



EDITORIAL

A new perspective on the regulatory role of miRNAs. Cross-kingdom regulation

Una nueva perspectiva sobre el papel regulador de los miRNAs. Regulación entre reinos

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Since the discovery of the first micro RNA (miRNA) in the worm *Caenorhabditis elegans* in 1993,¹ research into these regulatory molecules has made a spectacular quantitative and qualitative leap. It was not until 2001 that the term microRNA was clearly introduced into the scientific literature and a gradual interest in the study of these molecules began.² If in 2001 5 publications with the term miRNA appeared in PubMed, in 2010 it appeared in 3999 articles and in 2020 it was the subject of study in 19,803 publications. An important turning point in this field was the description that miRNAs similar to those found in *C. elegans* are also present in mammals, including humans.³ From then, the interest of researchers has increased exponentially, with numerous regulatory effects on gene expression in practically all physiological and pathological processes, which has redefined numerous dogmas of the mechanisms of gene regulation.

miRNAs are small non-coding RNA molecules, usually 22 nt in size, produced by most tissues and secreted into the circulation mainly in exosomes,⁴ although they can also circulate bound to lipoproteins or other plasma proteins.⁵ Some of these miRNAs are ubiquitously expressed, while others are specifically expressed by specific tissues and/or at specific times during development.⁶ Each of these miRNAs can have only one, few or many target tissues. The mechanism of action of miRNAs is based on binding to the 3 untrans-

lated region (3' UTR) of messenger RNA, thus repressing gene expression. The study of miRNA-mediated gene regulation is an exciting field, although it is still a puzzle that is far from being fully understood. Another relevant aspect in biomedical research is the possibility of using its plasma quantification as a possible risk biomarker.⁶

One of the pathological processes where miRNAs play a prominent regulatory role is cardiovascular disease.⁷ More specifically, they play a very important role in the metabolism of lipoproteins and in the regulation of their pro/anti-atherogenic properties. This is the subject of the study that López de las Hazas and collaborators present in this issue of *Clínica e Investigación en Arteriosclerosis*,⁸ specifically on the effect of certain miRNA on cholesterol efflux mediated by HDL, one of the most relevant mechanisms for these lipoproteins to exert their anti-atherogenic function. But beyond the effect of one or several specific miRNA on physiological processes, what is really relevant about this study is that it is related to a relatively recent concept, which is the cross-kingdom regulation mediated by miRNAs, of different metabolic pathways. This concept was proposed by Zhang and collaborators in 2012.⁹

Many miRNAs are highly conserved throughout evolution, with their diversity and number correlating with the complexity of the organism.¹⁰ The presence of miRNAs in plants was already described by the first studies developed during the 2000s, and a high similarity with mammalian miRNAs has been verified, including their biological function.¹⁰

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Zhang and collaborators described that certain miRNAs from plants, in this case MIR168a, abundantly present in the rice plant, resist the harsh conditions of the gastrointestinal tract, and can reach plasma circulation, even reaching distant organs such as the liver and regulating plasma cholesterol levels. This raised the question of whether these plant miRNAs can have some regulatory role on the organism that ingests these plants, opening an exciting field of study.^{11–13}

Since this first study, numerous investigations have been carried out. Although there has been no lack of contradictory results, a role of plant miRNAs in inflammatory processes, metabolism, cancer, defense against pathogens and viral infections in different experimental animal models has been suggested.¹⁴ For there to be an action of ingested plant miRNAs on the organism, it is essential that they withstand the difficult conditions found in the digestive tract. This is possible because plant miRNAs are methylated in the 2'-OH position of the ribose located at the 3' end, which gives them greater resistance to degradation.¹⁵ The second condition is that these miRNAs are efficiently captured by human cells. And the third, that plant miRNAs exert a regulatory function on certain metabolic pathways. The article by López de las Hazas et al., focusing on 4 miRNAs from broccoli and their effect on HDL-mediated cholesterol efflux, demonstrates that approximately 1% of miRNAs can withstand the harsh conditions present in the digestive tract, which would allow them to reach plasma circulation.⁸ They also demonstrate that miRNAs are efficiently taken up by human macrophage lines that are involved in cholesterol efflux. Finally, they demonstrate that these plant miRNAs stimulate cholesterol efflux in human macrophages. The *in silico* predictive analysis points to a number of possible signaling pathways and therapeutic targets of these miRNAs that could be involved in cholesterol metabolism.

Although this is an “*in vitro*” study, and undoubtedly more in-depth studies in animal models are necessary, the results reported by López de las Hazas and collaborators open up the possibility that some beneficial effects of diets rich in certain vegetables may be attributable, at least in part, to the presence of certain miRNAs. From here, the development of possible future therapeutic strategies based on plant miRNAs will require much more complex studies. Current knowledge in this regard is limited, since a significant part of the studies have been carried out in “*in vitro*” cell and tissue cultures, and more “*in vivo*” evidence is still needed, something that researchers working in this exciting field of biology will undoubtedly devote themselves to in the coming years.

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