



Extracellular Vesicles and Resistance to Anticancer Drugs: A Tumor Skeleton Key for Unhinging Chemotherapies

Simona Pompili[†], Antonella Vetuschì[†], Roberta Sferra[‡] and Alfredo Cappariello^{*‡}

Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, L'Aquila, Italy

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*Correspondence:

Alfredo Cappariello
alfredo.cappariello@guest.univaq.it

[†]These authors have contributed
equally to this work and share
first authorship

[‡]These authors have contributed
equally to this work and share
last authorship

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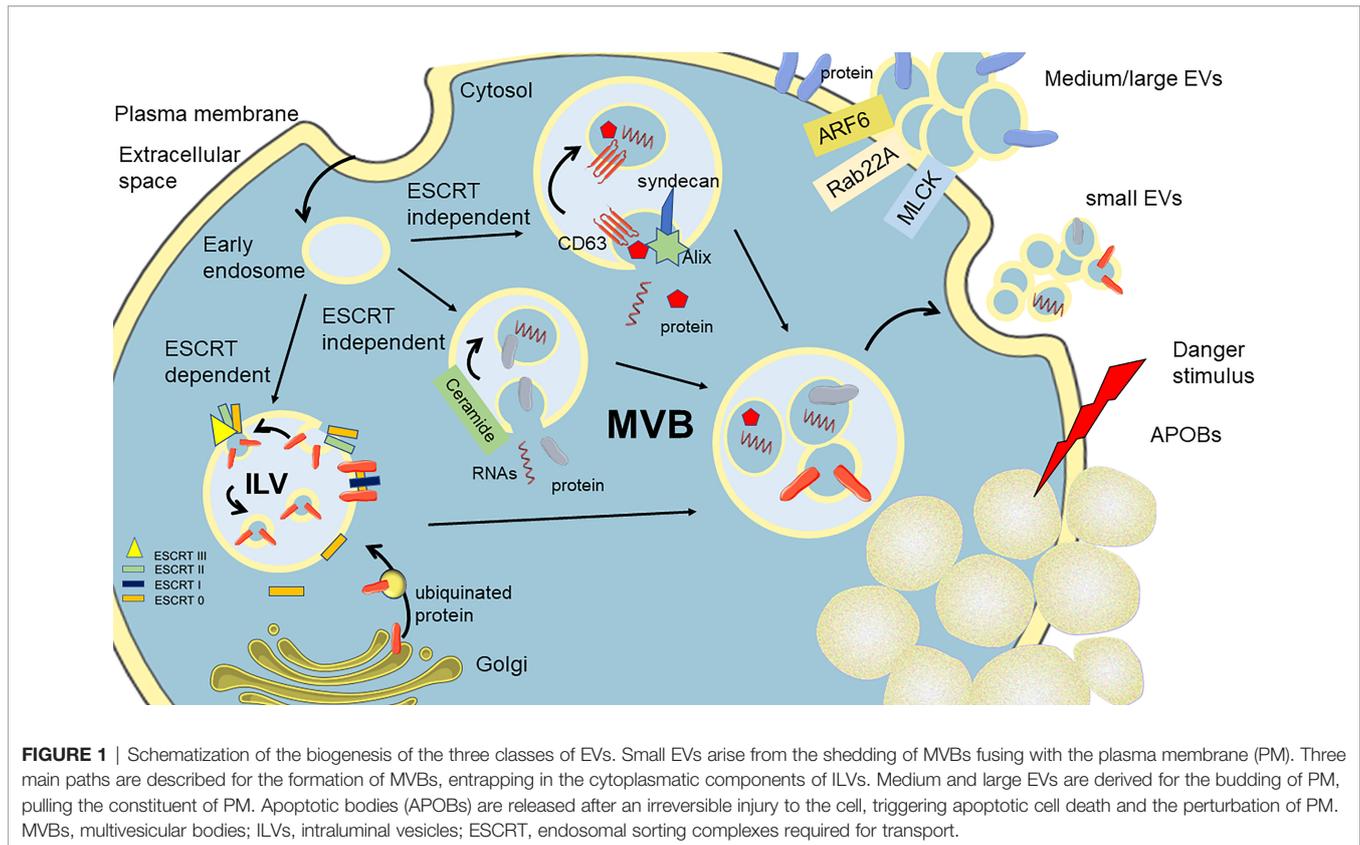
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Although surgical procedures and clinical care allow reaching high success in fighting most tumors, cancer is still a formidable foe. Recurrence and metastatization dampen the patients' overall survival after the first diagnosis; nevertheless, the large knowledge of the molecular bases drives these aspects. Chemoresistance is tightly linked to these features and is mainly responsible for the failure of cancer eradication, leaving patients without a crucial medical strategy. Many pathways have been elucidated to trigger insensitiveness to drugs, generally associated with the promotion of tumor growth, aggressiveness, and metastatization. The main mechanisms reported are the expression of transporter proteins, the induction or mutations of oncogenes and transcription factors, the alteration in genomic or mitochondrial DNA, the triggering of autophagy or epithelial-to-mesenchymal transition, the acquisition of a stem phenotype, and the activation of tumor microenvironment cells. *Extracellular vesicles* (EVs) can directly transfer or epigenetically induce to a target cell the molecular machinery responsible for the acquisition of resistance to drugs. In this review, we resume the main body of knowledge supporting the crucial role of EVs in the context of chemoresistance, with a particular emphasis on the mechanisms related to some of the main drugs used to fight cancer.

