Editorial Commentary

Clinical significance of extracellular vesicles in plasma from pancreatic cancer patients

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Despite intensive research over more than a decade, pancreatic ductal adenocarcinoma cancer (PDAC) remains an increasing source of cancer related death. The survival rates are still poor with no significant improvement in the last decades (1). Its high mortality rate is mainly due to complex pancreatic cancer biology and difficulty in early-stage diagnosis. Thus, tools for fast and accurate diagnosis of PDAC are necessary for improving outcomes.

Currently, the tumor-derived extracellular vehicles (EVs) seems to be an attractive approach to monitor cancers using plasma samples. Recent data support that EVs are more abundant than other circulating biomarkers, more stable regarding their structure, and contain protein, nucleic acids, mRNA profiles that significantly reflect those of parental cancer cells (2).

Yu *et al.* (2020) provides the first genome-wide analysis of EV long RNAs (exLRs) in plasma from PDAC patients. The authors suggested that is feasible to identify cancer biomarkers using the exLR profile. Furthermore, Yu *et al.* developed an exLR-based diagnostic signature that showed great precision for the PDAC diagnosis (3). More specifically the authors studied 501 participants, PDAC (n=284), chronic pancreatitis patients (n=100) and healthy controls (n=117), before surgery regarding the patients with resectable tumors and before chemotherapy regarding the patients with unresectable tumors. However, 5 patients had received neoadjuvant chemotherapy. Yu *et al.* established a diagnostic signature that comprised eight exLRs (FGA, KRT19, HIST1H2BK, ITIH2, MARCH2, CLDN1, MAL2 and TIMP1) for PDAC detection (3). Even though long RNAs have an effect on various cancers, their biological function and molecular mechanisms in carcinogenesis remain largely unknown. Long RNAs are well-known as epigenetic regulators that have a role in various cellular processes such as cell proliferation, development, differentiation, apoptosis and therefore oncogenesis (4). As they are highly specific and easily detectable in tissue, serum, plasma, and urine, interest in studying long RNAs in cancers continues to increase (5). Currently several studies have found higher levels of H19, HOTAIR, HOTTIP and MALAT-1 in pancreatic cancer cases. Additionally, PVT1, HULC, AF339813, LOC389641 and AFAP1-AS1 also has been reported to be upregulated in PDAC, however the exact mechanism of action of these long RNAs in PDAC remains to be clarified (6). Even though long RNAs have been shown to be implicated in PDAC pathogenesis, and seems to be promising biomarker for diagnosis and prognosis, their usefulness as clinical biomarkers has not been evaluated yet. Interestingly, none of those previously mentioned long RNAs have been found in EVs tested by Yu *et al.* (3).

To develop a new, noninvasive diagnostic approaches, recent research has focused on EVs. It is well known that tumors-derived EVs have a dual role in that they have antitumor activity and also promote tumor growth. Specific long RNAs contained in tumor-derived EVs can be the quantifiable, and noninvasive biomarkers (7). EV-associated RNAs, such as microRNAs (miRNAs), mRNAs, long RNAs, and other small RNAs, can be transferred between cells

and endorse their roles in recipient cells (8). Regardless the various studies of exosomal long coding RNAs functioning as cancer diagnostic/prognostic biomarkers, a number of these studies did not define the sensitivity and specificity of the long RNAs when applied to patients, or sensitivity and specificity to a specific tumor. It will be interesting if Yu *et al.* (3) investigate if the proposed diagnostic exLRs signature is specific to PDAC, since the long RNAs reported are implicated also in other cancer types i.e., breast cancer, colorectal cancer, etc. (9,10). Additionally, the majority of the existing studies cannot indicate the direct relationships of the tested exosomal long RNAs and cancers (11). Another issue is the methodological differences in EV isolation make this approach inadequate in achieving reproducibility between the different studies.

Recent studies have also shown that exosomes released by gemcitabine-treated cancer-related fibroblasts increased the proliferation and survival of pancreatic cancer cell lines (12). Thus it would be interesting if Yu *et al.* (3) reported if the five patients received gemcitabine based neoadjuvant chemotherapy exhibit different exLRs diagnostic signature.

Undoubtedly, the research on EVs as cancer diagnostic/prognostic biomarkers is increasing even if there are many issues to be solved. Studies such as this of Yu *et al.* (3) are very important since they confer to better understanding of the nature and function of exosomes, and give insights for the improvement of diagnostic and therapeutic techniques. Future studies will likely put more efforts into *in vivo* models and clinical application in order to help clarify the function and importance of exosomes, and it's contain on carcinogenesis.

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