A better understanding of cell to cell communication

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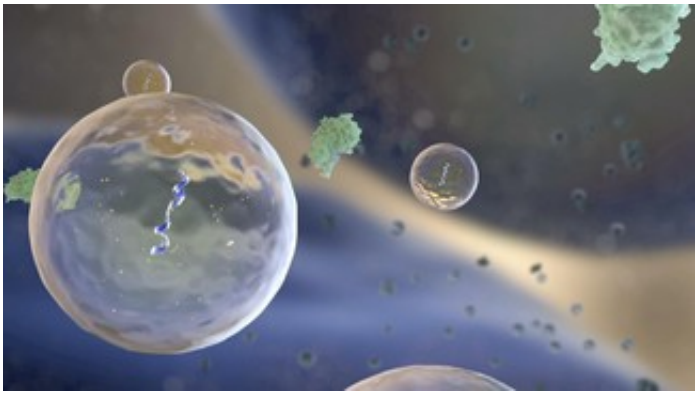

Credit: National Institutes of Health (common fund)

Researchers of the ISREC Institute at the School of Life Sciences, EPFL, have deciphered the mechanism whereby some microRNAs are retained in the cell while others are secreted and delivered to neighboring cells.

There are many ways cells can communicate with each other. One important mode is the release by a cell of signaling molecules that can bind receptors expressed on the surface of another cell to initiate a specific response. In other cases, cells release small vesicles that are packed with signaling molecules of one or more types; such vesicles can fuse with, or be uptaken by, other cells that internalize their content. Exosomes are small vesicles (also called microvesicles) produced by

virtually all cell types. After their release to the extracellular environment – like the interstices amongst cells, the blood or other body fluids – exosomes can fuse with neighboring or distant cells, to which they transfer their cargo of functional molecules. Remarkably, exosomes not only contain conventional signaling molecules like proteins and peptides but also nucleic acids, such as RNAs and DNA fragments, which can horizontally transfer genetic information from one cell to another.

Modulators born within the cells

microRNAs are small RNA molecules that can tune cell behavior by directly modulating the stability of other RNA molecules, called messenger RNAs (mRNAs), which are the precursors of all cellular proteins. Several dozen functional microRNA species are produced by each cell type. These may target hundreds of mRNAs to finely modulate the global protein output of the cell. Recent studies have shown that microRNAs are packed, along with other molecules, into exosomes and are secreted to the extracellular environment by many distinct cell types. This discovery suggests a new mechanism of cell communication involving the ability of exosomal microRNAs to "reprogram" the gene expression of cells that have internalized them. For example, some of the internalized microRNAs could influence the cell's ability to produce certain proteins that, in turn, may affect the cell functions and behavior.

Sorting out microRNAs

Interestingly, the microRNA composition of exosomes may differ from that of the producer cell. Indeed, some microRNA species can be abundant in the cell but scarce in its exosomes, and vice versa. This finding suggests that the sorting of specific microRNAs to exosomes may be actively regulated, although the underlying mechanisms have

remained elusive. With the financial support of the Fonds National Suisse de la Recherche Scientifique (SNSF), Michele De Palma and his colleagues at EPFL and at the Swiss Institute of Bioinformatics (SIB) of the University of Lausanne, have now identified a mechanism that may explain the differential incorporation of microRNAs into exosomes. By performing RNA sequencing and bioinformatic modeling of the data, the researchers found that the sorting of microRNAs to exosomes is directly controlled by the abundance of the mRNAs they target in the producer cell. When the target mRNAs of a given microRNA increase in the cell – for example as a consequence of cell activation – the microRNA is more likely to be retained in the cell and excluded from exosomes. Conversely, if the mRNA levels decline, the microRNA is loaded into exosomes and secreted. These findings imply that the secretion of microRNAs through exosomes is a mechanism whereby cells rapidly dispose the microRNAs that are in excess of their target mRNAs.

"It may seem a quite intuitive and straightforward mechanism," explains Mario Leonardo Squadrito, a leading author of the study, "but investigating the cross-talk between microRNAs and their targeted transcripts has proven challenging and required complex bioinformatic analyses." The authors also took advantage of lentiviral vectors they had developed to specifically introduce or delete selected microRNAs, or their targeted mRNAs, in the cells. "These experiments have been crucial to document how microRNAs can dynamically traffic from the cell cytoplasm to exosomes, in response to changes of the RNA levels," adds Squadrito.

Biological markers

The microRNAs contained in circulating exosomes ("microRNA signatures") are increasingly recognized as potential biomarkers of disease and response to therapy. The findings of De Palma and

colleagues not only identify a general mechanism regulating microRNA sorting to exosomes, but may also help understand how the microRNA signatures observed in circulating exosomes originate from within the cells. For example, patients with some types of cancer display specific microRNA signatures in their blood that may reflect the altered, and possibly evolving, mRNA (and protein) expression profiles of their tumors. Another important area of research is the analysis of the fate of the microRNAs once the exosomes are internalized by cells. "Although our findings suggest that a significant proportion of the internalized microRNAs may be degraded, we employed sensitive new techniques to demonstrate that they retain the ability to modulate gene expression in the target cell," explains Caroline Baer, another leading author of the study. "A fascinating side of the story is that cells produce profuse amounts of exosomes packed with microRNAs. If cells of different type and origin can effectively exchange this form of genetic information, their boundaries must be less tight than we used to think."

More information: Squadrito, M.L., Baer, C., Burdet, F., Maderna, C., Gilfillan, G.D. Lyle, R., Ibberson, M., De Palma, M. "Endogenous RNAs modulate microRNA sorting to exosomes and transfer to acceptor cells." 21 August 2014 (online publication ahead of print). *Cell*, www.cell.com/article/S2211-124 … (14)00619-6/abstract

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