Review Article

The extracellular RNA and drug resistance in cancer: a narrative review

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Background and Objective: Extracellular RNA (exRNA) is an evolving concept. In one hand, more endogenous RNA types are detected in various biofluids or found in local extracellular space. These endogenous exRNAs include microRNAs (miRNAs), long non-coding RNAs (lncRNAs), circular RNAs (circRNAs), piwi-interacting RNAs (piRNAs), transfer RNAs (tRNAs) and protein-coding messenger RNAs (mRNAs). ExRNA profilings are associated with many physiopathological conditions, including drug resistance in cancer. Endogenous exRNAs are also significantly involved in the molecular mechanisms of cancer drug resistance. In the other hand, exRNA types are expanded to include exogenous RNA therapeutics which started to headline in recent years with the approval of several RNA-based drugs. This review discusses current knowledge of exRNAs function in cancer drug resistance, including their value as biomarkers, the significant roles of modulating cancer drug resistance and the usage of exogenous RNA-based therapeutics to relieve cancer drug resistance.

Methods: The relevant publications, which are covering the exRNAs' involvement in cancer drug resistance, were searched in the PubMed database and published up to Aug 28, 2022.

Key Content and Findings: Specific RNA profiles in biofluid can work as biomarkers to help test cancer early and reflect clinical status of tumor, which are intrinsic determinants of drug responses in cancer patients. Endogenous exRNAs play roles in multiply aspects regarding drug resistance in cancer. These roles include modulating chemotherapeutic drug transport or efflux, promoting different adaptive responses, maintaining cancer stem cells (CSCs) status and constructing resistance-related tumor microenvironment (TME) as cancers experiencing chemotherapy, or activating immunosuppressive cell lines, inducing immunosuppressive cytokines and interfering with cytotoxic effector immune cells as cancers experiencing immunotherapy. RNA interference (RNAi), antisense oligonucleotides (ASOs) and mRNA based RNA therapeutics have been widely applied to combat drug resistance in cancer treatment, which will be included as one part inside the evolving scope of exRNAs.

Conclusions: ExRNAs profiles are suitable biomarkers to predict drug responses of cancer. Specific exRNA could explain the rise of drug resistance and serve as the target to cure cancer drug resistance. As the special form of exRNA, RNA-based therapeutics can be used to address cancer drug resistance.

Keywords: Extracellular RNA (exRNA); biomarkers; cancer drug resistance; RNA therapeutics

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Introduction

Extracellular RNA (exRNA) firstly emerged as the activators of Toll-like receptors (TLRs) when released from 'foreign' pathogens or disrupted host cells, which stimulated the innate immune responses (1,2). The application of nucleotide modifications and appropriate delivery systems to diminish the immunogenicity of therapeutic RNA, laid the foundation of the victorying

Table 1 Summary of the search strategy

Items	Specification
Date of search	August 28, 2022
Databases and other sources of searched	PubMed
Search items	Extracellular RNA, extracellular vesicles, exosome, miRNA, lncRNA, circRNA, biomarker, RNA therapeutics, cancer drug resistance
Time framed	Papers published before August 28, 2022
Inclusion and exclusion criteria	Focus was placed on original articles in English about exRNAs in cancer drug resistance or cancer immunotherapy resistance. The articles regarding RNA therapeutics, which were described as treating cancer drug resistance, were included as well. Literature in language other than English was excluded
Selection process	Selection process was carried out by the author

usage of exRNA in combating SARS-Cov-2 (mRNA-1273 vaccine) (3), hereditary transthyretin amyloidosis (hATTR) (patisiran, siRNA) (4) and cytomegalovirus (CMV) retinitis [fomivirsen, antisense oligonucleotides (ASOs)] (5). Along with these exogenous therapeutic RNAs, the scope of exRNA research was widely expanded when different types of endogenous RNAs, such as microRNAs (miRNAs), long non-coding RNAs (lncRNAs), circular RNAs (circRNAs), piwi-interacting RNAs (piRNAs), transfer RNAs (tRNAs) and protein-coding messenger RNAs (mRNAs), were detected and profiled in various biofluids (6). ExRNAs were protected from being easily degraded by encapsulated inside lipid nanoparticle (3), extracellular vesicle (EV), exosomes or by binding to lipoprotein complex (6). These exRNAs play different pathophysiological roles in facilitating cell-cell communications and the presence of exRNAs in biofluids might reflect the pathophysiology status of host. So the current researches focus on elucidating the function of individual exRNA or profiling groups of exRNAs as biomarkers in various disease conditions, such as cancer (7,8), neurodegenerative disorders (9), diabetes (10,11). As we start hitting the long journey for curing cancer, cancer relapse, which is mainly caused by drug resistance, is emerging as the biggest challenge. Thus, elucidating the footprints of exRNAs in cancer drug resistance is providing novel perspectives of how cancers could be eradicated.