Keywords: chemoresistance, extracellular vesicles, metastasis, tumor recurrence, tumor microenvironment

INTRODUCTION

Extracellular vesicles (EVs) are a heterogeneous population of double membrane-enclosed lipidic structures, which are actively secreted by eukaryotic and prokaryotic cells (1, 2). EVs are recently recognized as mediators of communication due to their molecular cargo consisting of biomolecules (lipids, nucleic acids, carbohydrates, and proteins) transferable to neighboring cells (3–5). EVs can be classified into three different subtypes according to their size, biophysical properties, and biogenesis: small EVs (exosomes), medium EVs (microvesicles), and apoptotic bodies (6) (**Figure 1**). Small EVs are nano-sized vesicles smaller than 150 nm, which originate from intraluminal vesicles (ILVs) through the formation of multivesicular bodies (MVBs) (7). As a next step, these ILV-containing MVBs can either be redirected to degradation in the lysosome or fused with the plasma membrane (PM), thus leading to the release of exosomes. The three main mechanisms of ILV formation are described. The first mechanism requires the presence of



endosomal sorting complexes required for transport (ESCRT) complex members (8). These proteins have been described to select ubiquitinated proteins and segregate them into microdomains found on the endosomal membrane. ESCRT-0, ESCRT-I, and ESCRT-II are held responsible for the binding, through the tumor susceptibility gene 101 (TSG101), of specific cargoes selecting ubiquitinated proteins and segregating them into microdomains found on the endosomal membrane. Subsequently, these complexes recruit the apoptosis-linked gene 2-interacting protein X (ALIX), which aids in recruiting the ESCRT-III complex containing proteins involved in vesicle budding and the release from the plasma membrane. The second pathway, independent of ESCRT, requires only ALIX, and transmembrane proteins, such as syndecan and syndecan, which are responsible for recruiting tetraspanin CD63 (the main marker of small EVs) and other specific molecular cargoes (i.e., adhesion molecules, growth factors, and integrins) along with the interaction with proteins involved in the release from the cellular membrane (8). The third mechanism of ILV biogenesis mainly involves the participation of membrane lipid microdomains or lipid rafts. One of the main players is ceramide, generated by the neutral sphingomyelinase enzyme finally favoring the bending toward the lumen of the MVB membrane (9). Finally, MVBs can be degraded by fusion with lysosomes or can be shuttled to the membrane for the fusion and release of their cargo. On another side, medium/large EVs, also known as microvesicles, ectosomes, or microparticles, range between 50 and 1,000 nm. They are described to be released from the cell

