The role of extracellular vesicles in the transfer of drug resistance competences to cancer cells

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Keywords: Cancer drug resistance; Extracellular Vesicles; Tumor microenvironment; Intercellular transfer of drug resistance competences.

Abstract

Drug resistance remains a major hurdle to successful cancer treatment, being accountable for approximately 90% of cancer-related deaths. In the past years, increasing attention has been given to the role of extracellular vesicles (EVs) in the horizontal transfer of drug resistance in cancer. Indeed, many studies have described the dissemination of therapy resistance traits mediated by EVs, which may be transferred from drug resistant tumor cells to their drug sensitive counterparts. Importantly, different key players of drug resistance have been identified in the cargo of those EVs, such as drug efflux pumps, oncoproteins, antiapoptotic proteins, or microRNAs, among others. Interestingly, the EVs-mediated crosstalk between cells from the tumor microenvironment (TME) and tumor cells has emerged as another important mechanism that leads to cancer cells drug resistance. Recently, the cargo of the TME-derived EVs responsible for the transfer of drug resistance traits has also become a focus of attention. In addition, the possible mechanisms involved in drug sequestration by EVs, likely to contribute to cancer drug resistance, are also described and discussed herein.

Despite the latest scientific advances in the field of EVs, this is still a challenging area of research, particularly in the clinical setting. Therefore, further investigation is needed to assess the relevance of EVs to the failure of cancer patients to drug treatment, to identify biomarkers of drug resistance in the EV's cargo, and to develop effective therapeutic strategies to surmount drug resistance.

This up-to-date review summarizes relevant literature on the role of EVs in the transfer of drug resistance competences to cancer cells, and the relevance of tumor cells and of TME cells in this process. Finally, this knowledge is integrated with a discussion of possible future clinical applications of EVs as biomarkers of drug resistance.

List of abbreviations: ABC, ATP-binding cassette; Akt, v-Akt Murine Thymoma Viral Oncogene; ALK, anaplastic lymphoma kinase; ALOX15, arachidonate lipoxygenase 15; AML, acute myeloid leukemia; APAF1, apoptotic protease activating factor 1; ARSR, Activated in Renal Cell Carcinoma with sunitinib resistance; BCRP, breast cancer resistance protein; CAFs, cancer-associated fibroblasts; CAT, catalase; Cav1, caveolin; CCAL, colorectal cancer-associated; CDX2, caudal-related homeobox 2; CM, conditioned media; EMT, epithelial-mesenchymal transition; EphA2, Ephrin type A receptor 2; ERK, extracellular-signal-regulated kinase; ERM, Ezrin-Radixin-Moesin; EVs, extracellular vesicles; FAK, focal adhesion kinase; FDA, Food and Drug Administration; HBEC, human bronchial epithelial cell; HEPH, hephaestin; HOTAIR, HOX antisense intergenic RNA; HOTTIP, HOXA transcript at the distal tip; ISEV, International Society of Extracellular Vesicles; lncRNAs, long-noncoding RNAs; LRRC1, leucine-rich repeat-containing protein 1; MDR, multidrug resistance; miRs/miRNAs, microRNAs; MPs, microparticles; MRP1, multidrug resistance-associated protein 1; MSCs, mesenchymal stem cells; mtDNA, mitochondrial DNA; MVBs, multivesicular bodies; ncRNAs, non-coding RNAs; NFATc3, nuclear translocation of activated T-cell isoform c3; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; P-gp, P-glycoprotein; PPI, proton pump inhibitor; PUM2, pumilio homolog 2; ROS, reactive oxygen species; rTNF-α, recombinant TNF-α; SNHG14, small nucleolar RNA host gene 14; SOD, superoxide dismutase 2; TAMs, tumor-associated macrophages; TME, tumor microenvironment; TRAIL, TNF-related apoptosis-inducing ligand; TRPC5, transient receptor potential channel 5.

1. Drug resistance in cancer: an overview of mechanisms

The availability of drugs for cancer treatment has seen a tremendous increase in the past couple of decades, but drug resistance has been invariably documented, including some cases of multidrug resistance (MDR), severely hindering the efficacy of cancer treatment (Assaraf et al., 2019; Icard et al., 2018; Nussinov et al., 2021; Wijdeven et al., 2016). The mechanisms underlying drug resistance are multifactorial and may involve tumor factors, host factors (Alfarouk et al., 2015), or factors associated with tumor-host interactions (Alaoui-Jamali et al., 2004). It is well established that the chemotherapeutic drug treatment itself imposes a selective pressure on surviving tumor cells from a highly heterogeneous tumor, which may contribute to the selection of drug resistant cells ultimately leading to acquired drug resistance (Bram et al., 2009; Kaufman et al., 2006; Levin et al., 2021; Turajlic et al., 2019). The presence of stem-like cells in the heterogeneous tumor possibly contributes to the selection of such resistant clones (Freitas et al., 2014; Koren and Fuchs, 2016; Najafi et al., 2019; Sharifzad et al., 2019).

Some anticancer drugs may induce drug resistance by increasing the expression of genes encoding for proteins directly which are involved in drug resistance mechanisms, such as the genes from the ATP-binding cassette (ABC) transporters family (Li et al., 2016; Theile and Wizgall, 2021; Wang et al., 2021), allowing adaptation of cancer cells to the cytotoxic drug treatment. Indeed, multidrug efflux pumps belong to this family of drug efflux pumps and their overexpression is one of the main causes for chemotherapy failure, given their ability to actively extrude drugs from cancer cells, thus decreasing intracellular drug concentration and diminishing their cytotoxic effects (Domenichini et al., 2019; Li et al., 2016; Wang et al., 2021). Other mechanisms of drug resistance include escape from cell death mechanisms (Gao et al., 2021; Lima et al., 2004; Mollaei et al., 2021; Qiao and Wong, 2009; Shahar and Larisch, 2020), enhanced DNA damage response and repair mechanisms (Li et al., 2021b), mutations in drug targets (Bailey et al., 2021; Dagogo-Jack and Shaw, 2018), epigenetic and microRNA (miRNA) alterations (Garnier-Suillerot et al., 2001; Lima et al., 2011; Ozyerli-Goknar and Bagci-Onder, 2021; Seca et al., 2013; Seca et al., 2014), or metabolic alterations (Goncalves et al., 2021). Moreover, some drugs may induce drug tolerance, by inducing an epithelial-mesenchymal transition (EMT) phenotype or cellular plasticity (Qin et al., 2020).

The communication between cells present in the tumor microenvironment (TME) and cancer cells may also contribute to the selection and expansion of drug resistant clones (Correia and Bissell, 2012; Erin et al., 2020; Rapisarda and Melillo, 2009). Indeed,

drug resistance in tumor cells may be mediated by intercellular communications with stromal cells present in the TME, such as cancer associated fibroblasts (CAFs) (Bu et al., 2020; Kadel et al., 2019) or immune cells such as tumor associated macrophages (TAMs) (Xavier et al., 2021). In recent years, the intercellular communication between tumor cells or between tumor cells and cells from the TME has been documented to contribute to the acquisition of drug resistance, occurring through direct contact between cells or by paracrine signal exchanges of cytokines and growth factors.

Recently, it has become clear that secreted extracellular vesicles (EVs) are important intercellular communication mediators, participating in a highly and complex network that influences the malignant potential of cancer cells. Therefore, the current paper reviews evidence for the intercellular transfer of drug resistance competences mediated by EVs.

2. Introduction to EVs and their relevance to the intercellular transfer of drug resistance competences

EVs is a collective term for cell-derived particles (30 to 5,000 nm) enclosed by a lipid bilayer and that do not replicate; EVs comprise exosomes, microvesicles, microparticles (MPs), ectosomes, oncosomes and apoptotic bodies (Thery et al., 2018). They are key mediators of intercellular communication and can be found in several biological fluids, including blood, urine, saliva, breast milk, semen, amniotic and cerebrospinal fluids (Colombo et al., 2014; Yanez-Mo et al., 2015). Although highly heterogenous, EVs can be divided into three major subclasses, according to their size and/or biogenesis: i) exosomes (30-150 nm), which result from the endocytic pathway by inward budding of endosomal membranes and are secreted upon fusion of multivesicular bodies (MVBs) with the plasma membrane; ii) microvesicles (100 to 1,000 nm), which are formed by direct outward budding from the plasma membrane; iii) apoptotic bodies (100 to 5,000 nm), which are released by cells undergoing apoptosis by blebbing of the cell membrane **(Figure 1)** (Kanada et al., 2016; van Niel et al., 2018; Yanez-Mo et al., 2015).

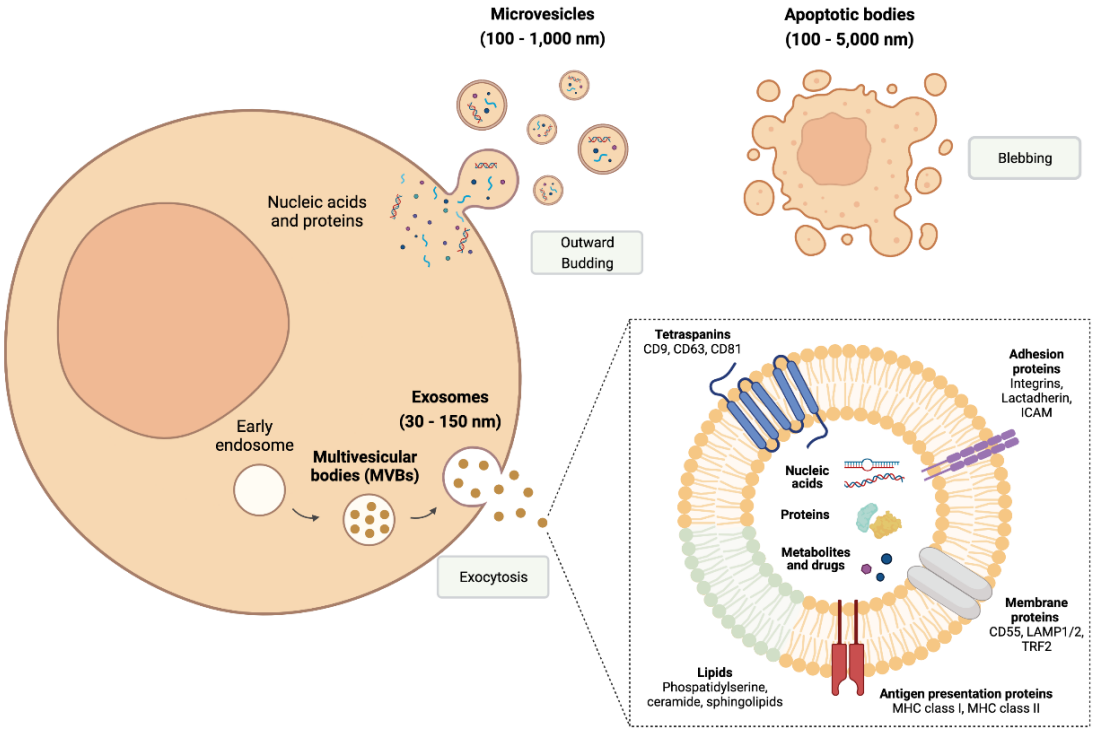

Figure 1. Main sub-populations of Extracellular vesicles (EVs): exosomes, microvesicles and apoptotic bodies. Exosomes (30 to 150 nm) originate from the endocytic pathway, concentrated in multivesicular bodies (MVBs) and released to the extracellular environment by exocytosis. Microvesicles (100 to 1,000 nm) derive from the outward shedding of the plasma membrane to the extracellular space. Apoptotic bodies (100 to 5,000 nm) are secreted by apoptotic cells, being characterized by an enrichment of phosphatidylserine on their surface. Figure was created with BioRender.com.