Increasingly-expanded treatment options for different cancers diversified the roles of exRNA in predicting, underlying or combating cancer drug resistance, especially within the context of clinical applications. So in this narrative review, up-to-date studies will be discussed, mainly regarding the following four sections: (I) exRNAs working as biomarkers in cancer drug resistance; (II) exRNAs and mechanisms of cancer drug resistance against chemotherapy; (III) exRNAs and mechanisms of cancer drug resistance against immunotherapy; (IV) prospects of therapeutic exRNAs in combating cancer drug resistance. I present the following article in accordance with the Narrative Review reporting checklist (available at https://exrna.amegroups.com/article/view/10.21037/exrna-22-19/rc).

Methods

A literature review was conducted with PubMed to go through published articles up to Aug 28, 2022. The search terms included "extracellular RNA", "extracellular vesicles", "exosome", "miRNA", "lncRNA", "circRNA", "biomarker", "RNA therapeutics", "cancer drug resistance". The articles were chosen as these were original articles in English to cover the current knowledge of exRNA's function in cancer drug resistance. We use a table (*Table 1*) to present detailed search strategy.

ExRNAs working as biomarkers in cancer drug resistance

ExRNAs are secreted by host cells and cancer cells, so may reflect the clinical stages of tumor, tumor-host interactions and the responses of tumor/host to clinical practices, which make exRNAs excellent biomarkers as considering drug resistance in cancer, not mentioning the enormous benefits ensured by implementing non-invasive methods to check presence of exRNAs in various biofluids [e.g., plasma, serum, cerebrospinal fluid (CSF) and urine]. The profiling of exRNAs could be carried out by applying sequencing based methods, such as small RNA-Seq to detect miRNAs (12), next-generation sequencing (NGS) to detect lncRNAs and

circRNAs (6,13). The progress in methodology of RNA-seq, such as SILVER-seq (Small Input Liquid Volume Extracellular RNA Sequencing), even made it possible to classify cancer and noncancer samples by profiling exRNAs in only a single droplet of human serum (14). So exRNA profiling studies are extensively covering several aspects regarding cancer drug resistance.

The most universal determinant as predicting efficacy of cancer therapies within different cancer types would be tumor burden or size of the tumor as in solid tumor types (15), along with the clinical stages of cancer, which are widely used to instruct the drug usage in cancer patients and even predict the relapse after clinical practices (16). So exRNA profiling studies deserved to be reviewed as specific single exRNA or combination could reflect the tumor stages or even fulfill early prediction of cancer beyond the limit of practical clinical diagnoses (17). In one of the earliest studies covering miRNA profile in cancer serum, miR-25 and miR-223 were validated to show significantly higher level in lung cancer serum than in normal serum (7). The advantage of using biofluid samples to detect cancer was further strengthened when publication talked about using salivary exRNA biomarkers to detect gastric cancer (18) as this type of specimen is absolutely noninvasive and easy-to-go for repetitive sampling. In a recent study including 378 breast cancer patients, plasma cell-free has_circ_0008673 was found higher in larger tumor size, and was associated with later tumor stage (indicated by positive distant metastasis) (19). Moreover, this study showed that higher level of specific exRNA was associated with significantly worse overall survival or disease-specific survival, which might be partially underlined by drug resistance acquired after treatments. Serum RNA biomarkers were also reported for early detection of lung cancer within prediagnostic samples by applying optimized machine learning algorithm for modeling. Briefly, sampling time range, within 10 years before the diagnosis of lung cancer, were divided into seven time intervals, and serum RNAs were profiled and the show-up of specific RNA biomarkers are depending on the timing prior to diagnosis, tumor stages or histological status (20,21). These studies shed the light on how exRNA biomarkers could be used for non-invasively diagnosing, early detection or validating clinical stages of cancer, which could help instructing drug usage in clinical practices to minimize cancer drug resistance.

The rise of cancer drug resistance is also buried within intrinsic characters of tumor, as shown by tumor heterogeneity within the same tumor type or heterogeneity of cancer cells within one specific tumor (15,22,23). More and more studies have demonstrated that exRNA biomarkers can be used to differentiate tumor subtypes, such as in breast cancer (14,19), glioblastoma (24), and lung cancer (25). In brief, these studies obtained the specific exRNAs profiles which could validate and classify the histological subtypes within the same cancer type. The other layer of tumor heterogeneity is the existence of different cancer cells within the same single tumor, which gave rise to 'untouched' cancer cells after either single or even combined drugs treatment, leading to relapse if these cells harbor the advantage to proliferate and be resistant to cell death. Single-cell sequencing technology makes it possible to reveal different cell populations in one tumor, but might be restrained by hard-to-resect tumors (26,27). With the development of single EV or exosomes analysis platform (28,29), capturing and analyzing single tumor-cell-secreted-EV from biofluid samples offer an easier way to understand the tumor heterogeneity, which would provide more insights when considering drug resistance in cancer.