surface by blebbing from the plasma membrane. The biogenesis of EVs involves many partners, among which are small GTPases (such as ADP-ribosylation factor 6, ARF6), Ras-related proteins (Rab-22A), and phospholipases (PLD), the latter inducing a phospholipid redistribution and positioning of phosphatidylserines to the outer shell in EVs (10). The final recruitment of extracellular signal-regulated kinase (ERK) and the phosphorylation of the myosin light-chain kinase (MLCK) induce the invagination of the plasma membrane and EV release. Apoptotic bodies (APOBs) are the third subtype of EVs and vary in size, ranging from 50 to 2,000 nm in diameter, ultimately produced by the programmed cell death apoptosis (11). One of the main features of apoptotic bodies is that mechanisms for specific sorting of organelles, RNA, and DNA fragments can be detected, which are absent in other EV subtypes. APOBs are far to be inactive particles but are now shown to be lively involved in biological processes. During their biogenesis, EVs entrap different macromolecules, such as nucleic acids (DNA, mRNA, miRNAs, long non-coding RNAs), lipids, proteins (cytosolic factors, receptors, and ligands), and organelles, which are then shuttled to surroundings where they exert metabolic changes in target cells.

A physical/molecular interaction between EVs and cell membranes triggers the EV uptake. This interaction has been shown to occur *via* different routes, including a direct fusion between EVs and the plasma membrane (12), as well as EV internalization *via* clathrin-, lipid draft-, and caveolae-dependent endocytosis, macropinocytosis, and phagocytosis (13–15).

Indeed, the EV uptake is likely dependent on many factors: the EV subtype, protein, and lipidic composition of the released EVs as well as the composition of the plasma membrane of recipient cells, cell metabolic status, and extracellular space conditions (i.e., pH, oxygen tension, and extracellular matrix components). The exchange of EVs is nowadays recognized as a crucial axis in the intercellular communication, exerting autocrine, paracrine, and systemic effects. EVs orchestrate physiological regulation in all tissues. The involvement of EVs is reported in many physiological processes such as angiogenesis [i.e., *via* the shedding of EV-encapsulated angiogenetic factors such as tetraspanin8, L-selectin, vascular endothelium growth factor receptor 1 (VEGFR1), and CD147], liver function and metabolism (i.e., asialoglycoprotein receptor-, apolipoprotein E/AV- and glutathione S-transferase-enriched EVs), bone resorption (i.e., pro-osteoclastogenic RANKL-positive EVs from osteoblasts), cornea wounding (i.e., fibronectin- and thrombospondin 1-enriched EVs from corneal epithelial cells), lung cell differentiation (i.e., EV-mediated shuttling and *de novo* transcription of pulmonary epithelial cell mRNAs), muscle regeneration (i.e., shuttling of α -Klotho transcript inducing muscle rejuvenating), bowel barrier integrity (epithelial cell-derived EVs alleviate gut injury after intestinal ischemia/reperfusion by miR-23a-3p), gut microbiota (*Escherichia coli* Nissle 1917 release vesicles positively modulates the intestinal epithelial barrier through upregulation zonulin-1/-2 and claudin-14), and immunity (macrophage-derived EVs contains alarmins orchestrating immune regulation) (16–24). Similarly, tissue dysfunctions and diseases are sustained by EV exchange including but not limited to stroke, obesity, skeletal muscle atrophy, colitis, and major depressive disorder (25–32). Finally, malignant transformation and cancer progression are fueled by a massive switch of EVs in many types of tumor (33–38). Carcinogenesis is a complex transformation of a cell by which specific traits or “hallmarks” are acquired, shifting from a healthy cell to a cancer one (39). According to Hanahan and Weinberg’s theory, the mandatory hallmarks include the following: sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, and activating invasion and metastasis. All of them are reported to be triggered by EVs. EVs from gastric cancer SGC7901 cells sustain proliferation by PI3K/Akt and MAPK/ERK activation; EVs are able to directly or epigenetically reduce the cytoplasmic levels of phosphatase and tensin homologue (PTEN) to evade the growth suppressor (40–42). Many papers reported the mechanisms of resisting cell death induced by EVs: multiple myeloma cells reduced by EVs the levels of the proapoptotic protein Bcl-2-like protein 11 (Bim); the antiapoptotic protein survivin is shuttled in EVs from HeLa cervical carcinoma cells irradiated with a sublethal dose of proton, and both gastric- and bladder cancer-derived EVs suppressed the apoptosis of respective cancer or suppressive immune cells *via* the upregulation of Bcl-2 and cyclin-D1 expression and the downregulation of Bax and caspase-3 (43–48). The examples of replicative immortality triggered by EV cargoes are described for the shuttling of telomerase (TERT) transcript in target cells, as

