Opinion Paper

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Exogenous extracellular vesicles and microRNAs cargo can be considered micronutrients?

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It is well recognized that diet components are important genomic regulators even if RNA transcripts as messenger RNAs (mRNAs) represent less than 2% of the whole genome. In the old-fashioned understanding of genetics, mRNAs are encoded to synthesize a specific protein. Nevertheless, this representation has substantially increased in complexity with the discovery of non-coding RNAs in which microRNAs (miRNAs) gained significant attention in the past 15 years - because its discovery was awarded by the Nobel Prize in physiology or medicine in 2006 to Andrew Z. Fire and Craig C. Mello. MiRNAs are small (18 to 25 nucleotides-long), endogenous non-coding RNA-nucleotide evolutionary conserved, shown to modulate gene expression at the posttranscriptional level through the binding to the complementary sequences of their target mRNAs at the 3' untranslated regions (3' UTRs) (1,2). Based on the interactions between the 3′ UTR of mRNAs, miRNAs can control numerous genes' expression levels. MiRNAs are secreted in lipid bilayer-delimited nanoparticles called extracellular vesicles (EVs), along with proteins and other biomolecules with no replication ability. EVs include microvesicles, apoptotic bodies, and exosomes (Exo), a unique subpopulation of nanosized, spherical membrane vesicles with sizes between 30 and 150 nm. Therefore, EVs and Exo represent a new paradigm in cell biology and medicine, with the idea that the available content may be directly delivered to cells (3).

Similarly, exogenous miRNAs derived from dietary sources and kept in EVs-Exo have been transferred to the mammalian system. Lanfang Wang et al. show that miRNAs present in bovine milk are found in human blood circulation (4). However, it is still to prove if remain active to regulate the host-gene expression and to be effective on their targets in mammalian miRNAs should be around 1000 copies (5).

These special groups of miRNAs were categorized as xenomiRs. Some of them have been found to enter the host through food ingestion, like breast milk from mother to infant may modulate the immune system of newborns through dietary miRNA present in milk (6). This gives rise to a new concept of food-derived miRNAs or dietary miRNAs. Although, we point out with a systematic review that it is crucial further to investigate the bioavailability of miRNAs in different milk fractions and characterize other non-coding RNAs that are largely unstudied (7).

RegardigIn this view, recently, Kleinjan et al. fractionated the bovine milk. Demonstrating also that industrial pasteurization alone or homogenization does not decisively influence the vesicles' stability (8). These findings align with our results from human milk in which pasteurization at 62.5°C for 30 minutes does not significantly affect miRNAs abundance (9). The presence of EVs and exo-miRNAs in human milk, which remain stable after gastric/pancreatic digestion,

via in vitro simulation (10), led studies in mice - using bovine, porcine, and murine milk which - demonstrated that the exo-miRNAs have a unique tissue distribution (11). The Ultra Heat Treatment (UHT) used in industrial processes to ensure long-life commercial milk has a detrimental effect on the EVs structure containing miRNAs. Destroying the lipid nanoparticles of the EVs envelope makes miRNAs vulnerable to RNAse enzyme degradation.

Consequently, these components of bovine milk EVs are reduced in processed milk (8). The presence and the abundance of miRNAs in human milk compared to other body fluids (12) could designate them as EV-miRNA-based micronutrients in the future? More than 100 are highly conserved amongst species, particularly the pool involved in the regulatory activity of innate and adaptive immune response, which balances inflammatory response (2, 12). Even if the inflammatory process is valuable for dealing with pathogens, it can lead to severe disease if not properly controlled.

MiRNAs are negative regulators of inflammation (13), and, in this view, nutrition-dependent microRNAs regulation, the so-called nutrimiromics (14), has been proposed to manage inflammation and chronic disease (15). Nutrimiromics studies the influence of miRNAs and nutrition on changes in gene expression due to miRNAs' epigenetic process (16). In conclusion, scientists learn from nature, and the first SARS-CoV-2 vaccine mRNA-based encapsulated in lipid nanoparticles now exists (17). Therefore, the scenarios could move from a new food miRNAs based.

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