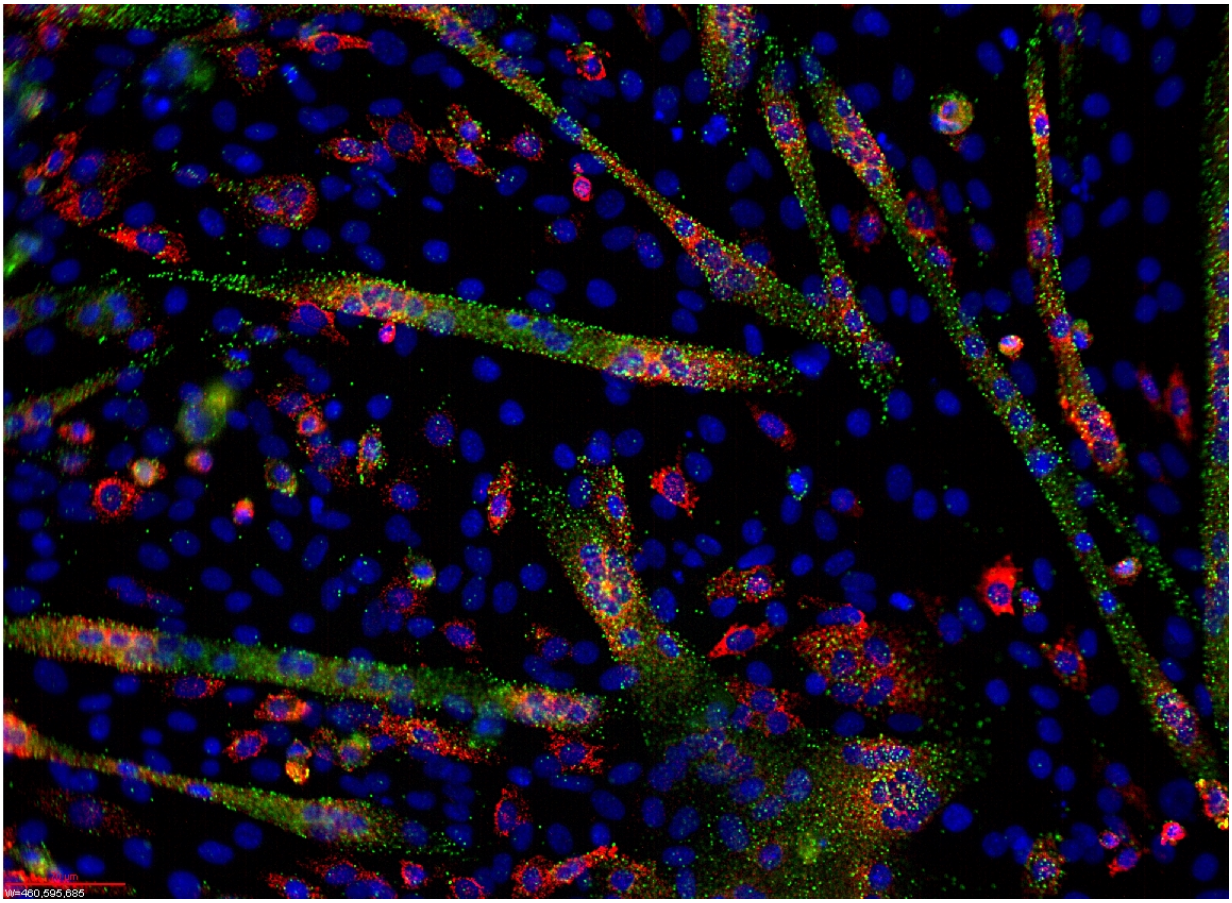
Researchers unlock mysteries of complex microRNA oncogenes

June 27 2019



MicroRNA and mRNA visualization in differentiating C1C12 cells. Credit: Ryan Jeffs/Wikipedia

MicroRNAs are tiny molecules of nucleic acid that control gene

expression, acting like a dimmer switch to tone down gene output at key positions in the network of information that governs a cell's function. MicroRNAs are important for the day-to-day inner working of cells and especially important during development. They also become profoundly defective in diseases such as cancer. Unlike most other human or animal genes, microRNAs are often encoded in genomes and expressed as beads-on-a-string groupings, known as polycistrons. The purpose for this organisation has, until now, been a mystery.

A new collaborative study, led by researchers at McGill University's Goodman Cancer Research Centre (GCRC), and published in the journal *Molecular Cell*, set out to solve this mystery, uncovering novel functions for polycistronic microRNAs and showing how cancers such as lymphoma twist these functions to reorganize the information networks that control gene expression.

A discovery thanks to a single oncogene

The researchers made their discovery by examining how strongly the oncogenic microRNA polycistron miR-17-92 was over-expressed in several types of cancer. Surprisingly, this led to only small increases in the mature microRNA expression in the same types of cells. This meant a lot was happening during their biogenesis, especially in cancer, and that there may be more to the purpose of microRNA polycistrons than previously thought.

"Why some microRNAs are expressed as polycistrons, and how cancers such as lymphoma change microRNA biogenesis were not known," explains Dr. Thomas Duchaine, Professor in the Department of Biochemistry at McGill, member of the GCRC and the study's senior author. "We were able to identify some mysterious steps in microRNA biogenesis that occur in cell nuclei, which had been completely missed for the nearly 20 years since the discovery of the conservation of

microRNA's."

Understanding microRNA's role in cancer

While researchers knew that microRNAs are important in a broad variety of cancers, how and why was not fully understood. "We discovered an entirely new function for microRNA polycistrons and showed how deep an impact it has in certain types of cancer," notes Dr. Duchaine. The findings will help make sense of many of the genomic reorganizations that occur in microRNA loci in those cancers. "We also think this may be happening in physiological conditions, early in development, in embryonic stem cells for example, in placenta, and in other types of tumours."

Knowing what drives specific types of cancer is critical in stratifying cancer sub-types, in developing new therapeutic strategies, or anticipating treatment outcomes in precision medicine.

"The breadth of the impact of the amplification of a single microRNA locus on the gene networks is pretty amazing, in my opinion," says Dr. Duchaine. "Especially considering that this occurs through a mechanism entirely outside of the traditional targeting function of microRNAs. We are not done understanding microRNA mechanistics. I am always amazed at how complex their functional relationships are within our genomes."

While it is not always easy to anticipate the practical implications of basic research findings, Dr. Duchaine believes that they will be diverse. "Besides forcing a reinterpretation of the function of the miR-17-92 proto-oncogene, it will prompt new potential therapeutic strategies. For example, the depth of the impact on the gene network in cells wherein miR-17-92 is amplified indicates a completely different gene network state. To me, this is a screaming opportunity for the testing of genotype-

specific treatments in a precision medicine perspective."

More information: Ariel O. Donayo et al, Oncogenic Biogenesis of pri-miR-17~92 Reveals Hierarchy and Competition among Polycistronic MicroRNAs, *Molecular Cell* (2019). DOI: 10.1016/j.molcel.2019.05.033

Provided by McGill University