Exosomes, a class of small extracellular vesicles (sEVs) having a diameter of 40–100 nm, are produced by all cells and found circulating freely in all body fluids, including sputum, plasm, urine and bronchoalveolar lavage (1-3). This biogenesis of exosomes originates in the endosomal compartment of a parent cell, and then mediate specific cell-to-cell communication by transferring information (e.g., proteins, RNAs, and DNAs) to target cells (4). The process is completed through three main mechanisms: endocytosis by phagocytosis, direct fusion with the plasma membrane and receptor-ligand interactions (5). Recently, studies have shown that exosomes play a role in tumorigenesis, invasion, metastasis, and drug resistance via specific cell-cell communication involving the transfer a series of small molecules, including microRNAs (6,7). The weight of evidence supports that exosome-derived microRNAs is associated with the development and progression of various cancers, such as esophageal cancer (8), bladder cancer (9), lung cancer (10), nasopharyngeal carcinoma (11) and colorectal cancer (12), etc. Over the years, abnormally elevated levels of exosome-derived microRNAs in cancer tissues have fueled a large number of studies attempting to determine their potential as new diagnostic biomarkers and therapeutic targets for cancer.

A recent article in Cancer Letters by Zhang et al. (13) provides a novel insight into the association of exosome-derived microRNAs and hepatocellular carcinoma (HCC) tumorigenesis. In this study, the authors used contrasting approaches by selecting the down-regulated expression of exosome-derived miR-320a that was released from cancer-associated fibroblasts (CAFs) of HCC human patients, and demonstrated that stromal cells could transfer miR-320a to HCC cells via transferring exogenous miR-320a. Moreover, miR-320a could inhibit HCC cell proliferation and metastasis ability both in vitro and in vivo by directly targeting PBX3-Erk1/2 pathways, thereby presenting the exosome-derived miR-320a as a novel strategy for the treatment of HCC. However, in our opinion, the conclusion drawn by Zhang et al. needs further validation for the following reasons. Firstly, it is unclear whether the exosome-derived miR-320a of para-cancer fibroblasts (PAFs) can be transferred to the HCC cells. In Figure 3, the authors appear to compare CAFs to the stromal cells, stating that exosome-derived miR-320a of CAFs are transferred into the HCC cells. Moreover, if enough amount of endogenous miR-320a of PAFs fails to be transferred to HCC cells, it is difficult to understand why the exogenous miR-320a of CAFs is transferred into HCC cells. Secondly, it is not clear whether the miR-320a inhibits the survival of CAFs. Although CAFs are derived from normal stromal...
cells, they have the characteristics of cancer cells because they are ‘educated’ by the tumor microenvironment. Meanwhile, CAFs can induce the formation of tumor microenvironment by recruiting immune cells and releasing cytokines to promote the development and progression of cancer. Figure 4 demonstrated that miR-320a strongly inhibits the proliferation and metastatic ability of HCC cells. However, it is difficult to predict the effect of CAFs after transfection with the lentiviral pre-miR-320a plasmid. Indeed, if the CAFs are considered as a class of cancer cells, miR-320a may be speculated to promote apoptosis and inhibit the survival of CAFs. Finally, it is not known whether the exosome-derived miR-320a of CAFs that was transferred to HCC cells, is functional or not. Recent studies demonstrated that despite the induction of exosomes into the recipient cells, the contents of the exosome did not lyse the intracellular membranes to be further degraded by the lysosomal degradation pathway of the recipient cells. As shown in Figure 3, the authors only demonstrate that CAFs allow the transfer of miR-320a to tumour cells, however, we cannot judge whether the exosome-derived miR-320a is functional after its transfer into the HCC cells.

In conclusion, the authors provide a novel point of view suggesting that in the event of cancer, the reversed the loss of exosome-derived microRNAs expressed via an exogenous means, such as wrapping the microRNA mimics into exosomes in vitro followed by injection into the corresponding cancer tissues, can be developed as a therapy for cancer. More recently, exosome-derived ncRNAs have been recognized as a ‘new star’ in cancer research and subsequently several more exosome-derived ncRNAs have been reported as being associated with the development and progression of cancer. However, the functions of exosome-derived microRNAs in vivo remain an outstanding question, and additional research utilizing convenient in vivo model systems is needed (14). Therefore, a long path needs to be traversed from scientific research to clinical application. Further research in the development of novel methods and technology will eventually clarify the function and mechanism of these exosome-derived ncRNAs, thereby providing a novel strategy for the prevention, early diagnosis, and treatment of cancer.

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**Footnote**

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

**References**