EVs are involved in several biological processes, such as immune response modulation, antigen presentation, coagulation, pregnancy, reproductive biology, and tissue repair (Yanez-Mo et al., 2015). The EVs generating (donor) cells perform selective packaging of nucleic acids, proteins and other molecules into the EVs cargo, which are protected from degradation by their lipid bilayer, and can be responsible for the transfer of physiological or pathological information from donor cells to recipient (either neighboring or distant) cells (Yanez-Mo et al., 2015).

In cancer, EVs have been associated with different stages of the oncogenic process, from tumor initiation to tumor progression, metastasis and chemotherapeutic failure, across different types of tumors (Bandari et al., 2020; Xavier et al., 2020). Numerous studies have disclosed the role of EVs in the cancer hallmarks, namely in cellular proliferation and resistance to cell death, angiogenesis, invasion and metastasis,

deregulation of cellular energetics and evasion from immune response (Xavier et al., 2020; Xu et al., 2018). Besides mediating a horizontal communication between cancer cells, EVs also mediate intercellular communication between cancer cells and non-malignant cells from the TME, promoting an immunosuppressive, pro-angiogenic and pro-metastatic landscape in which some stromal cells may be conditioned/re-educated to favor tumorigenesis, invasion and drug resistance (Becker et al., 2016; Haderk et al., 2017; Han et al., 2019; Hu et al., 2020; Shinohara et al., 2017). Furthermore, EVs also play a role in the priming of the pre-metastatic niche by transporting key modulators secreted by primary tumors to distant organs, promoting the "education" of bone marrow-derived cells, remodeling the extracellular matrix (ECM), and increasing vascular permeability, among other mechanisms (Dong et al., 2021; Hernandez-Barranco et al., 2021; Peinado et al., 2012).

Different players have been implicated in the transfer of drug resistance traits mediated by EVs, such as drug efflux pumps, antiapoptotic proteins, oncoproteins, miRNAs, long-noncoding RNAs (lncRNAs) and lipids. Indeed, several studies demonstrated that drug efflux pumps, like P-glycoprotein (P-gp) or multidrug resistance-associated protein 1 (MRP1/ABCC1), can be transferred from drug resistant to drug-sensitive cancer cells by EVs (Levchenko et al., 2005; Lu et al., 2013; Lv et al., 2014; Zhang et al., 2014). Regarding the miRNAs selectively packed into EVs released by drug-resistant cells, once internalized by recipient cells, they can modulate the expression of cellular transcripts, altering their chemosensitivity (Chen et al., 2014; Jaiswal et al., 2012). Other modulators of drug resistance traits, such as Annexin A3, transient receptor potential channel 5 (TRPC5) and inhibitors of apoptosis proteins, may also be transferred from drug resistant to drug sensitive cells by EVs (Ma et al., 2014; Yin et al., 2012). Interestingly, lipids present in EVs can also play a role in cancer drug resistance. For instance, EVs with a high content of sphingomyelinase were shown to contribute to the transfer of a drug resistance phenotype to chemosensitive multiple myeloma cells (Faict et al., 2019). Additionally, distinct phospholipid signatures were found in EVs derived from a gefitinib-resistant lung cancer cell line and its sensitive parental cell line (Jung et al., 2015), suggesting a link between lipid composition of EVs and drug sensitivity.

Other factors, such as the pH of the extracellular environment (Federici et al., 2014; Logozzi et al., 2018; Parolini et al., 2009) and hypoxia (Dong et al., 2019; Dorayappan et al., 2018; Endzelins et al., 2018; King et al., 2012; Wang et al., 2014; Yue et al., 2019), can also affect EVs' release and therapeutic response, highlighting the

importance of the TME in cancer dynamics and drug resistance. In fact, tumor acidity stimulates EVs' secretion by cancer cells of different histotypes (e.g. colon, breast and prostate cancers, melanoma or osteosarcoma), a process that can be inhibited by alkalinization/buffering of the TME (Boussadia et al., 2018; Logozzi et al., 2018; Parolini et al., 2009). Similarly, hypoxia is also known to trigger EVs' release by human cancer cells (Logozzi et al., 2019). For example, under hypoxic conditions, non-small cell lung cancer (NSCLC) and glioblastoma cells secreted more EVs than their normoxic parental cells and transported higher levels of miR-21 and miR-301a, respectively, which were associated with higher chemoresistance (Dong et al., 2019; Yue et al., 2019). Likewise, in an ovarian cancer model, hypoxic cells released more EVs than normoxic cells, and, interestingly, were also found to extrude more cisplatin via EVs than their normoxic counterparts, presenting a 5-fold increase in drug content (Dorayappan et al., 2018). Furthermore, when co-treated with sensitive ovarian cancer cells, hypoxic cell-derived EVs improved their resistance to cisplatin treatment (Dorayappan et al., 2018).

In the past years, increasing attention has been given to EVs due to their potential as biomarkers of diagnosis, prognosis and therapeutic response. Indeed, since they carry the donor cell's content (such as RNA transcripts, DNA fragments or lncRNAs, that are protected from degradation by a lipid bilayer) and are present in multiple biological fluids that may be easily collected, EVs have an enormous potential as a source of cancer biomarkers (Vasconcelos et al., 2019; Xu et al., 2018). Another major attractiveness of EVs is their potential use as drug carrier systems for targeted delivery, since they have an increased ability to infiltrate cells and evade immune surveillance when compared to conventional synthetic carriers (Herrmann et al., 2021). Nevertheless, the lack of gold-standard protocols for EV isolation, with rapid clinical translation, and the need of more sensitive tools for biomarker detection, are some of the major technical challenges that still need to be overcome.

There are several methods that can be used for EVs isolation/enrichment e.g. differential centrifugation, density gradient centrifugation, size-exclusion or affinity chromatography, filtration, etc. However, it is noteworthy that the content of EVs subfractions will depend on the source of the sample, as well as, on the isolation/enrichment technique (Thery et al., 2018; Yanez-Mo et al., 2015). Contaminants, such as lipoproteins, chylomicrons, protein aggregates and cell debris, are commonly co-isolated with EVs and are usually undistinguishable (Mathieu et al., 2019;

Thery et al., 2018). Therefore, a combination of EVs isolation/enrichment techniques is recommended, to improve purity and yield (Gandham et al., 2020).

3. Evidence for the transfer of drug resistance competences mediated by EVs released by drug resistant cancer cells

As mentioned above, the production and release of EVs has been described to be relevant for the intercellular transfer of a drug resistance phenotype (Fontana et al., 2021; Lobb et al., 2017; Torreggiani et al., 2016). Indeed, drug sensitive cancer cells can become more drug resistant after incorporation of EVs that had been released by drug resistant cancer cells. This has been shown for drug resistance to targeted therapies, to immunotherapy and to conventional chemotherapy (Vasconcelos et al., 2019).

It has been suggested that MDR tumor cells possibly produce more microvesicles and less exosomes than their drug sensitive counterparts (Lopes-Rodrigues et al., 2016). Furthermore, MDR tumor cells release more EVs than their drug-sensitive counterparts. On the other hand, drug sensitive cells capture more EVs than their MDR counterparts. The differences between the release and capture of EVs have been associated with alterations in the endocytic pathway between drug sensitive and MDR cells (Sousa et al., 2021). Scientific evidence for an EVs-mediated transfer of drug resistant traits to cancer cells has been described in many types of cancer **(Figure 2**).

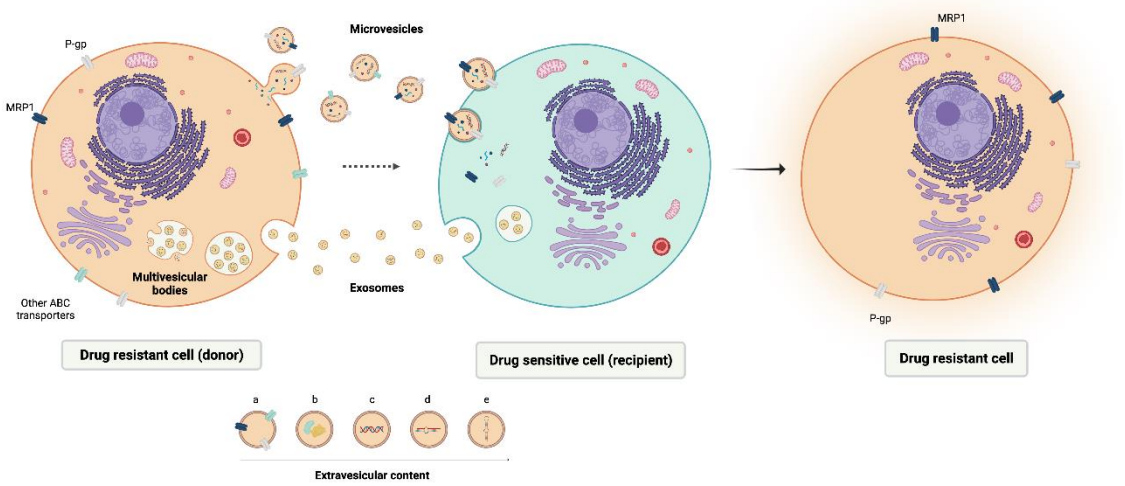

Figure 2. **Representation of intercellular transfer of drug resistance mediated by extracellular vesicles (EVs).** Drug-resistant (donor) cells may release different types of EVs (exosomes or/and microvesicles) into the intercellular space. These EVs reach the drug sensitive (recipient) cells, where they are incorporated by plasma membrane fusion or endocytic pathway, altering the phenotype of recipient

cells (from drug sensitive to drug resistant). EVs may contain: (a) drug-efflux pumps such as P-glycoprotein (P-gp), multidrug resistance-associated protein 1 (MRP1), other ATP-binding cassette (ABC) transporters, (b) other proteins, (c) mitochondrial DNA, (d) microRNAs (miRNAs), and (e) long noncoding RNAs (lncRNAs). Figure was created with BioRender.com.