well as of TP53 and β -catenin (49–51). Angiogenesis is one of the most described event regulated by EVs, due to the enrichment in the EVs of VEGF, VEGFR, MMPs, and correlated agonists (52). Finally, metastatization support by EVs is widely investigated in a large body of literature reporting the plethora of their molecular cargo involved in the process, such as amphiregulin, C-X-C chemokine receptor type 4 (CXCR4), epidermal growth factor receptor (EGFR), interferon regulatory factor (IRF)-2, miR-105 (downregulating zonula occludens-1), and many others (53).

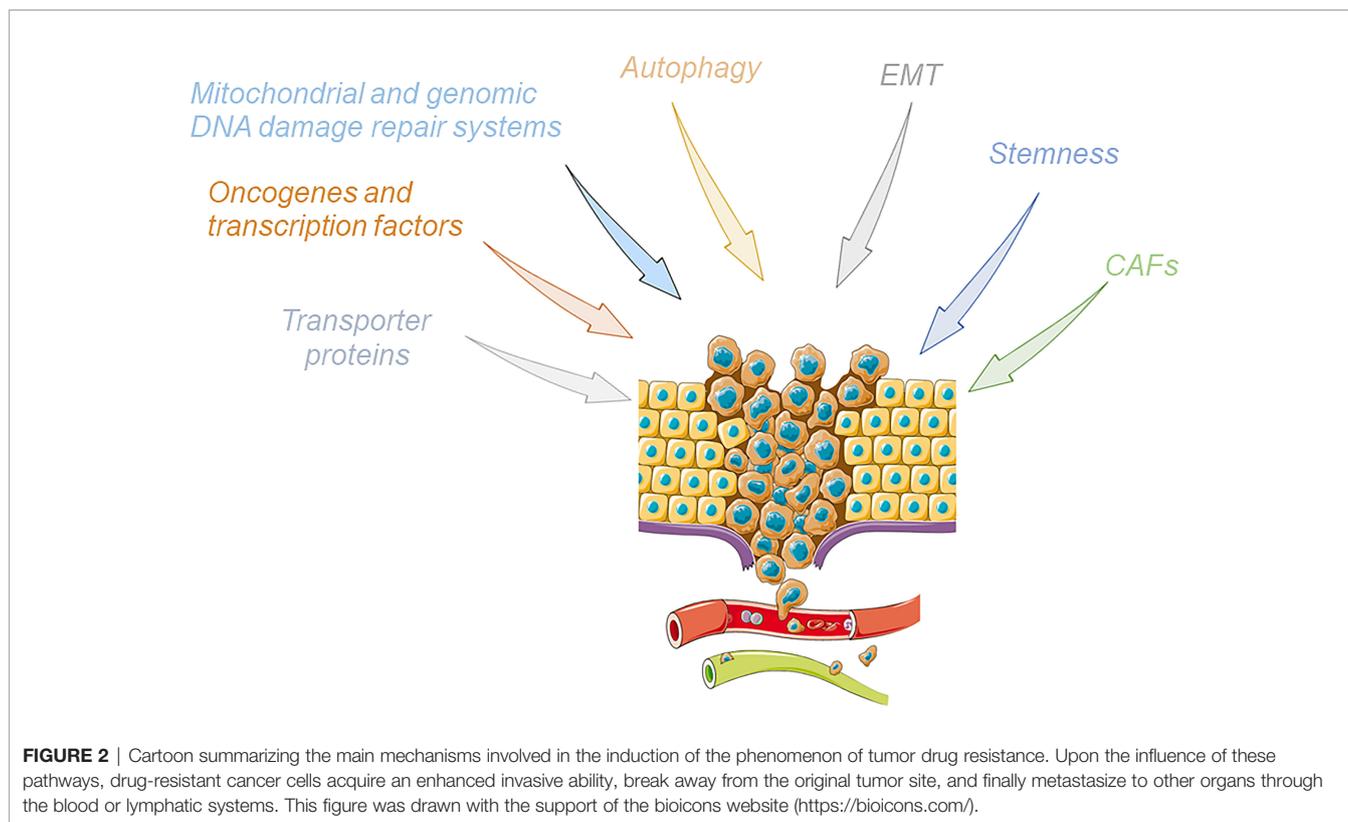
In this review, we will discuss the involvement of tumoral EVs in the insurgence of chemoresistance.

