Future directions of extracellular vesicle-associated miRNAs in metastasis

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Provenance: This is a Guest Editorial commissioned by section editor Dr. Mingzhu Gao (Department of Laboratory Medicine, Wuxi Second Hospital, Nanjing Medical University, Wuxi, China).

Comment on: Dhondt B, Rousseau Q, De Wever O, *et al*. Function of extracellular vesicle-associated miRNAs in metastasis. Cell Tissue Res 2016;365:621-41.

Abstract: Numerous studies have demonstrated the dynamic cell-to-cell communication mediated by extracellular vesicles (EV) in cancer cell survival and metastasis development. EV content includes proteins, lipids, DNA, and RNA like microRNAs. Non-protein coding microRNAs play a very active role in almost all cellular processes targeting mRNAs for silencing. Different miRNA profiles have been found in different cancer types, and clarification of miRNAs packed in EV from different types of cancers will allow the understanding of metastasis and the application of miRNAs as biomolecules in diagnostic, prognostic and therapeutic approaches to fight cancer. The profound review of Dhondt *et al*., 2016, provides a wide view of EV miRNAs involved in various steps of the metastasis process to illustrate how the cancer cell interaction with the near and long distance microenvironment allows metastasis. These studies will surely conduce to additional patient studies to prove the relevance of EV miRNAs in metastasis *in vivo*. It remains to be elucidated how the tumoral cell sorts the miRNAs for secretion to send a message, and to well recognize the type of EV performing this message delivering. It will be very useful to identify whether miRNAs are delivered with post-transcriptional modifications since this is an important feature for miRNAs activity and stability.

Keywords: Microvesicles (MV); microvesicles particles; exosomes; extracellular vesicles; microRNAs

Submitted Dec 15, 2016. Accepted for publication Dec 23, 2016.
doi: 10.21037/atm.2017.01.26
View this article at: http://dx.doi.org/10.21037/atm.2017.01.26

Significant amount of information supporting extracellular vesicle (EV) associated miRNA mediated cell-cell communication has accumulated along the years (1,2). Specific miRNA vesicle loading is an important question to be unveiled due to its implication in tumor cells communication to near and long distance tissue cells. There are three types of EV involved in molecules secretion: microvesicles (MV), exosomes (with different types of biogenesis pathways, implying different types of exosomes) and apoptotic bodies. The variety of EV has emerged the question whether different types of vesicles are related to different miRNA loading and miRNA function in recipient cell. However, from the studies shown in the profound review of Dhondt *et al*., 2016, miRNA loaded exosomes are found either from primary tumors and from metastasis cells, lowering the possibility that this type of EVs are preferentially secreted by one or the other type of cell (3). Nevertheless, more studies discriminating between MV and exosomes and differentiating between exosomes sizes or types would lead to more definitive conclusions. The question of miRNA load selection still remains open. In the same review it is

shown that some anti-oncomirs are discarded in exosomes favoring tumoral cell hallmarks as miR-145 (4), miR-146b, miR-122 (5) and miR-23b (6). It still remains to know whether miRNAs in these exosomes are active or not, since recently it has been shown that post-transcriptional regulation mediates miRNA activity and stability (7). It is known that total miRNA cell profile differs depending on the type of cancer cell (8-10). It is interesting to notice that the majority of studies shown in this review focused in oncomirs and less in anti-oncomirs analyses, whether there is a preference of the type of miRNA secreted by these cancer cells is not known. Therefore, additional miRNA loaded EV studies in different cancer cell types will widen the understanding of this cancer progression mechanism. On the other hand, it is shown in Dhondt *et al.*'s review that oncomirs loaded in exosomes of primary tumors or metastasis cells favor the metastasis process for example preparing other tissues niches like exosomes carrying miR-105 secreted by breast metastatic cancer cells and internalized by endothelial cells (11); favoring angiogenesis like miR-214 found in exosomes of epithelial cells (12); inducing migration by miR-409 from cancer associated fibroblasts in EV (13); stimulating invasion by mir-105 found in breast cancer cell exosomes (11); promoting proliferation like miR-429 in hepatocellular carcinoma (14); potentiating invasive and adhesive capabilities as miR-210 in brain metastasis competent cell-derived exosomes (15); triggering epithelial to mesenchymal transformation by miR-409 from cancer associated fibroblasts in EV (16) and miR-221 in extra-hepatic cholangiocarcinoma (17); or additionally, participating in mesenchymal to epithelial transition (18). These results direct to the question: how do cells tag a type of miRNA to be discarded or used to enhance cancer traits? The study of the mechanisms responsible of vesicles miRNA specific loading will be useful to respond this question. If there are proteins or miRNA post-transcriptional modifications involved in miRNA sorting is a tentative subject of study. There are important studies supporting this question. Recently, Janas *et al.*, 2012, suggested that miRNA sorting could be explained by contacting of the miRNAs and the microvesicular body (MVB) membranes due to the well-known affinity of RNAs to the raft-like membrane regions (19). Besides this mechanism, secretion of miRNAs could additionally be more specific. Makarova *et al.*, 2016 (20) suggested the presence of universal sequence-specific sorting mechanisms for miRNA loading into EVs since miRNA repertoires in EVs derived from different cell types shared a higher similarity than that of EVs and their corresponding parental cells (21), moreover, significant differences in intracellular and extravesicular miRNA profiles reported by several research groups strengthen this hypothesis (22-28).

