Discovery could lead to new RNA therapeutics for many cancers

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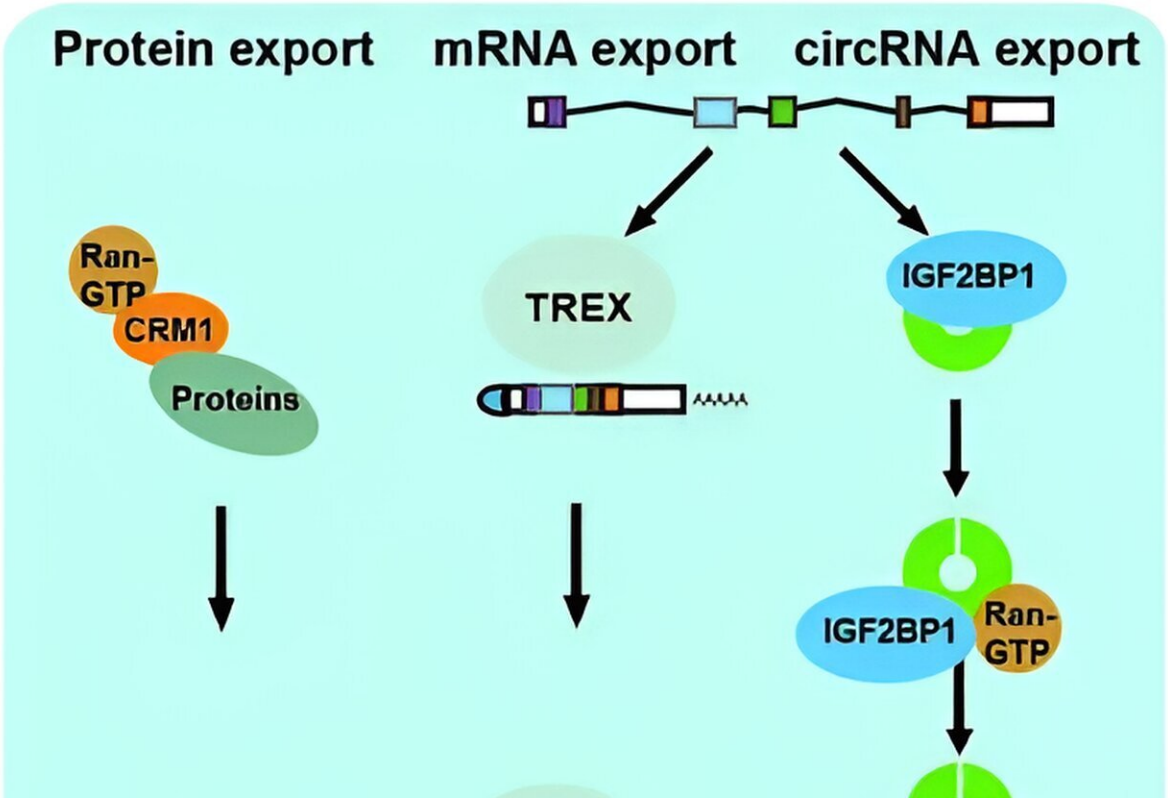

Model describing a nuclear export pathway involved in the transport of circular RNA that is dependent on Ran-GTP. This pathway requires Exportin-2 as an export receptor, IGF2BP1 as an adaptor protein that physically interacts with circRNA and Exportin-2, and Ran-GTP which interacts with circRNA, Exportin-2 and IGF2BP1. In the cytoplasm, the circRNA export cargo is released upon conversion of Ran-GTP into Ran-GDP. Credit: *Nature* (2024). DOI: 10.1038/s41586-024-07060-5

Australian scientists have made a major discovery that could underpin the next generation of RNA-based therapeutics and lead to more potent and longer-lasting RNA-based drugs with an even wider array of potential uses.

In a paper published in *Nature*, Peter MacCallum Cancer Center scientists Vi Wickramasinghe and Linh Ngo and collaborator Greg Goodall at the University of South Australia and SA Pathology's Center for Cancer Biology, have described a new pathway that could help to overcome a major drawback of RNA-based therapeutics to date.

Currently, these breakthrough therapeutics utilize mRNA—injectable genetic material that produces a desired therapeutic or vaccine effect, but mRNA can also break down quickly once absorbed into the human body.

"It's the linear shape of mRNA that makes it relatively unstable and lack durability inside the body and this has been a limiting factor in the potential application of RNA-based therapeutics for diseases such as cancer," explains Dr. Wickramasinghe, senior author on the paper.

"For this reason, there's a rising interest and excitement about another more robust form of RNA—known as circular or circRNA—which has the shape of a closed loop of genetic material, making it much more durable. However key features of how circRNA operates within cells has remained a mystery—until now."

The scientists have discovered how circular RNAs, which are made in the nucleus of cells, are actively transported out of the nucleus to their site of action in the body of the cell (the "cytoplasm"). Understanding this pathway is a major step toward harnessing circRNA for therapeutic purposes, in much the same way as mRNA.

"Intriguingly, this mechanism resembles the way some proteins are transported out of the nucleus rather than the mechanisms employed to export other types of RNA," says Prof. Goodall.

"This further cements evidence these circular RNAs, of which there are many different types, are made to carry out important functions in the cell—a contention that has been unclear for most of the circular RNAs discovered to date.

"Now this molecular mechanism is worked out, it opens up possibilities for manipulating it for beneficial outcomes such as disease therapies."

Dr. Wickramasinghe says when this work began in 2017 it was "purely fundamental, blue sky discovery research" and years before the COVID pandemic would herald the arrival of the world's first mRNA vaccines.

"No one could have predicted how mRNA-based therapeutics would change medicine, nor the tremendous potential for circRNAs in underpinning the next generation of RNA-based therapeutics," Dr. Wickramasinghe says.

More information: Linh H. Ngo et al, Nuclear export of circular RNA, *Nature* (2024). DOI: 10.1038/s41586-024-07060-5

Provided by University of South Australia