MECHANISM OF RESISTANCE TO CHEMOTHERAPEUTICS

Chemoresistance and radioresistance remain the main complications of cancer therapy, hindering the improvement of clinical outcomes for patients suffering from cancer since they cause cancer relapse and metastasis (54–56). Multiple mechanisms of resistance to drugs are reported, and the tight interconnection and support among them are one of the main issues for overcoming this crucial tumor feature. In the next section, we will provide an overview of the main mechanism of drug resistance reported in cancers (Figure 2).

Transporter Proteins

The exchange across the plasma membrane is a pivotal mechanism of cellular homeostasis. The translocation of ions, lipids, amino acids, sugars, and xenobiotics occurs mainly through transporters or channels. The ATP-binding cassette (ABC) proteins and major vault protein (MVP) are the main players in these mechanisms. P-glycoprotein [P-gp, ABCB1, or multiple drug resistance 1 (MDR1)] is an ATP-dependent efflux pump widely expressed in many tissues: capillary endothelial cells, intestinal epithelium, liver cells, and the renal proximal tubule (57). P-gp is one of the most powerful detoxification tools for cytotoxic drugs in cancer cells *via* direct efflux. P-gp overexpression has been observed in different kinds of hematological and solid tumors, such as leukemia, neuroblastomas, and ovarian and breast cancers, demonstrating its contribution to chemoresistance (58, 59). The ABCG2 encodes for another member of the ABC superfamily, also known as breast cancer resistance protein (BCRP) (60, 61). It has been reported that ABCG2 is an estrogen-inducible gene, associated with a higher tolerance of breast cancer cells against cytotoxic drugs (i.e., mitoxantrone) (62). Major vault protein (MVP) is a protein localized to a nuclear pore as a ribonucleoprotein with a hollow barrel-like structure responsible for gating ribosomes, hormones, and drugs (63). MVP was first discovered as a new 110 kD drug transporter in doxorubicin-resistant lung cancer cells, and it was later reported in many types of tumors (64). In triple-negative breast cancer cells MDA-MB-231, MVP has been demonstrated to be upregulated by the Notch1 intracellular domain and the



activation of the AKT pathway and promoting the epithelial-to-mesenchymal transition (EMT) and the chemoresistance of cancer cells (65).

Oncogenes and Transcription Factors

The overactivation and mutations of genes encoding for proteins involved in pivotal cellular processes (proliferation, survival, and transformation) is a frequent strategy of cancers to overcome the effect of cytotoxic drugs. The most upregulated pathways in chemoresistance are JAK/stat3, PI3K/Akt/mTOR, Src/FAK/ROS, and SOS/Grb2/Ras cascades. In turn, oncogenes can be upstream activated by receptors. For example, all the above pathways can be commonly activated by the EGFR. Accordingly, the overexpression or gain-of-function mutations of EGFR are reported in different types of aggressive and chemoresistant cancers. EGFR promotes metabolic processes critical for cancer cell proliferation both directly by phosphorylating rate-limiting enzymes or indirectly through the activation of the MYC transcription factor and of the AKT signaling cascade (66–68). A mutated p53 is another common feature of many cancers (69). The protein p53 is involved in the sensitivity of cells to DNA-damaging drugs through DNA damage-response sensors ataxia telangiectasia mutated protein (ATM) and ataxia telangiectasia and Rad3-related protein (ATR) and their downstream cell cycle regulator checkpoint kinases 1 and 2 (Chk1 and Chk2) (70, 71). Some mutated p53 forms are very stable to degradation and ubiquitination and heterodimerize with wild-type p53, working as a dominant-negative able to