3.1. Breast cancer

It has been shown that EVs released by drug resistant cancer cells, transfer integral plasma membrane proteins, such as P-gp to recipient drug sensitive cells, effectively conferring functional MDR to the recipient cells within a short time (Bebawy et al., 2009; Lu et al., 2013). Using proteomic profiling and comparative analysis of EVs derived from resistant breast cancer cells, Pokhalrel *et al.,* showed the selective packaging of Ezrin-Radixin-Moesin (ERM) and CD44, among other proteins, in EVs shed from drug resistant breast cancer cells (Pokharel et al., 2014) and demonstrated that this protein complex plays a role in the cell-to-cell transfer of P-gp via EVs and in conferring MDR to recipient cells (Pokharel et al., 2016).

In addition to the transfer of the ERM-CD44 complex, the importance of TrpC5 has been shown in adriamycin-resistant human breast cancer cells (MCF-7/ADM). TrpC5 protein regulates the MDR transporter P-gp; furthermore, high levels of TrpC5 cause EVs formation and the trapping of adriamycin in those EVs. EV-mediated intercellular transfer of TrpC5 allowed the recipient cells to gain TrpC5, therefore stimulating P-gp production through a Ca^{2+} influx and a nuclear translocation of activated T-cell isoform c3 (NFATc3)-mediated mechanism, conferring chemoresistance upon drug sensitive cells. Interestingly, in human breast cancer patients, the expression of TrpC5 protein was high in the tumors and the levels of TrpC5 positive EVs were high in the circulation, suggesting that TrpC5-containing EVs in circulation could potentially be used to predict the clinical outcome of chemotherapy (Ma et al., 2014). TRPC5 is a Ca^{2+}-permeable cation channel predominantly.

Moreover, EVs isolated from doxorubicin- and docetaxel-resistant breast cancer cells showed the ability to increase resistance of a non-tumorigenic breast cell line (MCF10A) to those drugs, by increasing the expression of genes associated with cell proliferation and apoptosis pathways, such as PI3K/Akt (Ozawa et al., 2018). In addition, activation of Akt2, FAK and ERK1/2 in MCF10A cells, caused by EVs released from MDA-MB-231 breast cancer cells, increased invasiveness and migration abilities of this non-tumorigenic breast cell line (Leal-Orta et al., 2019).

Interestingly, Sansone *et al.*, have reported a remarkable evidence for horizontal transfer of mitochondrial DNA (mtDNA) in human breast cancer, which was mediated via EVs (Sansone et al., 2017). Specifically, they identified the complete mitochondrial genome packaged in CAF-derived EVs and in EVs from patients with hormonal therapy-resistant metastatic disease. These authors suggested that these EVs can in turn transfer their mtDNA to hormone therapy sensitive cells or HT-treated metabolically dormant cell populations with impaired metabolism, leading to the restoration of the metabolic activity. Moreover, this horizontal transfer of mtDNA through EVs can lead to endocrine therapy resistance in oxidative phosphorylation-dependent breast cancer (Sansone et al., 2017).

The potential role of lncRNAs contained within EVs for the development of chemoresistance in human breast cancer was investigated by Dong and collaborators. These authors verified that lncRNA small nucleolar RNA host gene 14 (SNHG14) was upregulated in trastuzumab-resistant cells, when compared to parental breast cancer cells. Furthermore, extracellular lncRNA-SNHG14 was able to be incorporated into EVs and transmitted from SKBR-3/Tr (trastuzumab-resistant breast cancer cell line) to SKBR-3/Pr (trastuzumab sensitive cell line), consequently disseminating trastuzumab resistance. Interestingly, lncRNA-SNHG14 was found to target the apoptosis regulator Bcl2/ apoptosis regulator BAX signaling pathway, thus promoting the effect of trastuzumab (Dong et al., 2018).

3.2. Lung Cancer

EVs secreted by a drug resistant mesenchymal $30KT^{p53/KRAS/LKB1}$ cell line promoted a chemoresistance phenotype in the recipient human bronchial epithelial cell (HBEC) line, 30KT, and increased the mRNA levels of the EMT transcription factor ZEB1 in the recipient cells. Thus, the recipient cell line became significantly more resistant to gemcitabine and to the combination therapy with cisplatin and gemcitabine. Interestingly, EVs released by mesenchymal but not by epithelial HBEC cells contained ZEB1 mRNA (Lobb et al., 2017).

The importance of lncRNAs to the transfer of a MDR phenotype was demonstrated in NSCLC. The lncRNA RP11-838N2.4 has been described to be up-regulated in erlotinib-resistant NSCLC cells while the knockdown of the lncRNA RP11-838N2.4 reversed resistance to erlotinib in erlotinib-resistant cells. Furthermore,

incubation of sensitive cells with exosomal lncRNA RP11-838N2.4 promoted erlotinib resistance (Zhang et al., 2018).

Anaplastic lymphoma kinase (ALK) translocation is an actionable mutation in lung adenocarcinoma. Interestingly, another study using next-generation sequencing (NGS) verified that EVs from an ALK-tyrosine kinase inhibitor resistant subclone can induce resistance to crizotinib or ceritinib in the originally sensitive subclone. EV-RNA profiling revealed that miR-21-5p levels were decreased but miR-486-3p and the lncRNAs MEG3 and XIST were increased in EVs secreted by the drug resistant subclones. These circulating EV-RNA levels were found to correlate with disease progression of EML4-ALK-translocated lung adenocarcinoma in patients treated with ALK-tyrosine kinase inhibitor (Kwok et al., 2019).

3.3. Leukemia

In vitro evidence shows the ability of acute myeloid leukemia (AML) cells to transfer daunorubicin resistance through EVs, mediated by direct transfer of MRP1 and their microRNA cargo, miR-19b and miR-20a. These microRNAs were four times more present in EVs from resistant cells than in EVs from their sensitive counterparts. A direct transfer of proteins, specifically MRP1 transported by EVs, occurred between resistant and sensitive cells with a rapid impact (in less than 20 h) on the chemoresistance of recipient cells. However, the simultaneous transfer of nucleic acids ensured the modification of the phenotype of the recipient cells (Bouvy et al., 2017).

The overexpression of the multidrug efflux transporters P-gp and MRP1 in leukemia cells and/or their intercellular transfer mediated by EVs are responsible for MDR in numerous cancers. Interestingly, the intercellular transfer of miR-326 mediated by EVs has been identified as a novel pathway that regulates the expression of these drug efflux pumps (Lu et al., 2017).

Interleukins have also been reported as key players in the intercellular transfer of the MDR phenotype in leukemia, mediated by EVs. Specifically, the role of TNF-α in a MDR TME has been studied. Recombinant TNF-α (rTNF-α) regulated endogenous TNF-α and P-gp expression levels in parental and resistant cell lines, supporting the EVs release by cancer cells and the intercellular transfer of P-gp to maintain a MDR phenotype. Evidence suggests that rTNF-α differentially regulated drug resistance in

sensitive and MDR cell lines, supporting EVs release, and contributing to aberrant cell proliferation of non-tumor recipient cells (Berguetti et al., 2019).

Moreover, in EVs secreted from AML resistant cells, subunits of spliceosome, SRSF1, SRSF9 and SF3B2 were found, which may regulate splicing of BCL-x and caspase 9 proteins, thus influencing apoptosis regulation (Cloutier et al., 2008; Moore et al., 2010).

3.4. Glioblastoma

Zeng *et al.*, identified 3 miRNAs, let-7i, miR-93, and miR-151a, which were down-regulated in temozolomide resistant glioblastoma cell lines, when compared to the paired sensitive cells, with miR-151a presenting the highest fold change of expression. The importance of miR-151a for the intercellular transfer of a drug resistance phenotype mediated by EVs was shown in glioblastoma. miR-151a levels in temozolomide -resistant EVs were significantly lower than in temozolomide-sensitive EVs. EVs derived from resistant glioblastoma cells could confer drug resistance to sensitive glioblastoma cells. Remarkably, loading exogenous miR-151a into EVs abrogated their ability to confer temozolomide resistance to recipient cells (Zeng et al., 2018).

Similarly, Yin *et al*., identified 77 differentially expressed miRNAs, when comparing the EVs content from glioma stem-like cells under normoxic and hypoxic conditions, 45 of which were upregulated in EVs released under hypoxic conditions. Moreover, EVs released under hypoxia had a significant increase in miR-30b-3p, when compared to EVs released under normoxia conditions. This study also revealed the binding of miR-30b-3p with hnRNPA2B1, resulting in its incorporation into EVs. Importantly, EVs released from hypoxic glioma stem-like cells induced the development of acquired resistance to temozolomide *in vivo* (Yin et al., 2021).

Recent evidence has pointed out the relevance of the spliceosome protein mechanism in glioblastoma cell communication, based on EV-mediated protein transfer. In an interesting study, Pavlyukov *et al.,* demonstrated that apoptotic glioblastoma cells stimulated proliferation and therapy resistance of surviving tumor cells, by secreting EVs enriched in various components of spliceosomes. In recipient cells, those EVs altered the RNA splicing, contributing to therapy resistance phenotype and aggressiveness. These authors reported RBM11 as a splicing factor upregulated in tumors after therapy and shed into EVs upon induction of apoptosis. The RBM11 will then change MDM4 and cyclinD1 to more oncogenic isoforms in recipient cells (Pavlyukov *et al.*, 2018).

3.5. Pancreatic Cancer

The production of reactive oxygen species (ROS) by some chemotherapeutic drugs is proposed to be one important mechanism for their cytotoxic activity. Tumor cells respond to treatment with such drugs, trying to counterbalance this deleterious effect by altering the expression of ROS-detoxifying enzymes. Interestingly, Patel *et al.*, demonstrated an EVs-mediated mechanism of development of chemoresistance in pancreatic cancer, by modified levels of ROS-detoxifying enzymes on EVs released by resistant cells. Indeed, these authors showed that the conditioned media (CM) of gemcitabine (Gem)-treated pancreatic cancer cells (Gem-CM), and more specifically their EVs (Gem-EVs), conferred chemoresistance to pancreatic cancer sensitive recipient cells. Moreover, gene expression analysis demonstrated an upregulation of the levels of superoxide dismutase 2 (*SOD2*) and catalase (*CAT*), two ROS-detoxifying genes, and downregulation of *DCK* (the gene catalyzing the rate-limiting step in the bioactivation of gemcitabine) in Gem- EVs-treated cells. The SOD/CAT upregulation was due to the transfer of their transcripts, while DCK downregulation occurred through EVs-delivered miR-155, which lead to chemoresistance (Patel et al., 2017).

