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RNA as an endocrine signal

Multi-cellular organisms have developed a network of circulating body fluids to deliver nutrients, remove waste products, and communicate between cells. It has been demonstrated that, in addition to other known biomolecules, such a nutrients and hormones, RNAs can be transported in blood and other body fluids. The concept that RNA molecules are secreted from cells, transported in body fluids, and act as endocrine signals to alter the phenotype or functionality of target cells, both locally and at distant sites, has recently emerged. Current research is focused on exploring the origins, functions, and applications of these extracellular circulating RNA molecules (exRNA). Questions that remain to be answered include: what are the mechanisms of export and cellular uptake, what is the nature and source of their stability, what molecules do they interact with in blood, and what are the possible biological functions?

Biogenesis and mode of action

MicroRNAs are small non-coding RNAs that play an important role in regulation of various biological processes by interacting with messenger RNAs (mRNAs). The initial step in miRNA biogenesis is the generation of primary miRNA (pri-miRNA) transcripts in the nucleus. A microprocessor complex, consisting of Drosha and DGR8, subsequently cleaves pri-miRNAs, resulting in the formation of miRNA precursors with characteristic stem-loop structures (pre-miRNA). A single pri-miRNA transcript can contain up to six distinct pre-miRNAs. These pre-miRNAs are, upon transportation to the cytoplasm, cleaved by an endonuclease called Dicer, yielding ~22 nucleotide miRNA/miRNA* duplexes. One strand of the miRNA duplex can selectively be incorporated into a RNA-induced silencing complex (RISC) that contains a large number of proteins, including DICER and members of the Argonaute family (AGO1, AGO2, AGO3, or AGO4). The incorporated miRNA strand eventually serves as a guide for RISC-mediated mRNA targeting, resulting in either cleavage or destabilization of mRNA or impaired protein translation.

Extracellular circulating miRNAs

Mature miRNAs have been observed in cell-free blood plasma and serum. These extracellular circulating miRNAs (exRNAs) are usually associated with AGO proteins. To avoid RNAse mediated degradation, exRNAs need to be packaged. Different types of packaging system are used by exRNAs, including apoptotic bodies, high-density lipoprotein (HDL) particles and lipid vesicles, such as exosomes and microvesicles,. ExRNAs play an important role in intercellular communication and modulation of the functionality of distant target cells. Tumor-derived exRNAs have, for example, have been shown to promote tumor growth. In addition, endothelial cell-derived exRNAs can regulate gene expression in smooth muscle cells. Furthermore, exRNAs from rice have been observed in the circulation of humans where they modulate LDL levels. ExRNAs not only play a role in intercellular communication but also in inter-species communication. Microbes have, for example, been shown to influence the functionality of distant host cells by secretion of RNA in extracellular vesicles.
Although it is evident that exRNAs act as intercellular communicators, the mechanisms underlying

exRNA secretion, delivery, and target cell regulation are, to date, relatively unknown. It is therefore important to identify the mechanisms underlying these processes. This may eventually lead to the establishment of new paradigms for intercellular and inter-species communication.

Clinical relevance

The levels of specific exRNAs have been shown to be either elevated or decreased in plasma from patients suffering from various diseases, including different types of cancer. Current research is therefore focused on exploring the possibilities of utilizing exRNAs as biomarkers for the presence or absence of a disease. In addition, efforts are made to assess their usefulness as a prognostic tool for monitoring disease progression and response to therapy. Since exRNAs can reduce protein levels in distant target cells, thereby affecting the functionality of these cells, research is also focused on exploring the possibilities of utilizing exRNAs as therapeutic molecules. To determine the clinical use of exRNAs, a number of questions need to be addressed. It remains, for example, to be investigated whether exRNAs can be engineered for targeted delivery and whether they can be selectively incorporated in vesicles that are capable to cross the blood-brain barrier. In addition, it remains to be investigated whether exRNA profiles of people suffering from diseases can be distinguished from those of healthy people and whether these profiles could be used as diagnostic or prognostic indicators?

The challenges for this novel research field are to develop profiles of exRNAs in different body fluids, to identify the mechanisms through which exRNAs are generated, secreted and delivered to recipient cells, and to demonstrate their clinical potential.