disrupt most or all normal p53 functions, such as apoptosis or cell cycle arrest (72–74). Many mutated p53 forms can stimulate the mammalian target of rapamycin (mTOR) and block autophagy, leading to proliferative and anti-apoptotic responses in breast and pancreatic cancers (66). On other hand, the nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) is another master player in dampening apoptosis induced by a variety of stimuli, including tumor necrosis factor- α (TNF- α), γ -radiation, and chemotherapeutics (75). Cancer usually expresses high levels of constitutive NF- κ B activity and the exposition to cytotoxic agents increases NF- κ B activity, resulting in cell growth and survival and finally resistance to the therapeutic agents. NF- κ B induces the overexpression of downstream anti-apoptotic genes, such as the radiation-inducible immediate-early gene (IEX-1L), the inhibitor of apoptosis (IAP), and growth arrest and DNA damage-inducible 45 beta (Gadd45 β), B-cell lymphoma-extra large (Bcl-xL), cyclin D1 and c-Myc, and many others, finally contributing to the chemoresistance. Thus, the NF- κ B signaling pathway could be a potent target for improving the chemosensitivity of the tumor cells (76).

Mitochondrial and Genomic DNA Damage Repair Systems

Many types of tumors harbor somatic mutations in the mitochondrial genome (mtDNA), resulting in mitochondrial dysfunction. Many mutations in the mitochondrial genes of cancer cells overload mitochondrial activity mainly because

cancer cells shift their metabolism, requiring more glycolysis or oxidation. Proliferator-activated receptor gamma co-activator (PGC)-1 α and mitochondrial transcription factor A (TFAM) are overexpressed in cisplatin-resistant ovarian cancer; similarly, PGC-1 β confers the chemoresistance of lung cancer cells to cisplatin associated with mtDNA mutations (77, 78). Mitochondrial dynamics (fission and fusion) are critical for metabolic adaptations. Mitochondrial fusion with efficient ATP production was frequently observed in chemoresistant cancer cells (79). Dynamin-related protein 1 (DRP1) promotes mitochondrial fission, and its hyperexpression induces chemoresistance in lung, breast, thyroid, and colon cancers (80–84). DNA damage is the goal of many chemotherapeutic drugs, acting as alkylating (i.e., cisplatin) or antimetabolites (5-fluorouracil) to the DNA molecules. Cancer cells counteract their effects through a strengthening of the DNA repair, occurring mainly *via* nucleotide excision repair and base excision repair machinery. Excision Repair Cross-Complementation Group (ERCC) 1 is involved in the nucleotide excision repair pathway and has been reported to be associated with chemoresistance in melanoma and ovarian cancer and colorectal cancer (CRC) (85–87). Similarly, ERCC2 also supports chemoresistance in ovarian cancer (88). Reversionless 3-like (REV3L), the catalytic subunit of DNA polymerase ζ , modulates sensitiveness to 5-fluorouracil in lung and esophageal carcinoma (89, 90).

Autophagy

Cells upon nutrient starvation, hypoxia, cellular stress, or metabolic alteration initiate autophagy to degrade cellular-damaged organelles and recycle amino acids or fatty acids *via* autophagosome formation. This adaptation strategy aims to favor cell survival and proliferation and is therefore adopted by cancer cells to fight drugs. CRC tissues were reported to be characterized by a significantly higher expression of autophagy-related genes such as Beclin-1, microtubule-associated protein 1A/1B-light chain 3 (LC3), and Rictor, which levels are positively correlated with the level of MDR-1 (91). The pro-survival role of autophagy was also confirmed in breast, ovarian, esophageal, lung, prostate, glioma, bladder, renal, and pancreatic cancers (92). The crucial role of autophagy was confirmed by the use of autophagy inhibitors, such as 3-methyladenine, able to sensitize tumor cells to drugs (93). Human leukemia cells resist doxorubicin and vincristine by secreting high mobility group box 1 (HMGB1), responsible for overexpressing LC3-II in cancer cells (94). HMGB1 overexpression also contributed to the chemoresistance of neuroblastoma cells by inducing Beclin-1-mediated autophagy (95).