In addition, Fan *et al.*, analyzed EVs secreted by pancreatic cancer cell lines with variable gemcitabine sensitivity and identified Ephrin type A receptor 2 (EphA2) among the proteins required for the transfer of gemcitabine resistance between pancreatic cancer cell lines, suggesting that EphA2 as a protein receptor tyrosine kinase represents a promising target for future cancer therapy of pancreatic cancer (Buckens et al., 2020; Fan et al., 2018).

3.6. Melanoma

ALK is a tyrosine kinase receptor that is normally involved in the development of the nervous system. A novel truncated form of ALK (ALK^{RES}) has been described in resistant melanoma cells. Overexpressed ALK^{RES} was secreted into EVs by melanoma resistant cells and then transferred to sensitive melanoma cells, transferring a MDR phenotype within 24 h. In recipient cells, ALK^{RES} was able to activate the MAPK signaling pathway. Thus, the combined inhibition of ALK and BRAF dramatically reduced tumor growth *in vivo*. These findings make ALK a promising clinical target in patients with melanoma (Cesi et al., 2018).

4. Evidence for the transfer of drug resistance competences by EVs released by TME cells

Apart from cancer cells, the TME includes the surrounding stromal cells (such as fibroblasts, inflammatory and immune cells), cellular stroma, microvessels and biomolecules. The communication between cancer cells and non-malignant cells within the TME may be mediated by EVs, as has been nicely demonstrated in several studies. This intercellular communication between the TME and cancer cells may contribute to the progression and dissemination of cancer, and also to the development of drug resistance. Most of these studies focused on the impact of EVs released by CAFs, TAMs and mesenchymal stem cells (MSCs) on cancer drug resistance (**Figure 3**).

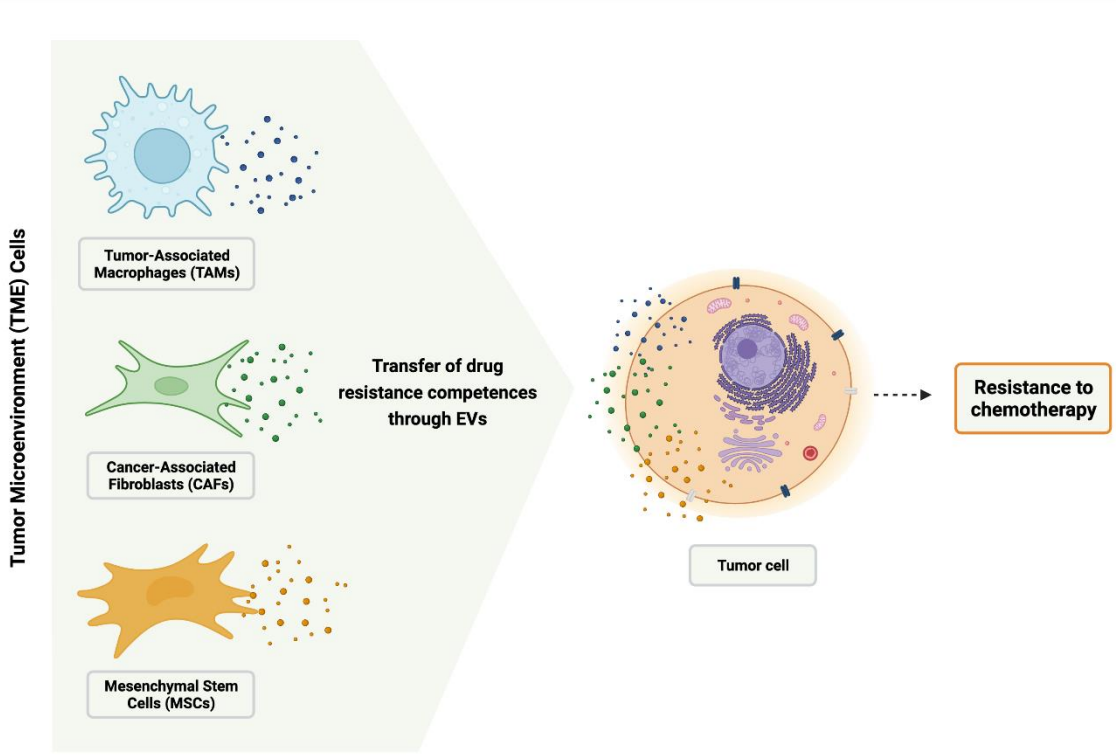

Figure 3. Extracellular vesicles (EVs) mediate the communication between cells from the tumor microenvironment (TME) and tumor cells. EVs released by tumor-associated macrophages (TAMs), cancer-associated fibroblasts (CAFs) and mesenchymal stem cells (MSCs) transfer drug resistance competences to tumor cells, contributing to resistance to different types of chemotherapy. Figure was created with BioRender.com.

In the TME, activated fibroblasts are named CAFs, and demonstrate an important tumor-promoting role. In fact, there are many studies reporting the impact of EVs released

by CAFs on chemoresistance of different types of cancers. For instance, in gastric cancer, EVs derived from CAFs transferred their cargo to cancer cells, enhancing drug resistance (Uchihara et al., 2020). In pancreatic cancer, EVs derived from CAFs promoted gemcitabine resistance (Fang et al., 2019; Richards et al., 2017). Other studies also revealed that EVs secreted by CAFs, in addition to promoting metastasis and inducing stemness, contributed to the resistance of colorectal cancer cells to treatment with oxaliplatin plus 5-fluorouracil (Hu et al., 2019a), or to treatment with each of these drugs individually (Deng et al., 2020; Hu et al., 2015; Ren et al., 2018). Additionally, EVs isolated from CAFs induced paclitaxel resistance in ovarian cancer cells (Au Yeung et al., 2016). Most recently, EVs released by CAFs induced resistance to the antifolate methotrexate in colon cancer (Zhang et al., 2021a). Similarly, EVs-derived from CAFs conferred cisplatin resistance upon NSCLC and head and neck cancer (Qin et al., 2019; Zhang et al., 2021b). Incubation of gastric cancer cells with EVs released by CAFs, resulted in cisplatin and paclitaxel resistance (Zhang et al., 2020). In addition, EVs shed by prostate fibroblasts induced chemoresistance in prostate cancer (Cao et al., 2019).

In the human body, once oncogenesis occurs, immune cells are crucial in the combat against cancer cells. Nevertheless, cancer cells have a capacity to evade immunosurveillance and suppress the immune response against cancer. Importantly, macrophages are the immune cells most abundant at the TME. While M1 macrophages are believed to be inhibitors of cancer, M2 macrophages or TAMs are cancer-promoting. Indeed, macrophage polarization from classically M1 macrophages (pro-inflammatory profile) to alternatively activated M2 macrophages (anti-inflammatory profile) plays a crucial role in tumor-promoting phenotype and in repressing anti-cancer immune response. Therefore, several studies have reported the impact of EVs released by M2 type macrophages on chemoresistance. For instance, a reduced sensitivity to gemcitabine was observed in pancreatic cancer cells exposed to EVs shed by M2 type macrophages (Binenbaum et al., 2018). In agreement with this, in gastric and epithelial ovarian cancers, EVs released by M2 polarized macrophages enhanced cisplatin resistance (Zheng et al., 2017; Zhu et al., 2019). EVs released by M2 type macrophages, but not M0 type macrophages, promoted resistance to paclitaxel in ovarian cancer cells (Kanlikilicer et al., 2018). Interestingly, a study reported that EVs released by M2 polarized macrophages induced carboplatin resistance in breast cancer cells via cycling quiescence, and that a switch to macrophages expressing the M1 phenotype reversed breast cancer dormancy, thus sensitizing cancer cells to drug treatment (Walker et al., 2019). Curiously, an

interesting study showed that EVs derived from monocytes, independently of their macrophage polarized profile, induced cisplatin resistance in neuroblastoma cells (Challagundla et al., 2015). Likewise, some of us have recently demonstrated that EVs released by human macrophages, either with pro-inflammatory or anti-inflammatory profiles, decreased pancreatic ductal adenocarcinoma cellular sensitivity to gemcitabine *in vitro* (Xavier et al., 2021).

It is worth noting that, although with fewer studies reported, MSCs in the TME also have the potential to contribute to tumor progression, and therefore their released EVs interfere with drug therapy response and resistance. For example, EVs from MSCs contributed to chemoresistance in multiple myeloma (Xu et al., 2019). EVs derived from MSCs also conferred 5-fluorouracil resistance in gastric cancer (Ji et al., 2015), and cisplatin resistance in NSCLC (Wu et al., 2020). Interestingly, one study reported that breast cancer cells induced MSCs to release EVs, which contained a subset of miRNAs that induced quiescence in a subset of breast cancer cells, thereby conferring drug resistance (Bliss et al., 2016).

Surprisingly and contrarily to most of the reported studies, EVs derived from TME cells may also reverse drug resistance. For instance, a study showed that EVs released by adipose tissue-derived MSCs, contained microRNA(miR)-122 that increased the sensitivity of hepatocellular carcinoma cells to sorafenib (Lou et al., 2015). Another study demonstrated that EVs shed by MSCs that overexpressed TRAIL (TNF-related apoptosis-inducing ligand) contained miR-7 which, in addition to increasing apoptosis and suppressing tumor growth in glioblastoma, also sensitized glioblastoma to therapies based on TRAIL-induced apoptosis (Zhang et al., 2017).

Taken together, all these studies reinforce the importance of disrupting the communication mediated by EVs, between different cells from the TME and cancer cells, which may be a promising therapeutic strategy to impair cancer drug resistance.

5. Cargo of tumor-derived EVs responsible for the transfer of drug resistance competences

It has been largely demonstrated that EVs may be loaded with macromolecules, such as proteins or RNAs that are able to transfer drug resistance competences to drug sensitive cells, converting them into drug resistant cells and reducing anticancer drug response. The cargo of tumor-derived EVs that transfers drug resistance competences may be divided into different categories, as discussed below.