Therapeutic drug monitoring is definitely needed during cancer treatment to ensure the exposure of suitable drug at appropriate dose and timing, and to monitor efficacy when drug is administered, so monitoring cancer drug response would provide the information of how cancer drug resistance evolves (30). Omics, like metabolomics (31), genomic profiling (32) and transcriptomics (33), have been widely used to monitor cancer drug response as different omics could offer enormous information reflecting responses of host and cancer cells to therapeutics, and hold the potential of establishing easy-accessible biomarkers, which are also sitting within the strengths of exRNAs profiling. Stevic *et al.* reported 4 significantly changed miRNAs (miR-27a, miR-155, miR-376a and miR376c) before and after neoadjuvant therapy by profiling miRNAs from exosomes in the plasma, which need further confirmation as only 9 breast cancer plasma samples were included as directly after the therapy before surgery. Further analysis found exosomal miR-155 and miR-301 level could predict the pathological complete response (pCR) to carboplatin-based therapy within 435 breast cancer patients (34). Another study covered the miRNAs profiles in EV, which were isolated from plasma samples of 28 patients before and during the application of mitogen activated-protein kinase pathway inhibitors (MAPKis) to treat metabolic IV *BRAFV600* mutated cutaneous malignant melanoma (CMM), and found (I) higher EV let-7g-5p during MAPKi treatment compared to before treatment predicts higher

overall response; (II) elevated plasma EV miR-497-5p level during treatment were indicating prolonged progression free survival (PFS) (35). ExRNAs is also studied to monitor the response to immunotherapies, as dynamic levels of plasma exosomal programmed death-ligand 1 (PD-L1) mRNA could reflect the response of melanoma and NSCLC patients to anti-PD-L1 antibodies (36).

Overall, exRNAs, as profiled and used as biomarkers, have been widely reported of: (I) indicating tumor burden or clinical stages; (II) reflecting tumor heterogeneity; (III) monitoring and predicting drug responses; all of which helped to instruct drug usage, to predict drug resistance with various treatment options. Then, the next sections will summarize the specific exRNA's role in the rise of cancer drug resistance to chemotherapy and immunotherapy.

ExRNAs and mechanisms of cancer drug resistance against chemotherapy

Chemotherapy is widely used as the first-line drug in cancer treatments, but the efficacy of chemotherapies could be hindered by the appearance of drug resistance sooner or later (37). The mechanisms of how drug resistance is induced after chemotherapy treatment, could be general as in cytotoxic drugs, or drug-specific as in molecularly targeted therapies, and exRNAs were reported to be extensively involved in these mechanisms which will be discussed in the following sections.

As the primary carrier of exRNA in biofluid, EVs were reported to directly reduce the presence of chemotherapeutic drug in cancer cells by sequestering the drug inside vesicles and/or promoting the efflux of drugs along with EVs secretion, which were covered in details within previous reviews (38-40). At the same time, there were several reports to demonstrate the different functions of exRNA in regulating cancer drug resistance.

Interfering with drug transport and efflux

As the name indicating, the multidrug resistance protein 1 gene (*MDR1* or *ABCB1*) was deeply participating in the processes of drug resistance, which were fulfilled by encoding the major drug transporter P-gp and promoting drug efflux (41). In addition to the report of demonstrating that protein P-gp is transferred as the cargo in exosomes from drug resistant cancer cells to drug-sensitive cells (42), exosomes secreted from multidrug resistant human osteosarcoma also contain higher level of MDR1 mRNA which mediate the transfer of drug resistance to drug sensitive cells (43). Other cargos in the exosome, like exosomal miR-107 was demonstrated to sensitize the resistant gastric cancer cells to chemotherapy drugs by inhibiting HMGA2/mTOR/P-gp (44). So exRNAs in exosomes or EVs can regulate the level of MDR/P-gp to influence transportation of chemotherapy drugs in recipient cells, leading to drug resistant or sensitive cancer cells.

