New mechanism that permits selective capture of microRNAs in nanovesicles that shuttle between cells

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A team of CNIC researchers directed by Prof. Francisco Sánchez-Madrid (Universidad Autónoma de Madrid & CNIC) has described for the first time how microRNAs— small RNA molecules that regulate the expression of specific genes—are encapsulated in nanovesicles that shuttle between cells.

The role of microRNAs (miRNAs) is fundamental for the correct moment-to-moment adjustment in the expression of target genes. "Before this study, we already knew that these small molecules could be packaged into small vesicles and exported to the extracellular space, to be later captured by other cells and in this way play an important role in intercellular communication," explains CNIC researcher Carolina Villarroya, the first author on the study.

What was not known until now was the mechanism by which miRNAs are encapsulated and exported. And this is precisely what graduate researcher Villarroya and Dr. María Mittelbrunn—from Prof. Sánchez Madrid's group—have discovered, working closely with Dr. Fátima Sánchez Cabo of the Bioinformatics Unit and Dr. Jesús Vázquez of the Proteomics Unit.

The article describes how a specific group of miRNAs that are actively exported in nanovesicles from human T lymphocytes share specific nucleotide sequence patterns called EXOmotifs. When these EXOmotifs

are mutated, export of these miRNAs is impeded; and when they are introduced into other miRNAs, export is facilitated. EXOmotifs provide the binding site for a protein called hnRNPA2B1, which is responsible for transporting miRNAs to the interior of nanovesicles.

hnRNPA2B1 is also implicated in the transport of the genomic RNA of viruses such as HIV to sites of exit to the cell exterior. This establishes a parallel between the secretion of vesicles loaded with RNA and the production of viruses that parasitize the cellular machinery to extend infection.

The discovery suggests a new route for packaging RNA molecules of interest into nanovesicles, which have enormous potential as vehicles for gene therapy, vaccines and antitumor treatments. These findings form the basis of a new patent by the researchers and their institutions the CNIC and the UAM.

The results of the study has been published in *Nature Communications*.

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