5.1. Drug efflux pumps (ABCB1, ABCC1, ABCG2, and ABCA3)

Some ABC transporters were shown to be carried by EVs, transferring their drug resistance ability from drug resistant to drug sensitive cells, including: ABCB1 (P-gp), ABCC1 (MRP1), ABCG2 (Breast cancer resistance protein; BCRP), and ABCA3. These drug transporters present in EVs may: i) protect their donor cancer cells from the cytotoxic effect of chemotherapeutic drugs; or/and ii) promote a horizontal transfer of these drug efflux pump proteins to recipient cells, contributing to the conversion of recipient drug sensitive cells into drug resistant ones (Fontana et al., 2021; Li et al., 2021a; Sousa et al., 2015), **Table 1**.

Table 1. Drug efflux pumps responsible for the transfer of drug resistance competences.

Drug efflux pump	Cancer type	Drug resistance	Reference
P-gp	Breast cancer	Docetaxel	(Lv et al., 2014)
	Breast cancer	Doxorubicin	(Ning et al., 2017)
	Ovarian cancer	Paclitaxel	(Zhang et al., 2014)
	Leukemia	Daunorubicin	(Bebawy et al., 2009)
	Prostate cancer	Docetaxel	(Kato et al., 2015)
	Ovarian cancer	Taxane	(Mir and Goettsch, 2020)
	Prostate cancer	Taxane	(Mir and Goettsch, 2020)
	Osteosarcoma	Doxorubicin	(Torreggiani et al., 2016)
MRP1	Acute myeloid leukemia	Idarubicin	(Barzegar et al., 2021)
	Acute myeloid leukemia	Daunorubicin	(Bouvy et al., 2017)
MRP2	Ovarian cancer	Cisplatin	(Safaei et al., 2005)
ABCA3	B-cell lymphoma	anti-CD20 antibody (Rituximab)	(Aung et al., 2011)
ABCG2	Laryngeal cancer	Cisplatin	(Zhao et al., 2021)
ABCG2	Breast cancer	Topotecan, Imidazoacridinones, Methotrexate	(Goler-Baron and Assaraf, 2011)

ABCB1 (P-gp) is the best studied member of the ABC transporter family and is responsible for resistance to multiple chemotherapeutic drugs (Domenichini et al., 2019). P-gp present in EVs was shown to transfer drug resistance competences to recipient breast cancer cells and protect them from docetaxel and doxorubicin cytotoxicity *in vitro* (Dong et al., 2014; Lv et al., 2014). Interestingly, the levels of P-gp found in recipient cells were directly correlated to the number of EVs taken up by these cells (Lv et al., 2014). Interestingly, ovarian and prostate cancer EVs carrying P-gp were responsible for recipient cancer cells protection against taxanes. The transfer of P-gp mediated by EVs from drug resistant to drug sensitive cells, was also shown for docetaxel-resistant prostate cancer (Corcoran et al., 2012). Of note, it has also been shown that P-gp protection against chemotherapeutic drugs can be obtained in recipient cells following EVs-mediated transfer of mRNA encoding for P-gp, as demonstrated in an osteosarcoma model treated with doxorubicin (Torreggiani et al., 2016). Importantly, the horizontal transfer of P-gp mediated by EVs and the resulting acquisition of drug resistance by recipient cells was also documented *in vivo*, in a model of doxorubicin-refractory breast cancer xenografts and colchicine-unresponsive neuroblastoma bearing mice (Jaiswal et al., 2013; Levchenko et al., 2005).

A horizontal transfer of other drug efflux pumps mediated by EVs was also shown for MRP1, BCRP and ABCA3, contributing to drug resistance in leukemia, laryngeal cancer or B-cell lymphoma cells, respectively (Barzegar et al., 2021; Bouvy et al., 2017; Zhao et al., 2021). Interestingly, MRP1 present in EVs shed by leukemia cells was transferred to both malignant and non-malignant cells (Barzegar et al., 2021).

Strikingly, the duration of the intercellular transfer of drug resistance is longer than the half-life of these drug efflux pumps. Therefore, even though the intercellular transfer of ABC transporters by EVs can partly explain the acquisition of a resistance phenotype by sensitive cells, additional mechanisms of EVs-mediated intercellular transfer of drug resistance must exist, possibly involving regulation of these pumps at the protein level in recipient cells (Fontana et al., 2021).

5.2. Antiapoptotic proteins

Drug resistance traits can be also transferred from drug resistant to drug sensitive cells by the intercellular transfer mediated by EVs of antiapoptotic proteins, such as survivin. Survivin is a member of the inhibitor of apoptosis protein family that inhibits caspases and blocks cell death, and it is highly expressed in most cancers and is associated

with a poor clinical outcome (Garg et al., 2016). Survivin was found in EVs isolated from prostate and cervical cancers, and also from EVs isolated from breast cancer cells (Khan et al., 2009; Khan et al., 2011; Khan et al., 2012; Kreger et al., 2016). Moreover, survivin derived from EVs strongly enhanced the survival of pancreatic ductal adenocarcinoma upon treatment with paclitaxel, or with a novel therapy that combines an ERK inhibitor with chloroquine (Chang et al., 2021).

5.3. Oncoproteins

EVs may also transfer oncoproteins from drug resistant to drug sensitive cells. This has been demonstrated in melanoma where a truncated isoform of ALK was delivered, promoting MAPK signaling pathway activation and drug resistance (Cesi et al., 2018). Similarly, in nasopharyngeal carcinoma it was found that EGFR-rich EVs caused EGFR overexpression and EGFR-mediated downregulation of intracellular ROS levels through the PI3K/AKT pathway, promoting the metastatic potential of poorly metastatic nasopharyngeal carcinoma cells (Li et al., 2020). In addition, the K562 chronic myeloid leukemia cell line produced EVs containing the BCR-ABL oncoprotein, able to promote the canonical survival of BaF3 cells under IL-3-deprivation, protecting them from cell cycle arrest and apoptosis (Layoun et al., 2011).

5.4. MicroRNAs (miRNAs)

miRNAs are very often deregulated in cancer of which may be responsible for drug resistance (Giovannetti et al., 2012; Iorio and Croce, 2012). Notably, miRNAs can be incorporated into EVs, which protects them from RNase activity, thus preventing their degradation (Cheng et al., 2014; Mir and Goettsch, 2020). EVs mediated transfer of miRNAs from drug resistant to drug sensitive cancer cells, may then modulate transcripts in recipient cells, and increase their drug resistance competences. For instance, miR-221 and miR-222 were transferred on the EVs cargo from tamoxifen resistant breast cancer cells to drug sensitive cancer cells, converting them into tamoxifen resistant cancer cells (Wei et al., 2014). Likewise, miR-22-3p, miR-185-5p, miR503-5p, miR-652-3p and miR-1280 carried by EVs isolated from resistant breast adenocarcinoma cell line were transferred to drug sensitive counterparts causing the acquisition of a drug resistance phenotype (Gong et al., 2014).

Interestingly, transfer of miRNAs may explain a long-lasting effect of EVs-mediated induction of resistance phenotype in sensitive cells; for example, both miR-451

and miR-27a contained in drug resistant cell-derived EVs were able to induce P-gp expression in sensitive cells (An et al., 2017; Sousa et al., 2015). Moreover, the miRNA content of EVs isolated from resistant or unresponsive tumors versus sensitive ones was different. For example, EVs isolated from docetaxel-resistant prostate cancer cell lines were rich in miR-598, miR-34-a, miR148a, miR146a and miR-34. miR-34 regulates BCL-2, thus may regulate apoptosis in response to drug treatment (Corcoran et al., 2014). miR-21-5p, miR-1246, miR-1229-5p and miR-96-5p were found more abundant in drug-resistant colorectal cancer cells than in their parental cells; in agreement with this, the same miRNAs were found significantly more abundant in the EVs of chemoresistant patients than in chemosensitive ones (Jin et al., 2019). Other miRNAs found in the cargo of EVs and which have been associated with a resistance phenotype, are shown in **Table 2**.

Table 2. miRNAs responsible for the transfer of drug resistance competences.

miRNA	Cancer type	Drug resistance	Reference
miR-27a	Prostate cancer	Cisplatin, Docetaxel, Doxorubicin	(Cao et al., 2019)
miR-21-3p **miR-21-5p** **miR-891-5p**	Ovarian Cancer	Carboplatin	(Alharbi et al., 2020)
miR-1246	Ovarian Cancer	Paclitaxel	(Kanlikilicer et al., 2018)
miR-21-5p **miR-96-5p** **miR-1246** **miR-1229-5p**	Colorectal Cancer	Oxaliplatin, 5-Fluorouracil	(Jin et al., 2019)
miR-145 **miR-34a**	Colorectal Cancer	5-Fluorouracil	(Akao et al., 2014)
miR-31-5p	Renal Cell Carcinoma	Sorafenib	(He et al., 2020)
miR-222-3p	Non-small cell lung cancer	Gemcitabine	(Wei et al., 2017)
miR-425-3p	Non-small cell lung cancer	Cisplatin	(Ma et al., 2019)
miR-221 **miR-222**	Breast cancer	Tamoxifen	(Wei et al., 2014)
miR-222	Breast cancer	Doxorubicin	(Yu et al., 2016)

miR-222	Breast cancer	Docetaxel	(Chen et al., 2014)
miR-19b **miR-20a**	Leukemia	Daunorubicin	(Bouvy et al., 2017)
miR-365	Chronic myeloid leukemia cells	Imatinib	(Min et al., 2018)
miR-1238	Glioblastoma	Temozolomide	(Yin et al., 2019)
miR-21	Squamous cell carcinoma	Cisplatin	(Liu et al., 2017)

5.5. Long non-coding RNAs (lncRNAs)

LncRNAs are non-coding RNA molecules containing over 200 nucleotides, known to be involved in regulation of various cellular processes, including cancer development, progression and drug resistance (Chen et al., 2016). It has been described that EVs might deliver lncRNAs to recipient cells, modulating their drug response. Indeed, in hepatocellular carcinoma, lncRNA-VLDR and lncRNA-ROR were found in EVs and were described as modulators of drug resistance in this tumor (Takahashi et al., 2014a; Takahashi et al., 2014b). LncRNA FMR1-AS1, also found in EVs, binds to endosomal toll-like receptor 7 (TLR7) and activates the NF-κB signalling to promote c-Myc expression, thereby inducing esophageal squamous cell carcinoma proliferation, escape from apoptosis and invasiveness (Li et al., 2019). In breast cancer, the horizontal transfer of EVs containing lncRNA SNHG14 from trastuzumab-resistant cells to trastuzumab-sensitive cells resulted in drug resistance of the recipient cells, presumably due to activation of Bcl-2/Bax signaling pathway and inhibition of apoptosis (Dong et al., 2018). Similarly, LncRNA RP11-838N2.4 transferred by EVs may promote erlotinib resistance in NSCLC cells by an unknown mechanism (Zhang et al., 2018). In temozolomide resistant glioblastoma, lncRNA SBF2-AS1 is overexpressed and can be secreted into EVs, helping recipient tumor cells to enhance their DNA double-strand break repair system, thereby inducing temozolomide resistance (Roos et al., 2018; Zhang et al., 2019b).

