Commentary

Expelling the "perpetrators": ovarian cancer cells discard miR-6126 through exosomes to promote survival

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Ovarian cancer is the leading cause of death among gynecological malignancies. High-grade serous ovarian cancer (HGSOC), the major ovarian cancer histological type, is mostly diagnosed at a late stage and is particularly prone to metastasis to the omentum and peritoneum. The majority of HGSOCs respond well to initial treatment by taxane- and platinum-based chemotherapy. However more than half of HGSOCs relapse within 2 years and become resistant to chemotherapy. In spite of decades of translational research there has only been a small improvement in overall survival of patients with HGSOCs (1). Early detection of the disease and novel therapeutic interventions based on better understanding of the disease oncogenic drivers are required for improving clinical outcomes in HGSOCs.

Exosomes are extracellular vesicles that are approximately 40–150 nm in diameter and are composed of a lipid bilayer that can carry proteins, DNA, mRNA, and microRNAs (miRNA) as cargo. Exosomes are released from many types of cells, including cancer cells, into the peripheral circulation and have been detected in many types of biological fluids, including plasma, saliva, urine, and ascites. Exosomes derived from cancer cells carry cargo that serve as a cancer signature. Therefore the detection and analysis of exosomes in liquid biopsies has the potential as clinically useful cancer biomarkers (2). Tumor-derived exosomes have the ability to influence cell-to-cell communication within the cancer microenvironment and, therefore, contribute to cancer progression and metastasis. In addition, the profile of integrins that are expressed on the surface of exosomes can potentially be recognized and taken up by cells at specific organs to prepare a metastatic niche and, therefore, guide selective distant organ metastasis (3). Exosomes have also been reported to contain miRNAs which can affect the expression of a broad range of mRNAs. miRNAs are endogenously expressed small noncoding RNAs that consist of approximately 22 nucleotides. They predominantly bind to the 3'-untranslated region (UTR) of target mRNAs to suppress their expression. In mammals, miRNAs are predicted to control the activity of more than half of all protein-coding genes (4). In many types of cancers including ovarian cancer, a number of miRNAs are reported to regulate genes which may have important biological functions in cancer cells. The analysis of 489 HGSOCs from the cancer genome atlas (TCGA) revealed that miRNAs were found to be clustered into three subtypes with prognostic significance (5). miRNAs that are upregulated in ovarian cancer have mostly oncogenic functions, while those that are downregulated have tumor suppressor functions (6). It is reported that tumor suppressor miRNAs, that inhibit key drivers of ovarian cancer, have the potential to be used as therapeutic tools in ovarian cancer (7). miRNAs secreted from cells into the circulation are stabilized in either exosomes or by binding to proteins, such as Argonaute 2 (AGO2). miRNA profiling from exosomes was reported to reflect the profile of the parent ovarian cancer cells, and, therefore, have the

potential to be used as biomarkers for early detection (8). miRNAs in exosomes also play important roles in cancer progression (9). Both oncogenic and tumor suppressor miRNAs have been identified in exosome from ovarian cancer cells, but the mechanism that control the content and the amount of miRNAs in exosomes is unknown. In addition, the reason why tumor suppressor miRNAs are packed in exosomes from ovarian cancer cells has remained unclear (10).

In a recent paper, Kanlikilicer *et al.* showed that ovarian cancer cells selectively release the tumor suppressor miR-6126 via exosomes to maintain their malignant phenotype. As miR-6126 directly targets the pro-survival integrin β-1 mRNA, its expulsion prevented the reduction of expression of this integrin (11). Integrins are cell surface receptors that consist of a heterodimer of α- and β-subunits. They can bind extracellular matrix (ECM) proteins, and drive intracellular signals in cancer cells, to promote invasion, migration, and proliferation. In ovarian cancer, integrin β-1 is known to promote cancer metastasis and spheroid formation by forming heterodimers as integrin α2β1, α4β1 and α5β1, which bind ECM proteins such as laminin, collagen, and fibronectin. This binding activates downstream pro-survival signaling, such as the MAPK and the PI3K/AKT pathways. Therefore, the inhibition of integrin β-1 is a potential therapeutic strategy in ovarian cancer. Kanlikilicer *et al.* also showed that the administration of a miR-6126-mimic is a potential new therapeutic strategy via interfering with integrin β-1 in ovarian cancer cells (11). First, the authors examined the difference between miRNA expression in exosomes and in their cell of origin. By using three pairs of chemotherapy-sensitive and chemotherapy-resistant ovarian cancer cell lines, they discovered that miR-6126 was released in exosome from both ovarian cancer cell types. In other words, they succeeded in identifying an exosome miRNA that is ubiquitously released from ovarian cancer cells. Next, the authors examined the function of miR-6126. Using protein arrays, they showed that the PI3K/AKT signaling pathway was altered in miR-6126-mimic transfected ovarian cancer cells, and confirmed that phosphorylated PI3K, AKT, and c-RAF were reduced following miR-6126-mimic transfection. Consequently, migration, invasion, and angiogenesis were also impaired in ovarian cancer cells following miR-6126-mimic transfection. To determine the mechanism of the tumor suppressor function of miR-6126, the authors performed in-silico computational predictions to identify miR-6126 target genes and focused on the 3'-UTRs of genes involved in PI3K/AKT signaling. This analysis identified the 3'-UTR of integrin β-1 (ITGB1) as a direct target of miR-6126. This finding was confirmed by transfecting ovarian cancer cells with a miR-6126 mimic. Next, the authors evaluated integrin β-1 and miR-6126 expression among 129 patients with late stage HGSOCs. An inverse correlation was found between the expression of ITGB1 and miR-6126. Combining the expression levels of ITGB1 and miR-6126 enhanced the ability to predict patient survival. Specifically, patients with tumors that had low expression of ITGB1 and high expression of miR-6126 had significantly longer survival rates compared to those with tumors expressing high ITGB1 and low miR-6126. Next, the authors examined the correlation between miR-6126 expression and exosome release. When a miR-6126 mimic was transfected to ovarian cancer cells, miR-6126 release was significantly and profoundly increased and ITGB1 mRNA expression in exosome was decreased. These results suggested that ovarian cancer cells eliminated miR-6126 via exosome to prevent the inhibitory effect of miR-6126 on exosome production and ITGB1 expression. Finally, the authors showed that the injection of miR-6126-mimic encapsulated within 1,2-dioleoyl-sn-glycerol-3-phosphocholine (DOPC) nanoliposomes inhibited proliferation and angiogenesis of ovarian cancer xenograft models in nude mice.

The recent paper by Kanlikilicer *et al.* identified a new mechanism for ovarian cancer cell survival by the selective expulsion of the tumor suppressor miR-6126 via exosome (11). Since miRNA-mimics have already entered clinical trials, the findings from Kanlikilicer *et al.* have important therapeutic potentials for treating ovarian cancer patients.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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