Promoting adaptive responses

Many chemotherapeutic drugs work in the way by inducing DNA-damage or inhibiting DNA replication, resulting in cell-cycle arrest and finally leading to cell death through mechanisms like apoptosis (37). Through or after the treatment, drug resistant cancer cells would be showing up when some cancer cells are responding 'well' with the mentioned stresses by acquiring adaptive responses. These responses could include the induction of DNA-damage repair or disruption of apoptosis (37), which can be fulfilled by exRNAs. In one report, higher level of miR-21 in exosomes, which were secreted from cisplatin-resistant oral squamous cell carcinoma, was proved to downregulate the expression of PTEN and PDCD4 in recipient cells, which decrease the DNA damage responses to cisplatin (45). In addition to the miRNAs that are derived from drug resistant cancer cells, which can transfer the characteristics of drug resistance from cancer cells to cancer cells, different cells residing in the same tumor microenvironment (TME) can also deliver RNAs to cancer cells through EVs and induce the rise of drug-resistant cancer cells. In one report, cancer-associated fibroblast (CAF) cells secret exosomes containing higher level of miR-196a, and when these exosomes were up-taken by cancer cells, higher miR-196a caused the downregulation of CDKN1B and ING5, which resulted in the relieve of cell-cycle arrest or suppressed apoptosis, respectively. All these lead to cisplatin resistance in head and neck cancer (46).

Molecularly targeted cancer drugs represent a critical step when we move forward with precision medicine. Mutations that can gift cancer cells with proliferation advantages, are widely targeted in the cancer treatment. But along the treatment using targeted therapies, cancer cells are prone to become resistant to these drugs, either by gaining new mutations within the target or activating alternative pathways (37), part of which can be accomplished by transferring exRNAs between cells. Sunitinib is an oral receptor tyrosine kinase (RTK) inhibitor, working on multiply targets including vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor

receptor (PDGFR) and stem cell growth factor receptor, which showed anti-angiogenic effects and anti-tumor activities. But drug resistance happened in renal cell carcinoma (RCC) patients after 6–15 months with Sunitinib administration. Non-coding RNA lncARSR was reported to express more in Sunitinib-resistant RCC cancer cells, and was also transferred in exosomes which were secreted from Sunitinib-resistant cancer cells, to recipient cells. The exosomal lncARSR could work as the competing endogenous RNA (ceRNA) and liberate mRNAs that were previously inhibited by miRNAs, which facilitate the expression of AXL and c-MET. The rise of these alternative oncogenic pathways would result in more Sunitinib-resistant cancer cells (47).

In addition to the chemical drugs that have been widely used to target related molecules in cancer treatment, monoclonal antibody (mAb) is increasingly becoming relevant as mAb can be easily designed to target molecule in various kinds of cancer types (48). Herceptin (Trastuzumab) is a mAb targeting human epidermal growth factor receptor 2 (HER2), which can inhibit cancer cells growth and proliferation, and is applied to treat HER2 positive breast cancer or metastatic stomach cancer (49). Resistance against Herceptin can be raised up through mechanisms like: activation of EGFR, HER-3, and HER-4 pathways and following signals; reduction of p27kip1 protein that can counteract Herceptin responses; or increased IGF-IR signaling (49). ExRNAs was reported to act through these mechanisms in contributing to trastuzumab resistance. In one study, exosomal circHIPK3 was demonstrated to promote trastuzumab resistance in recipient breast cancer cells by regulating apoptosis through circHIPK3/mir-582-3p/RNF11 axis as RNF11 can enhance transforming growth factor-beta (TGF-β) pathway and EGFR pathway (50,51).

As a brand-new form of therapy, antibody-drug conjugate (ADC) combined the selectivity conferred by mAb, and the cell-killing activity exerted by small molecule cytotoxic drugs, which were welded together by a linker. Currently, already nine ADCs were approved by the US Food and Drug Administration (FDA) with several based on the widely used trastuzumab to target HER2 positive breast cancer cells, such as trastuzumab emtansine (T-DM1) and trastuzumab deruxtecan (T-DXd) (52). Until now, few reports were published to mention the involvement of exRNAs in drug resistance with ADCs. As ADCs' functions rely on both antibody part and cytotoxic chemical part, so the mechanisms of drug resistance that were mentioned above (37), could be applied to ADC drugs as well. There will be researches showing up to study the association between exRNAs and drug resistance against ADCs.