5.6. Other modulators

EVs might also carry other molecules that transfer resistance capabilities and decrease efficacy of drug treatment. For instance, EVs may carry in their cargo a ZEB1 mRNA that induces EMT (Lobb et al., 2017); DNA methyltransferase 1 that modulates genomic DNA methylation (Cao et al., 2017), or STAT3 that functions as a transcription

factor (Zhang et al., 2019a). There are also reports indicating that EVs may deliver mtDNA to recipient cells, altering the metabolism of recipient cells and improving their survival after drug treatments (Sansone et al., 2017).

6. Cargo of TME-derived EVs responsible for the transfer of drug resistance competences

As mentioned above, EVs shed by diverse cells from the TME, have been described as being responsible for the intercellular transfer of drug resistance competences. Interestingly, the cargo of these EVs has been identified only recently, together with the drug resistance mechanisms triggered in recipient cancer cells. **Table 3** summarizes several studies which identified the cargo of EVs released by different TME cells, and which caused drug resistance in recipient cells.

Table 3. Cargo of EVs shed by different TME cells, reported recipient cells and resistance mechanisms identified.

Donor TME cell type	EVs cargo	Recipient cancer cell type	Drugs to which resistance was identified in recipient cells	Resistance mechanism(s) identified	References
Cancer-associated fibroblast (CAFs)	miR-27a	Prostate cancer	Cisplatin, Doxorubicin, Docetaxel	Decrease in p53 gene expression	(Cao et al., 2019)
	mirR-106b	Pancreatic cancer	Gemcitabine	Decrease in TP53INP1 expression	(Fang et al., 2019)
	miR-92a-3p	Colorectal cancer	Oxaliplatin / 5-Fluorouracil	Activation of Wnt/β-catenin pathway; Inhibition of mitochondrial apoptosis	(Hu et al., 2019a)
	lncRNA CCAL		Oxaliplatin	Activation of Wnt/β-catenin pathway	(Deng et al., 2020)
	lncRNA H19		Oxaliplatin	Activation of β-catenin pathway	(Ren et al., 2018)
	miR-24-3p	Colon cancer	Methotrexate	Downregulation of CDX2/HEPH axis	(Zhang et al., 2021a)
	miR-196a	Head and neck cancer	Cisplatin	Targeting CDKN1B and ING5	(Qin et al., 2019)
	miRNA-130a	Non-small cell lung cancer	Cisplatin	-	(Zhang et al., 2021b)
	miR-21	Ovarian cancer	Paclitaxel	Downregulation of APAF1	(Au Yeung et al., 2016)

	miR-522	Gastric cancer	Cisplatin, Paclitaxel	Targeting ALOX15 and lipid-ROS	(Zhang et al., 2020)
	Annexin A6		Cisplatin	Activation of FAK-YAP signaling via stabilization of β1 integrin	(Uchihara et al., 2020)
Tumor-Associated Macrophages (TAMs)	Chitinase 3-like-1; Fibronectin	Pancreatic cancer	Gemcitabine	Activation of ERK signaling	(Xavier et al., 2021)
	miR-365		Gemcitabine	Upregulation of the triphospho-nucleotide pool; Induction of cytidine deaminase	(Binenbaum et al., 2018)
	miR-21	Gastric cancer	Cisplatin	Enhancement of PI3K/Akt signaling	(Zheng et al., 2017)
	miR-223	Epithelial ovarian cancer	Cisplatin	Activation of PTEN-PI3K/Akt signaling	(Zhu et al., 2019)
	miR-1246	Ovarian cancer	Paclitaxel	Inhibition of Cav1	(Kanlikilicer et al., 2018)
	miR-155	Neuroblastoma	Cisplatin	Targeting TERF1	(Challagundla et al., 2015)
Mesenchymal stem cells (MSCs)	lncPSMA3-AS1	Multiple myeloma	Bortezomib	Increase in expression of PMSA3	(Xu et al., 2019)
	miR-22/223	Breast cancer	Carboplatin	Promotion of quiescence	(Bliss et al., 2016)
	-	Gastric cancer	5-Fuorouracil	Activation of CaM-Ks)/ Raf/Mek/Erk signaling pathway	(Ji et al., 2015)

6.1. Cancer-associated fibroblast (CAFs)

Several miRNAs and lncRNA have been identified in the cargo of CAFs and were found to be responsible for resistance to chemotherapy in recipient cells. For instance, a study demonstrated that EVs containing miR-27a, released by primary prostate fibroblasts (PSC27 cells) induced resistance of prostate cancer cells to three chemotherapeutic agents including cisplatin, doxorubicin and docetaxel by decreasing p53 expression (Cao et al., 2019). Moreover, CAFs-derived EVs also contained miR-106b, which plays a critical role in gemcitabine resistance by directly targeting TP53INP1 in pancreatic cancer (Fang et al., 2019).

In colorectal cancer, there are several studies that mention the importance of EVs released by CAFs to chemoresistance. For example, CAFs secrete EVs containing miR-92a-3p, which is transferred to colorectal cancer cells, activates the Wnt/β-catenin pathway and inhibits mitochondrial apoptosis, thus promoting resistance to the combined treatment of oxaliplatin and 5-fluorouracil (Hu et al., 2019a). Moreover, CAF-derived EVs also contained high amounts of lncRNA CCAL (colorectal cancer-associated lncRNA) that promoted resistance of colorectal cancer cells to oxaliplatin via activation of the Wnt/β-catenin signaling pathway, both *in vitro* and *in vivo* (Deng et al., 2020). Similarly, CAFs containing lncRNA H19 besides promoting stemness also induced resistance of colorectal cancer cells to oxaliplatin through activation of the β-catenin pathway (Ren et al., 2018). EVs containing miR-24-3p, released by CAFs, also enhanced resistance of colon cancer cells to methotrexate, by downregulating the caudal-related homeobox 2 (CDX2)/hephaestin (HEPH) axis (Zhang et al., 2021a).

Furthermore, miR-196a found in the cargo of EVs derived from CAFs conferred cisplatin resistance in head and neck cancer cells, by targeting CDKN1B (also known as p27, a potent inhibitor of cyclin-dependent kinase) and ING5 (a class II tumor suppressor that regulates p53-inducible genes, such as p21 and Bax) (Qin et al., 2019). Moreover, CAFs-derived EVs induced resistance of NSCLC cells to cisplatin, through the intercellular transfer of miRNA-130a, which was found to be packed into EVs with the help of pumilio homolog 2 (PUM2), a RNA-binding protein (Zhang et al., 2021b). Another study found that miR-21 present in the cargo of EVs released by CAFs was responsible for paclitaxel resistance in ovarian cancer cells, by binding and downregulating the apoptotic protease activating factor 1 (APAF1), which binds to cytochrome c and dATP to form an apoptosome, activating caspase 9 and 3 to initiate apoptosis (Au Yeung et al., 2016). CAFs also transferred miR-522 to gastric cancer cells, which inhibits ferroptosis (a novel form of regulated cell death involving iron-dependent lipid peroxides accumulation) by regulating arachidonate lipoxygenase 15 (ALOX15) expression and lipid-ROS, thus suppressing cell death and promoting resistance of cancer cells to cisplatin and paclitaxel (Zhang et al., 2020).

Although most of the studies reported the presence of miRNAs and lncRNAs in the cargo of EVs released by CAFs, some studies show the presence of proteins in the cargo of EVs released by CAFs, which are responsible for drug resistance. For instance, a recent study in gastric cancer showed that EVs released by CAFs contained in their cargo Annexin A6, which induced FAK-YAP signaling by stabilizing β1-Integrin,

increasing the resistance of gastric cancer cells to cisplatin (Uchihara et al., 2020). Moreover, another study reported that EVs released by CAFs contained Wnts, which are glycoproteins that activate the Wnt/β-catenin pathway by promoting the stabilization and nuclear translocation of β-catenin, causing resistance of colorectal cancer cells to oxaliplatin, both *in vitro* and *in vivo* (Hu et al., 2019b).

6.2. Tumor associated macrophages (TAMs)

Regarding the cargo of EVs that is shed by TAMs, the majority of the studies refer to miRNAs as being responsible for drug resistance. In addition, some of us recently reported the impact of two proteins, chitinase 3-like-1 and fibronectin, present in the cargo of EVs shed by human M2-polarized macrophages, on the sensitivity of pancreatic cancer cells to gemcitabine, suggesting an activation of the ERK pathway (extracellular-signal-regulated kinase) as a possible mechanism involved (Xavier et al., 2021). Interestingly, another study also reported a decrease in the sensitivity of pancreatic cancer cells to gemcitabine treatment under the presence of EVs derived from TAMs, which was mediated by miR-365 present in the cargo of EVs cargo. This miR-365 was able to impair the activation of gemcitabine, by upregulating the triphospho-nucleotide pool and inducing the enzyme cytidine deaminase, thus leading to the inactivation of gemcitabine and resulting in pancreatic cancer drug resistance (Binenbaum et al., 2018).

Furthermore, the cargo of EVs released by M2 polarized macrophages was found to interfere with therapy resistance in several types of cancers. For instance, EVs released by M2 polarized macrophages contained higher levels of miR-21, which could be directly transferred to gastric cancer cells, where it suppressed cellular apoptosis and enhanced the activation of the PI3K/Akt signaling pathway through downregulation of PTEN, promoting resistance to cisplatin (Zheng et al., 2017). In line with this study, other authors found miR-223 in EVs released by M2 polarized macrophages, which increased PTEN-PI3K/Akt pathway in ovarian epithelial cancer cells, leading to cisplatin resistance (Zhu et al., 2019). Moreover, miR-1246 present in the cargo of EVs released by M2-type macrophages contributed to paclitaxel resistance in ovarian cancer cells, through inhibition of caveolin-1 (Cav1), a protein that directly binds to PDGFRβ and inhibits its kinase activity (Kanlikilicer et al., 2018). Furthermore, mir-155 found in EVs derived from macrophages (regardless of M1- or M2- polarization) conferred cisplatin resistance to neuroblastoma cells, by targeting TERF1, an inhibitor of telomerase (Challagundla et al., 2015).