Extensive studies have shown that intracellular and extracellular miRNAs are mainly found bond to AGO proteins (29-32). However, recent findings suggest miRNA stabilization can be different as well. Makarova *et al.*, 2016, revealed that in HeLa cells, the amount of miRNA is approximately 13 times higher than the amount of AGO proteins (~200,000 and 15,000 molecules per cell, respectively) (20). Moreover, two recent studies have reported the discovery of more than a thousand new human miRNAs (19,33). In addition, a minor fraction of AGO proteins are associated with other classes of short RNAs (33,34) which further reduces the amount of AGOs available for the association with miRNA. All this information leads to speculate that other type of miRNA regulation may play a role in the different processes where miRNAs participate, as it could be miRNA sorting in EV.

In the same review, it is shown by in silico analyses that 50–70% of animal and plant miRNAs are able to form intrinsic secondary structures (hairpins and homoduplexes) (35,36). Many of these miRNA structures strongly resembled to anti-tenascin C aptamers (37) implying that miRNAs may directly modulate protein activity (36), but also it may imply that miRNAs may have the ability to bind to different proteins and become stabilized or be sorted for EV loading. Exosomes studies have shown that among several pathways of exosome biogenesis, the ceramide-dependent mechanism is a way contributing to circulating miRNA release since export of miRNA outside the cell was impaired upon inhibition of neutral sphingomyelinase 2 (nSMase2) an enzyme mediating ceramide biosynthesis (20,38-40). Another way of miRNAs secretion mediated by ESCRT machinery of exosome formation seems to be more controversial since in HEK293 cells, after transient knock-down of the ESCRT-associated protein ALIX, which regulates ESCRT-dependent intraluminal vesicle (ILV) formation (41) the levels of miRNA in conditioned media remained unaltered (42). However, another study reported that miRNAs activity is an ESCRT MVB dependent mechanism, suggesting this may be another way of miRNA secretion (2). Therefore, additional studies are needed to clarify the types of vesicles mediating

miRNA export. MiRNA sorting into the MV, the other type of EVs, is also unclear and it is subject of study (20). The existence of different ways of secretion may imply the existence of miRNAs sorting mechanisms for their specific secretion and could also be linked to the type of function that miRNAs are performing in recipient cells.

