescence.

"Ribosomes are complex machines composed of both RNAs and proteins that make all the proteins necessary for cells to grow," said UdeM biochemistry professor Gerardo Ferbeyre, the study's senior author. Cancer cells grow and proliferate relentlessly and thus require a massive amount of ribosomes, he explained. Growing cells must coordinate the production of both ribosomal RNAs and ribosomal proteins in order to assemble them together in strict proportion to each other.

"We were surprised, however, to find that if the production of ribosomal RNA-protein proportions are driven out of balance in a cancer cell, proliferation can be shut down by in a very simple and direct manner," said Ferbeyre.

In their research, led by UdeM biochemistry researcher Frédéric Lessard and done in collaboration with biochemistry professor Marlene Oeffinger of the UdeM-affilated Montreal Clinical Research Institute, Ferbeyre and his team uncovered a new mechanism that uncouples ribosomal RNA from ribosomal protein synthesis to stop the proliferation of cells bearing oncogenic mutations. The team demonstrated an unbalanced ribosomal RNA and ribosomal protein synthesis during oncogene-induced senescence, a response that prevents cancer formation. In the lab, senescent cells shut down ribosomal RNA synthesis but kept producing ribosomal proteins. The team then showed that excess copies of a ribosomal protein called RPS14 could now bind and inhibit a key protein – cyclin-dependent kinase-4, or CDK4 – required to drive cell proliferation.

Lessard noted immediate therapeutic implications of the team's discovery. "A drug that shuts down ribosomal RNA biogenesis would immediately lead to an accumulation of ribosomal proteins outside the ribosomes, and since tumor cells make more of them, they would be preferentially affected by these kinds of drugs," he said.

Added Oeffinger: "The physical interaction of RPS14 with CDK4 is the most direct link between ribosome synthesis and cell proliferation regulatory pathways discovered to date. It is therefore likely a very specific way for cancer progression to be prevented."

The study "Senescence-associated ribosome biogenesis defects contributes to cell cycle arrest through the Rb pathway" was published June 25 in *Nature Cell Biology*.

More information: Frédéric Lessard et al. Senescence-associated ribosome biogenesis defects contributes to cell cycle arrest through the Rb pathway, *Nature Cell Biology* (2018). DOI: 10.1038/s41556-018-0127-y

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