Cancer stem cell (CSC) maintenance

The presence of CSCs or the revert of more-differentiated tumor cells into being stem-cell like, is highly associated with resistance to various chemotherapies, as these drugs usually target rapidly dividing cells and while CSC or stem-cell like cells are relatively quiescent, also showing different characteristics to facilitate drug resistance, like higher level of ATP-binding cassette transporter proteins; appearance of anti-apoptotic proteins such as BCL-2 and BCL-X_L; and enhanced DNA damage repair activities (37). The maintenance of stem-cell like properties requires the suitable microenvironment niche, which absolutely need frequent cell-cell communication, and that could be accomplished through EV and its carries, exRNAs (53). Three miRNAs: miR-9-5p, miR-195-5p and miR-203a-3p were encapsulated and secreted within exosomes from breast cancer cells which were treated with sub-lethal dose of chemotherapeutic agent docetaxel or doxorubicin, and these miRNAs could down-regulate ONECUT2 level in exosome-recipient cells, which promote the CSC characteristics in breast cancer cells and induce the expression of stemness-associated genes such as *NOTCH1*, *SOX9*, *NANOG*, *OCT4* and *SOX2* (54). There are some similar reports as breast cancer exosomal miR-378a-3p and miR-378d promoting breast cancer stemness and chemotherapy resistance by activating EZH2/STAT3 pathway (55) and exosomal miR-92a-3p from CAF cells activating the Wnt/β-catenin pathway in colorectal cancer (CRC) cells which lead to the cell stemness and 5-fluorouracil (5-FU) and oxaliplatin resistance (56).

TME

TME is consist of multiply cell types, extracellular matrix (ECM), blood and lymph vessels within one specific solid tumor, or multiply circulating cells in the blood and bone marrow cells within haematological malignancies (37). As talked earlier, the cell-cell communication, exerted by miRNAs in exosomes or EVs that were secreted from CAFs, play roles in regulating many aspects of drug response within the cancer and contribute to drug resistance (46,57). Among the multiplex cellular interactions inside TME, cytokines and growth factors secreted by immune cells or stromal cells work in the autocrine, paracrine or endocrine way to regulate the drug responses in tumor. ExRNAs can work in

a similar way by regulating the secretion of these cytokines or growth factors, or modulating the downstream signaling pathway of these factors, which finally explain the drug resistance caused by TME (38,39,58). Several studies have revealed the exosomal miRNAs from various cancer cells can promote the M2 polarization of macrophages (59-61), As M2 macrophages secret interleukin (IL)-4, colony stimulating factor-1 (CSF-1) and IL-10 cytokines which could influence the drug resistance of cancer cells in a paracrine way (62,63). There were several reviews covering the association of TME with drug resistance in cancer treatment which would provide more details regarding how exRNAs residing in TME could influence the various cell types to promote the drug-resistant traits (64,65). Immune cells like macrophages, T cells and neutrophils are key cell types in TME, and extensive details will be presented in the following section when mechanisms of cancer drug resistance against up-to date immunotherapies were reviewed.

To summarize here, exRNAs were reported to be deeply involved in various aspects of how drug resistance was raised up with chemotherapy in cancer treatment. These exRNAs provide extra insights about the complexity of cancer drug resistance, but could also promote new strategies for combating cancer drug resistance with chemotherapies.

exRNAs and mechanisms of cancer drug resistance against immunotherapy

As the knowledges about the interaction between cancer cells and immune system expanded, discovery of cancer immune checkpoints paved the way for strategically utilizing immune checkpoint inhibitors, either mAb or small molecule, to treat various cancer types when tumor cells were confirmed to express CTLA-4 or PD-L1 checkpoints (66). Genetically modified immune cells represent the other type of up-to-date immunotherapy, such as several approved CAR-T cell therapies, in which autologous T cells were engineered to express chimeric antigen receptors (CARs) on their surface to recognize cancer specific antigens (67). Although cancer immunotherapies indicated unprecedented clinical response rate (100%) in specific cancer subtype (68), the majority of patients have no intensive response to immunotherapies, or some patients obtained relapsed cancer later after the primary response, all of which implied the primary and acquired resistance against cancer immunotherapies (69,70). Considering EV and RNA cargos deeply participating in the intensive communication between immune system and tumor cells, it was in line with speculation that exRNAs were increasingly reported to be involved in the mechanisms to explain resistance within cancer immunotherapies.

The existence of several types of immunosuppressive cells in TME, namely regulatory T cells (Tregs), myeloid derived suppressor cells (MDSCs) and M2 macrophages, is the primary or acquired traits that decide how cancer patients respond to immunotherapies (69). ExRNAs were demonstrated to transfer from cancer cells to these immunosuppressive cells to constitute the immunosuppressive microenvironment. In one study, Yin *et al.* presented higher level of miR-214 in microvesicles from various human cancer types, which could be delivered to T cells and downregulated the expression of phosphatase and tension homolog (PTEN). This would lead to the expansion of Tregs and higher IL-10 secretion in these Tregs, finally resulting in enhanced immune suppression which would lead to bigger tumor weight (71). Exosomal circGSE1 (72) and mir-208b (73) were also reported to induce the expansion of Tregs and led to immune escape of hepatocellular carcinoma (HCC) cells or oxaliplatin-treated CRC cells, respectively.