6.3. Mesenchymal stem cells (MSCs)

As with other TME cells, most of the studies identified mainly miRNAs and lncRNAs in the cargo of EVs released by MSCs and being involved in chemoresistance. For instance, the presence lncPSMA3-AS1 in the cargo of EVs shed by MSCs, followed by its transfer to multiple myeloid cells, conferred resistance to the proteasome inhibitor bortezomib (Velcade®) by increasing PSMA3 expression in the recipient cells (Xu et al., 2019). The miR-222/223, also found in the cargo of EVs released by MSCs, altered the cell cycle of some breast cancer cells, causing those cells to enter a quiescence state, leading to dormancy, which compromised chemotherapeutic response (Bliss et al., 2016). Another study reported that EVs derived from MSCs induced 5-fluorouracil resistance on gastric cancer, both *in vitro* and *in vivo*, through the activation of calcium/calmodulin-dependent protein kinase (CaM-Ks)/Raf/Mek/Erk signaling pathway. However, the cargo of the EVs responsible for such effect was not identified (Ji et al., 2015).

However, strikingly Wu *et al*., reported that EVs shed by MSCs contained miR-193a that reduced (rather than increased) cisplatin resistance in NSCLC cells by targeting the leucine-rich repeat-containing protein 1 (LRRC1) (Wu et al., 2020).

7. Drug sequestration in EVs

Several studies have suggested that EVs may sequester drugs from the intracellular and/or extracellular microenvironment, as a bypass mechanism of cancer cells to escape pharmacological cytotoxicity, since this may limit the intracellular concentration of drugs that target the cancer cells, leading to sublethal concentrations inside the cells (Chen et al., 2006; Cvjetkovic et al., 2016; Goler-Baron and Assaraf, 2011; Gong et al., 2013; Ifergan et al., 2005; Muralidharan-Chari et al., 2016; Parolini et al., 2009).

Ifergan *et al.,* (2005) described the presence of large EVs emerging from cell-cell attachment zones between neighbor cells of mitoxantrone-resistant human breast carcinoma cell lines MCF-7/MR and MCF-7/FLV1000, with the ability to sequester mitoxantrone via an ABCG2-dependent mechanism (Ifergan et al., 2005). An intravesicular drug accumulation of ~1,000-fold higher than the drug concentration found in the extracellular medium was observed in the EVs derived from MCF-7/MR cells

following 12 h of incubation with mitoxantrone, which could be abrogated by treatment with the ABCG2 efflux inhibitors Ko143 or fumitremorgin C, restoring drug sensitivity of these cancer cells (Ifergan et al., 2005). Similar results were reported regarding topotecan sequestration by the same type of EVs from MCF-7/MR cells, in an ABCG2-dependent manner, leading to a 25-fold resistance in donor cells MCF-7/MR when compared to their parental cell line MCF-7 (Goler-Baron and Assaraf, 2011). This was also reversed by ABCG2 inhibition with fumitremorgin C (Goler-Baron and Assaraf, 2011). Additionally, other ABCG2 substrates, such as imidazoacridinones and methotrexate (which have distinct structures and mechanisms of action) were found to accumulate in these EVs, emphasizing the role of ABCG2-overexpressing EVs (shed by MCF-7/MR cells) in MDR (Goler-Baron and Assaraf, 2011). Regarding the topology of this drug efflux pump on EVs, these authors suggested that ABCG2 is present in the membrane of EVs formed between two neighbor cells, with its ATP-binding fold and substrate binding domains facing the cytoplasm of the cells surrounding those EVs allowing drug transport from the cytosol (of donor cells) to the lumen of these vesicles, thus leading to sub-lethal concentrations inside the donor MCF-7/MR cells **(Figure 4A)**. Moreover, along with ABCG2, the drug efflux pumps ABCB1 and ABCC2 were also found in EVs membrane, but not on the cell membrane that is facing the medium or adjacent cells (Goler-Baron and Assaraf, 2011).

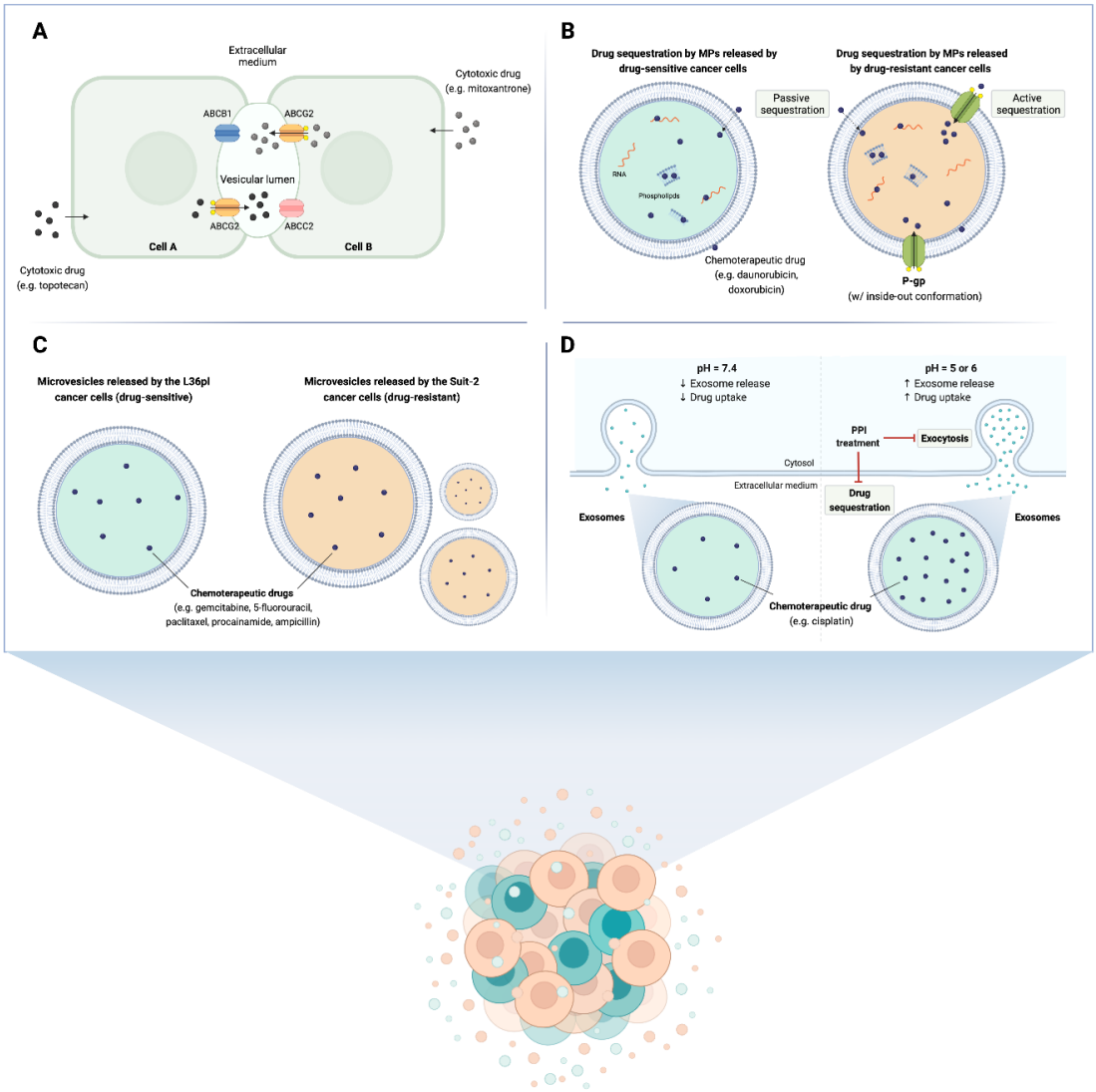

Figure 4. Mechanisms of drug sequestration mediated by extracellular vesicles (EVs). A) The drug efflux pump ABCG2 was found on the membrane of EVs emerging from cell-cell attachment zones of mitoxantrone-resistant human breast carcinoma cells, with its ATP-binding fold and substrate binding domains facing the cytoplasm of surrounding cells, enabling drug accumulation (e.g. mitoxantrone, topotecan) in the vesicular lumen, and decreasing its intracellular concentration. Other drug efflux pumps, like ABCB1 and ABCC2, are also present in the membrane of these EVs. **B)** EVs from drug-sensitive subclones of human breast adenocarcinoma and human acute lymphoblastic leukemia cells were able to passively trap chemotherapeutic drugs (e.g. daunorubicin and doxorubicin), whereas EVs derived from drug-resistant cells could actively sequester these drugs in addition to their passive sequestration. Passive sequestration seems to depend on MPs' size and on their amount of cargo (RNA and phospholipids), particularly in vesicles released by drug-sensitive cells. Active sequestration in EVs derived from drug-resistant breast adenocarcinoma cells seems to be partly sustained by the inside-out oriented P-gp, which hijacks chemotherapeutic agents away from cancer cells. **C)** Gemcitabine-resistant pancreatic cancer cells Suit-2 were shown. Figure was created with BioRender.com.

Drug sequestration by EVs (100 to 1,000 nm in diameter) was also reported by Bebawy and coworkers in breast adenocarcinoma and human ALL models (Gong et al., 2013). These authors demonstrated that EVs obtained by differential centrifugation from drug-sensitive cells were able to passively entrap the anthracyclines daunorubicin and doxorubicin, while EVs derived from drug-resistant cells could actively take up these drugs in addition to their passive sequestration (**Figure 4B)**. According to the authors, the extent of drug sequestration by these particles, especially in EVs derived from drug sensitive cells, is likely to depend on their size and amount of cargo, since an increased drug uptake was observed by EVs with a larger size and with higher content of RNA and phospholipids (Gong et al., 2013). Additionally, these authors verified that a significant proportion of EVs derived from drug resistant breast adenocarcinoma cells also presented P-gp with inside-out (i.e. inverted) orientation, possibly enabling drug influx rather than drug efflux into the EVs (Gong et al., 2013). Interestingly, a study conducted by Cvjetkovic *et al.,* (2016), which meticulously analyzed the protein topology on EVs released by the human mast cell line HMC-1, described the presence of several proteins with an inverted orientation on their surface (Cvjetkovic et al., 2016). However, as the authors pointed out, these topologically inverted proteins could be also found on EVs with their native orientation; hence, these proteins are likely present at both the native and inverted orientations on the surface of EVs. Among such proteins was the MRP1/ABCC1 drug efflux transporter (Cvjetkovic et al., 2016). Although more studies are required to elucidate the topology of these drug efflux pumps on the membrane of EVs, current evidence suggests that this could be one of the mechanisms limiting drug availability to cancer cells.