Different protein modifications are implicated in protein function and fate therefore miRNA modifications can probably serve as miRNAs sorting. The global localization of miRNAs in the cell has emerged the idea of multiple miRNA functions beyond that of gene silencing. It was strongly thought that miRNA activity was limited to P bodies (43-45) but it has been recently shown that miRNAs and miRNA machinery are also found in ER, Golgi apparatus, lysosomes and endosomes and that miRNAs are functionally active in ER (46,47). ER is a cell organelle where protein modifications are carried out (48). The fact that miRNAs are found very close to these organelles gives a possibility that post-transcriptional miRNA modifications may be happening in this place. MicroRNAs are modified through a series of processing events after transcription like 5'-end phosphorylation, 3'-end adenylation or uridylation, and terminal nucleotide deletion (49). The study of Salzman *et al*. showed that miR-34, a tumor-suppressor miRNA that is important in cell survival and that is transcriptionally upregulated by p53 in response to DNA damage is found in a pool of mature miRNA in cells that lack a 5'-phosphate and is inactive. Following exposure to a DNA-damaging stimulus, the inactive pool of miR-34 is rapidly activated through 5'-end phosphorylation in an ATM- and Clp1-dependent manner, enabling loading into Ago2. In a different study, it was shown that post-transcriptional addition of nucleotides to the 3' end of miRNAs is a mechanism for regulation of miRNA activity. For example, such modification in plants and C. elegans influence miRNA stability (49,50). In humans, miR-122 was shown to be adenylated by the RNA nucleotidyl transferase GLD-2, which resulted in an increase in the stability of the miRNA (51). On the other hand, uridylation of miR-26a had no effect on miRNA stability, but had an effect on the ability of miR-26a inhibition of its mRNA target (52). It has been shown that 3' modification of miRNA is a physiological and common post-transcriptional event that shows selectivity for specific miRNAs and is observed across species ranging from C. elegans to human (53). Thus, miRNA post-transcriptional modifications are important to this molecule for different purposes. This or other uncovered modifications may be taking place in order to select miRNAs for vesicles sorting. Concerning miRNA EV loading and release, some studies have focused on mechanisms involved in miRNA release from EV to recipient cells. The protein neurophilin 1 has been found implicated in the mechanism of EV and recipient cell interaction. miRNA EV loading on the other hand has been less documented (54).

Given that exosomes can be isolated from almost any cell, are involved in cell-to-cell communication, and participate in both normal and pathobiological mechanisms, there have been extensive studies exploiting their use both as diagnostics and therapeutics (55). For example, exosomes are used to detect tumors in patients with prostate, breast, and ovarian cancers (56-58). The naturality of exosomes to carry nucleic acids, such as DNA, RNA, and miRNAs to targeted cells, inducing genetic modifications in both biological and pathogenic processes, exosomes became a major interest in treatment strategies involving genetic therapy as drug delivery systems (55). The understanding of miRNA loading and sorting in EV will strongly improve the design and efficiency of this potential therapy approach. The recent revelation that miRNAs activity is modulated by phosphorylation (7) should be taken in consideration when designing diagnostic and therapeutic methodologies for more secure and effective methodologies. MiRNAs have been extensively reported to be implicated in the process of drug and radiation resistance, being both miRNA under or over expression important determinants of clinical response after cancer therapy (59-62). For example, Pedroza-Torres *et al*., 2016 (63) identified 101 miRNAs that showed significant differences between non-responders and complete pathological responders. Thus miR-31-3p, miR-3676, miR-125a-5p, miR-100-5p, miR-125b-5p, miR-200a-5p and miR-342 were significantly associated with clinical response. Expression of miRNAs above the median level was a significant predictor of non-response to standard treatment. Interestingly, it has also been reported that miRNA expression is affected after radio and/or chemotherapy (64). MiRNA signatures are currently being used to study miRNA based cancer prognosis after conventional therapy. How may this treatment influence the afflux of EV and miRNA load has not been profoundly investigated and would provide important information to the understanding of cancer relapse and the intervention of EV to this process. Dhondt *et al*.'s review is a very useful collection of sophisticated information that clarifies the important function of EV miRNAs in cell-cell communication in the metastasis process. It provides

researchers with potential candidates for diagnostic and prognostic markers and therapeutic targets to fight cancer. It is a scaffold that will lead researchers to perform new assays to gain additional reliable EV miRNA data as the elucidation of the miRNA sorting mechanism to EV loading that would also clarify the metastasis process and lead to new anticancer approaches.

Acknowledgements

Funding: The authors want to thank to Consejo Nacional de Ciencia y Tecnología (CONACYT)-Ciencia Básica Grant No. 177620, Fondo Mixto de Fomento a la Investigación Científica y Tecnológica CONACYT-Gobierno del Estado de Zacatecas (FOMIX-ZACATECAS) Grant No. 203155, and Programa de Mejoramiento del Profesorado (PROMEP) Grant No. 17192.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: López JA, Granados-López AJ. Future directions of extracellular vesicle-associated miRNAs in metastasis. Ann Transl Med 2017;5(5):115. doi: 10.21037/atm.2017.01.26