MDSCs were firstly described when being found expanding in pathological condition like cancer (74). MDSCs possess the suppressive activity and negatively regulate the immune response during cancer (75). In one study, a set of tumor-derived miRNAs (including miR-146a, miR-155, miR-125b, miR-100, let-7e, miR-125a, miR-146b and miR-99b) were responsible for the switch of monocytes to MDSCs when these miRNAs were transferred to circulating monocytes through EVs secreted by melanoma tumor cells. In melanoma patients, higher level of these miRNAs in plasma samples indicated a poor immunotherapy outcome (76). Another study about Lewis lung carcinoma (LLC) revealed that miR-21 was enriched in LLC exosomes, and this miRNA could induce the expansion of MDSCs in $CD14^+$ monocytes through downregulating programmed cell death protein 4 (PDCD4) (77). Up-to-date review (78) could be checked for more details regarding exRNAs' functions of regulating MDSCs in TME.

Tumor associate macrophages (TAMs) represent the most abundant normal cells in the TME. The polarized M2 type macrophages are showing pro-tumoral phenotypes, including suppressing T-cell responses to set up the immunosuppressive microenvironment, which contribute to the tumor initiation, progression and resistance during immunotherapies (79). As reported in HCC, macrophages were transformed into M2 type macrophages when came

across with miR-23a-3p containing exosomes, which were secreted from HCC cells with induced endoplasmic reticulum (ER) stress. Higher miR-23a-3p in macrophages inhibited the PTEN level, subsequently promoted the phosphorylation of AKT, and finally elevated the PD-L1 level in M2 macrophages which would reduce the ratio of cytotoxic T cells, decrease IL-2 production and induce T-cell apoptosis when co-cultured with T cells (80). Exosomal miR-146a-5p was also reported to secret from HCC cells and was responsible for the remodeling of macrophages into M2-polarized TAMs. T cells expressed higher level of inhibitor receptors such as programmed cell death protein 1 (PD-1) and CTLA-4 when co-cultured with HCC exosome educated macrophages. In HCC mouse model, inhibiting miR-146a-5p expression in HCC cells would reduce the level of PD-1 and CTLA-4 on T cells, also reverse T cell exhaustion and delay the tumor progression (81).

The local suppression of anti-tumor immune responses in TME is exerted not only by the suppressive immune cells mentioned above, but also by immune suppressive cytokines secreted by various cell types in TME. Specifically, there could be TGF-β in stimulating Tregs (82) or CCL5, CCL7 and CXCL8 in attracting MDSCs in TME (83), among others. Although tumor-derived exosomes have been reported to directly carry bioactive cytokines and contribute to the immunosuppressive environment in TME (84,85), there were some reports studying the functions of exRNAs in modulating the presence of cytokines in TME. Shang *et al.* reported that exosomal circPACRGL from CRC cells could work as the sponge of miR-142-3p/miR-506-3p, consequently relieving the expression of TGF-β1 who was the target of these two miRNAs. Higher level of TGF-β1 in neutrophils could promote the differentiation into N2 neutrophils which can suppress immunity and imply protumorigenic functions (86,87). CAF cells in the TME are the major regulator of TGF-β signaling pathway (88). One study validated that HCC derived exosomal miR-21 promote the conversion of hepatocyte stellate cells (HSCs) to CAFs by targeting PTEN to activate PDK1/AKT signaling in HSCs. And the activated CAFs secreted multiply cytokines: VEGF, basic fibroblast growth factor (bFGF) and TGF-β to facilitate tumor progression (89).

Anti-tumor efficacy with cancer immunotherapy is closely relying on efficiently presenting tumor-specific antigens by dendritic cells (DCs) and potent cytotoxic activities by $CD8^+$ T cells or natural killer (NK) cells (90,91). So exRNAs that circulate inside TME were reported to influence the outcome of cancer immunotherapies by regulating DCs or effector T cells. Although comprehensive studies were covering the roles of tumor-derived exosomes in regulating differentiation, maturation and function of DCs (92), few articles discussed tumor exosomal RNA cargos' effect on DCs, only when more VEGF was induced and secreted, either from CAFs in the context of HCC (89) or from cigarette smoke extract-transformed human bronchial epithelial cells (93), when exosomal miR-21 was up-taken. And higher VEGF would dysfunction the ability of DCs in stimulating antigen-specific T cell responses (94). Regarding cytotoxic T cells, there was one report to describe B16F0 melanoma secreted exosomal mRNA contents was associated with transcriptomic changes in cytotoxic T cells with exosome treatment, which showed the patterns related with increased mitochondrial respiration and more interferon-gamma (IFN-γ) secretion. So this is one good example to indicate tumor derived exosomal RNAs regulating effector T cells in the TME to influence anti-tumor immune responses (95). NK cells work as another major effector immune cells to implement anti-tumor responses. There was one report to state that CRC cells secret exosomal lncRNA SNHG10 which can suppress NK cells' viability and cytotoxicity by upregulating inhibin subunit beta C (INHBC) who is a regulator of TGF-β signaling pathway. At the same time, CRC exosomes treated NK cells were showing less IFN-γ production, less perforin-1 and granzyme B secretion, indicating compromised cytotoxic ability of NK cells (96).