Muralidharan-Char *et al.,* (2016) have also studied the influence of the drug-resistance phenotype of donor cells on larger EVs release (**Figure 4C**). Using a panel of pancreatic cancer cell lines with different levels of gemcitabine resistance, the authors observed an increased release of EVs (with 23 to 995 nm) by tumor cells that exhibited higher resistance to gemcitabine than by those with drug sensitivity (Muralidharan-Chari et al., 2016). Not only gemcitabine was found in the cargo of EVs released by drug sensitive and drug resistant pancreatic cell lines, but also other drugs including 5-fluorouracil, paclitaxel, procainamide and ampicillin (Muralidharan-Chari et al., 2016). Interestingly, inhibition of the release of EVs with MEK inhibitors (U0126 and AZD6244) or by induction of genetic mutation (expression of dominant negative mutant of ARF6, ARF6 T27N), sensitized (donor) tumor cells to gemcitabine treatment both *in*

vitro and *in vivo*, highlighting the importance of this process for anticancer drug resistance (Muralidharan-Chari et al., 2016).

Regarding studies with smaller EVs, Chen *et al.*, (2006) reported the accumulation of doxorubicin within MVBs of chronic myelogenous leukemia cells. Most cytoplasmic doxorubicin was found within cytoplasmic vesicles, and abrogation of Vacuolar Protein Sorting 4a, which is involved in MVBs and exosome biogenesis, impaired doxorubicin sequestration by MVBs. This suggests that the MVB-exosome pathway might be an exit mechanism for doxorubicin in this type of cancer cells (Chen et al., 2006). A similar modality of a dramatic lysosomal entrapment of hydrophobic weak base anticancer drugs like doxorubicin followed by extrusion via lysosomal exocytosis was reported by Zhitomirsky et al., in a series of studies with MDR tumor cells (Zhitomirsky and Assaraf, 2017, 2015, 2016; Zhitomirsky et al., 2018).

Interestingly, other authors, who have been studying the impact of the pH on EVs drug sequestration and the release of EVs by human metastatic melanoma cell lines, demonstrated that an acidic pH (pH 5 and 6) increased cisplatin uptake by EVs as well as EVs release by tumor cells (**Figure 4D**), when compared to the physiological pH (pH 7.4) (Federici et al., 2014; Parolini et al., 2009). Interestingly, pretreatment of cells with a proton pump inhibitor (PPI) at low pH conditions impaired EVs release by tumor cells and reduced cisplatin EV accumulation by 50% (**Figure 4D**), (Federici et al., 2014; Parolini et al., 2009). Similarly, in xenograft mouse models of human melanoma cells, PPI pretreatment decreased EVs plasma levels and cisplatin intravesicular content, thus increasing cisplatin availability within the tumor (although no alterations in tumor size were observed) (Federici et al., 2014). In this respect, treatment of malignant tumors with PPIs was reported as a strategy to reverse MDR (Taylor et al., 2015; Zhitomirsky and Assaraf, 2016).

Although some studies have investigated drug sequestration by EVs using cancer cell models, evidence from *in vivo* models and patients is scarce. More studies are needed to clarify the mechanisms underlying drug sequestration by EVs, which are released by cancer cells, and to assess the clinical relevance of this process in cancer patients. Moreover, the impact of other putative modulators of the TME (e.g. hypoxia, stromal cells and pH) on EVs drug sequestration should be also considered.

8. Clinical perspectives

Several preclinical studies have clearly demonstrated that EVs take part in most aspects of tumorigenesis (Peinado et al., 2012; Pucci et al., 2016; Stefanius et al., 2019), and the previous paragraphs reported a number of solid findings supporting the pivotal role of EVs in the intercellular transfer of drug resistance competences to cancer cells. However, the clinical relevance of such intercellular transfer of chemoresistance traits is limited.

The components of EVs that have attracted most attention are non-coding RNA (ncRNAs), such as the lncRNAs ARSR, which promoted resistance to sunitinib via overexpression of AXL and c-MET mediated by competitive binding to miR-34/miR-449 in renal cell carcinoma cells (Qu et al., 2016). These lncRNAs ARSR were also detected at higher levels in both the tissues and the plasma of renal cell carcinoma patients who suffered from tumor relapse, compared with patients who exhibited a good response to neoadjuvant therapy with sunitinib (Qu et al., 2016). Similarly, high levels of serum EV lncRNA HOTTIP were associated with poor response to cisplatin in advanced gastric cancer patients (Wang et al., 2019), while overexpression of EV lncRNA HOTAIR was correlated with a poorer response in breast cancer patients undergoing neoadjuvant chemotherapy (Tang et al., 2019). Of note, in the latter study, the levels of HOTAIR were related to tumor burden (i.e. they significantly decreased after surgical removal of the tumor), suggesting that the main source of these serum EVs was from the breast tumor tissue. As reported for ovarian cancer patients (Meng et al., 2016), breast cancer patients show indeed an active secretion of EVs into their blood circulation, and an interesting study within a randomized phase II neoadjuvant trial (paclitaxel and non-pegylated liposomal doxorubicin with or without addition of carboplatin), detected specific signatures with networks of deregulated exosomal miRNAs associated with both clinicopathological parameters and pathological complete response (Stevic et al., 2018).

Remarkably, the majority of ncRNAs detectable in body fluids is concentrated in EVs and their lipid membrane coverage protects from RNases degradation, resulting in higher specificity and stability than circulating RNAs (Nik Mohamed Kamal and Shahidan, 2019). Thus, the comprehensive characterization of EVs and their content in liquid biopsies is seen as an extremely promising alternative to tissue biopsies in order to better understand cancer development and response treatment. Liquid biopsies can indeed provide clinically-relevant minimally-invasive genomic and epigenomic signatures for cancer monitoring (Siravegna et al., 2017). In view of the advances of sequencing

technologies, and of the recent FDA approval of different assays for circulating tumor DNA analysis, several evidence-based recommendations regarding the use of liquid biopsy in therapeutic decision-making have been already established (Rolfo et al., 2021).

However, there are still several limitations regarding the use of EVs, and clinicians as well as scientists should critically evaluate different EVs signatures using solid models of biomarker validation to ensure the scientific rigor needed to translate these discoveries to the bedside (Connors et al., 2020). Firstly, a standardized method for collecting, processing, and separation of the EV samples has not been established. According to the recent recommendations of the International Society of Extracellular Vesicles (ISEV) (Poupardin et al., 2021), a more general nomenclature should be used when describing the results of most EV-based studies, because it is currently not possible to clearly state the origin of EVs in a complex mixture. Indeed, the EV population in body fluids is a heterogeneous mixture of EVs derived from different cell types (i.e. both cancer and normal cells, such as blood cells). In addition, the composition of EVs is not only cell-type dependent but can differ even when the EVs originate from the same parental cells because both the subcellular origin and cellular activation status contribute to EVs cargo, prompting a deeper dissection of EV heterogeneity (Mathieu et al., 2019). This heterogeneity can affect the tumor specificity of the identified EVs signatures, and biomarkers and methods to selectively enrich cancer EVs from plasma or serum have to be validated before they can be implemented in the clinical setting.

Despite the scientific robustness, the majority of the studies described above have been conducted in few preclinical models and with a very limited number of patient samples, within retrospective analyses. Large-scale validation studies on EVs biomarkers performed within prospective randomized clinical trials, are warranted in perspective of a clinical application.

Lastly, most of the previous analyses were restricted to specific panels of EV components, such as specific miRNAs, on the basis of literature or limited bioinformatics tools (Leonetti et al., 2019). Hopefully, future studies will exploit the most recent advances of deep sequencing and machine-learning technologies which are already showing promising results in the diagnostics setting (Hoshino et al., 2020).

9. Conclusions and Future Perspectives

EVs released by drug resistant tumor cells or by cells from the TME have an established role in the intercellular transfer of drug resistance traits to sensitive tumor cells. Nonetheless, this network of communication is not fully understood, particularly the mechanisms underlying EV's release and if there is selection of recipient cells by EVs *in vivo*. Indeed, most of the research carried out to date has been conducted with tumor cell line models and the relevance of this phenomenon to the "dissemination" of drug resistance in patients, and its clinical impact, has not been conclusively clarified. Similarly, it is accepted that EVs released by resistant tumor cells may contribute to drug sequestration and consequently to the resistance of donor cells. However, the clinical relevance of this phenomenon remains unknown. Further studies on cancer patients by analyzing EVs from paired liquid biopsies, before and after acquisition of drug resistance, may contribute to clarifying the true clinical impact of EVs to the intercellular transfer of drug resistance traits.

Understanding the selective packaging of EVs by donor cells and how to counteract such packaging might contribute to the identification of new modalities to circumvent or surmount drug resistance. Nevertheless, it is important to remember that the production of EVs by donor cells is a complex mechanism, possibly with feedback loops, and that EVs are produced by healthy cells too and not solely by tumor cells, presenting high heterogeneity among patients. Thus, targeting the release of specific EVs is a difficult task.

Most importantly, EVs have the potential to become the source of biomarkers of cancer drug resistance. However, scientific challenges on the establishment of standardized isolation techniques of EVs from biological samples remain to be addressed, for a possible translation of EV research into the clinical setting. Moreover, given the low abundance of tumor-derived EVs in liquid biopsies, further technological developments in the isolation of tumor-specific EVs and their analysis will be necessary. Thus, the use of EVs as tools for real-time monitoring of response to treatment and of emergence of drug resistance continues to be a challenge.

Clinical data will help to recognize the impact of EVs to the horizontal transfer of drug resistance competences and to patient's treatment response and clinical outcome, and to clarify their relevance as promising biomarkers of response to therapy. This is a fast-growing field of research and the next years might hopefully see clinically-relevant developments in this important area.

Declaration of Competing Interest

None of the authors have conflicts of interest to disclosure.

Acknowledgements

This article is based upon work from COST Action 17104 STRATAGEM, supported by COST (European Cooperation in Science and Technology). The Vasconcelos group is supported by FEDER – Fundo Europeu de Desenvolvimento Regional through COMPETE 2020 and by FCT - Foundation for Science and Technology, in the framework of project POCI-01-0145-FEDER-030457 and also by project "Cancer Research on Therapy Resistance: From Basic Mechanisms to Novel Targets" - NORTE-01-0145-FEDER-000051, supported by Norte Portugal Regional Operational Programme (NORTE 2020), under the PORTUGAL 2020 Partnership Agreement, through the European Regional Development Fund (ERDF). The Giovannetti group is supported by Cancer Center Amsterdam 2018 and KWF#13598 grants (The Netherlands), and AIRC IG-24444 grant (Italy). The Kopecka group is supported by Fondazione Cassa di Risparmio di Torino ID 2020.1648. Cristina P. R. Xavier is supported by the Fundação para a Ciência e Tecnologia (FCT) and Fundo Social Europeu (FSE), Portugal, through the post-doc grant SFRH/BPD/122871/2016.

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