To summarize this section, various exRNAs were reviewed and demonstrated to be playing intensive roles in regulating the host's immune responses to tumors, specifically modulating immunosuppressive cells lines' function, regulating cytokines secretion in TME and modifying each knotting cell line with the anti-tumor immune response, like DCs as antigen representing cells, cytotoxic T cells and NK cells as effectors. Considering these functions exerted by exRNAs, it is expected to see more studies covering exRNAs when drug resistance with cancer immunotherapy is to be explained and to be conquered.

Prospect of exRNA therapeutics in combating cancer drug resistance

When we talked about how exRNA is setting foot on drug resistance in cancer treatment within the above sections, endogenous exRNA was primarily touched and reviewed. As RNA therapeutics were gradually spreading out to various

indications, from mRNA vaccines for COVID-19 (3) to siRNA therapeutic targeting transthyretin mRNAs for the treatment of hATTR (4), it is rational to expand the scope of exRNAs as including exogenous RNA therapeutics. So the application of RNAs as therapeutics to combat cancer drug resistance will be discussed in the following section.

RNA interference (RNAi) based therapy was considered to harbor huge advantages as RNAi could potently down-regulate the expression of almost any gene, which provide an implementable strategy to clear 'undruggable targets' in cancer treatment. There were already several reports to utilize RNAi to target 'undruggable targets' such as *c-myc* (97,98), Stat3 (99) and MDM2 (100), among others. Utilizing RNAi to inhibit these targets for resolving chemotherapy drug resistance in cancer is well endorsed by mechanisms of how resistance is raised up within chemotherapies because these 'undruggable targets' represent some scenarios of intrinsic heterogeneity within tumor or activation of alternative signaling pathways (37). So *c-myc* siRNA was applied to treat cisplatin-resistant ovarian cancer as c-MYC protein levels were higher in ovarian cancer cells that were showing resistance to cisplatin (98). When lung cancer cells are experiencing chemotherapy, like paclitaxel, higher Stat3 or constitutively activated Stat3 signaling pathway represents the specific survival signal which results in the drug resistance. So Su *et al.* reported one novel nanoparticles system to deliver paclitaxel and Stat3 siRNA simultaneously, which induced more death in lung cancer cells, indicating a new strategy of overcoming cellular resistance to paclitaxel (99).

Inducing synthetic lethality represents one novel strategy to counteract single drug resistance and to kill cancer cells, as more cancer drug targets were screened out through CRISPR-based or RNAi-based screening methods (101), while inhibiting dual targets with RNAi therapies is considered feasible. In one study, authors used poly(DL-lactide-co-glycolide acid) (PLGA) nanoparticles to deliver MDR1 siRNA and BCL2 siRNA simultaneously to suppress both drug efflux and anti-apoptosis activities. So the dual RNAi system induced higher cytotoxic activity of paclitaxel and cisplatin on the drug resistant-ovarian cancer cells (102). Utilizing siRNAs to down-regulate dual targets also features the same dosage form, which is probably facilitating genomic-based precision therapy as readily switching drug contents in one dosage form.

RNAi therapy was also applied to conquer drug resistance with immunotherapy. Nanoparticles, targeting M2-like TAMs, were developed and loaded with siRNA against CSF-1 receptor which could lead to dramatic elimination of M2-like TAMs (52% *vs.* control), accompanied by more $CD8^+$ T cell infiltration in the TME of melanoma tumors. This strategy was validated in B16 melanoma with *in vivo* mouse model as showing smaller tumor size and prolonged survival (103). Wnt/β-catenin signaling pathway inhibits the secretion of cytokines, so can mediate the resistance to checkpoint inhibitor therapy as interfering with the recruitment of effector immune cells. So Ganesh *et al.* reported that down-regulating β-catenin by using RNAi-based method could promote the T cell infiltration in tumors and increase the immune responses of tumors to checkpoint inhibitor therapies (104).

ASO represents another type of RNA therapeutics that has been widely used in clinical contexts and FDA approvals were received with some therapies of this kind (105). It is completely unexpected to see tons of reports to cover the usage of ASO in cancer treatment (106), as well as in combating drug cancer resistance. Kang *et al.* reported the usage of ASO to inhibit MDR1 which would increase the intracellular accumulation of chemotherapeutic drug (107). In one report, ASO targeting STAT6 was delivered to M2 type TAMs as loaded with the engineered exosomes. Less STAT6 in M2 macrophages promoted the remodeling of macrophage subtypes, as typical M1 macrophages phenotypes showed up more which constructed the TME with more anti-tumor potencies (108).

mRNA based therapy works by expressing the protein product which is contrary to RNAi or ASO based therapy. Until now, mRNA drugs were mostly applied in cancer immunotherapy, from working as cancer vaccines to expressing immune stimulatory cytokines (109). mRNA based vaccination could be accomplished by loading mRNAs with autologous DCs followed by adoptive transfer or by directly injecting mRNAs into patients. The modified APCs could induce new or enhanced immune responses against tumor cells harboring the specific antigens, usually after the primary tumor were surgery removed or after patients went through the regular chemotherapy, intending to prevent recurrence of tumors and overcome the resistance to treatments (110). At the same time, several reports demonstrated that transfecting stimulatory cytokine mRNAs, such as IL-12, IL-15 and GM-CSF, into tumor mRNA loaded DCs can significantly intensify the anti-tumor efficacy (111,112). mRNA therapies have also been conducted to refine T cell-based treatment. Transfecting T cells with specific mRNAs to express T cell receptors (TCRs) or CARs endowed the cytotoxic T cells

of recognizing tumor cells containing specific antigens, and finally lyse the tumor cells. Reported mRNAs could express receptors for CD19 (113), CD33 (114) and kinase Met (115), among others.

To sum up, exogenous RNA therapeutics expanded the scope of exRNAs and gradually implied in multiply disease indications, including widely applied to combat cancer drug resistance. RNAi, ASO and mRNA based therapies are the main forms (116), which are currently in the pre-clinical or clinical phase. As the precise mechanisms accumulated more regarding cancer drug resistance, exRNA therapeutics would more applied for inhibiting cancer drug resistance with brand new targets and delivery strategies.

Summary

Cancer recurrence or relapse after primary treatment is critical to influence the overall survival rate of cancer patients, so needed to be addressed with intensive efforts. The understanding of cancer drug resistance partly provides insights of how cancer cells are coming back sooner or later after treatments, and exRNA is more and more involved in many aspects of cancer drug resistance. ExRNAs that are circulating in various biofluids, can be seen as informative, so specific exRNAs were profiled and found associated with clinical status of cancers, patient responses to specific treatment and prognosis after treatments, which promoted the application of exRNAs as biomarkers to predict or reflect drug resistance in cancer treatments, and even predict drug resistances. Additionally, exRNAs represent an important regulator in the cell-cell communication, which are playing big roles in explaining cancer drug resistance, not only with classic chemotherapies but also with up-to-date immunotherapies. These mechanisms provide us different angles to understand drug resistance in cancer treatment, and also underline the brand-new targets we could try working on to eliminate cancer drug resistance. Although most of these exRNAs are showing as non-coding RNAs, like microRNAs, circRNAs or lncRNAs, which were seen as hard to target with small molecules, RNA-based therapeutics, such as RNAi and ASO based drugs, could be a way worthy of more efforts to target these endogenous exRNAs in fixing cancer drug resistance. As a whole process, RNA therapeutics was accelerated by new modifications in RNAs and expanded arsenal to targeted delivery of RNAs, which vice versa depends on our increasingly deep understanding of endogenous exRNAs, as the knowledge of endogenous exRNAs teaching us how to minimize immunogenicity of exRNAs, how to protect exRNAs from being degraded and how to apply suitable delivery system to target specific cell types and tissues. Totally, participation of exRNAs in different directions of cancer drug resistance were increasingly elucidated and these knowledges would also promote the utilization of exogenous RNAs in treating cancer drug resistance.

This narrative review not only discusses the roles of endogenous exRNAs in the context of cancer drug resistance, but also expands the scopes of exRNAs by including various RNA molecules from potential RNA therapeutics against drug resistance in cancer. As multiple exRNAs existing and protected in the "natural" nanoparticles (exosomes, EVs), the integrated discussion of endogenous exRNAs and RNA therapeutics would raise mutual research interests.

As name shown, the review regarding drug resistance in cancer treatment readily focused more on clinical fields. The coverage of ongoing practices from clinical trials would be a significant complement to the topic of exRNAs and cancer drug resistance.

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