Epithelial-to-Mesenchymal Transition

EMT is a complex process wherein epithelial cells depolarize, lose their cell–cell contacts, and acquire an elongated, fibroblast-like morphology. This mechanism is a means by which tumor cells increase their metastatic potential and can be triggered by extracellular signals (collagen, hyaluronic acid, and integrins), growth factors and cytokines (TGF- β , VEGF, EGF, and HGF), non-coding RNAs, or hypoxia (96). Under EMT, cancer cells enhance mobility, invasion, and resistance to apoptotic stimuli.

Finally, through EMT, tumor cells acquire stemness (see next paragraph) and chemoresistance. Targeting EMT could indeed be an effective approach to obstacle chemoresistance (97). Colon cancer cells have been reported to encounter EMT and gain doxorubicin chemoresistance *via* the upregulation of TGF- β signaling (98). In hepatoma cells, gemcitabine supports EMT upon PDGF-D triggering, while oxaliplatin exposition induces EMT through BMP4/MEK1/ERK/ELK1 pathway activation (99, 100). In breast cancer cells MCF-7, EMT driven by Snail upregulation is reported to be associated with 5-fluorouracil insensitiveness (101).

Stemness

The concept of stemness in the cancer field is nowadays widely accepted, and cancer stem cells (CSCs) are the actual dogma for the basis of cancer recurrence and chemoresistance (102). The definition of CSCs is the same as the normal tissue stem cells: the ability of a small subset of cells in a tissue having the capacity for self-renewal and to reform in a host the complete tissues containing all the cellular hierarchy from whence the stem cells were derived (103). Similarly to stem cells, CSCs can be purified as a poorly or negatively stained side population (SP) by flow cytometry, so-called because of their characteristic hallmark to exclude the Hoechst from the nucleus, while other tumor cells are highly positive for the nuclear DNA staining (104). This feature is associated with a high expression of the ATP-binding cassette transporter protein ABCG2/Bcrp1 (105). The other molecular signatures of CSCs reported included Oct4, Nanog, Sox2, ALDH, CD44, CD117, CD133, Notches members, and many others (106–109). CD44, a hyaluronic acid receptor, is highly expressed by cancer stem cells and interacts with the WNT/ β -catenin pathway, leading to more aggressive tumors in pre-clinical models and patients suffering from CRC (110). CD44-expressing ovarian cancer stem cells are more resistant to platinum salts and to paclitaxel (PTX) than CD44-negative cells (111). CD133-expressing ovarian cancer stem cells have been shown to have increased engraftment capacities with chemoresistance to cisplatin (112).

Cancer-Associated Fibroblasts

CAFs are vital constituents of the tumor microenvironment, a special stroma that interacts with cancer cells to promote tumorigenesis and progression. CAFs are recognized as potential targets for anti-cancer therapy since they are described to promote both cancer metastasis and chemotherapy resistance. Tumor cells depend upon the tumor stroma since it provides nutritional support and survival signals for tumor maintenance and proliferation. Upon certain stimuli, the fibroblast inside tumor stroma becomes “activated” (113). Accordingly, fibroblasts acquire different morphology and expression profiles (114). These CAFs produce growth factors that promote tumor growth, angiogenesis, and the recruitment of protumorigenic inflammatory cells. For example, CAFs specifically produce fibroblast activation protein alpha (FAP), changing different processes such as the extracellular matrix remodeling and composition as well as immune surveillance. CAFs can also affect the sensitivity of tumor cells to chemotherapy or radiotherapy (115, 116). The main mechanisms

reported for CAF-mediated chemoresistance are the release of secreted factors, the promotion of cancer stemness, the modulation of cancer metabolism, and the induction of immune escape. The pleiotropic cytokine interleukin(IL)-6 is one of the main CAF-secreted factors. In esophageal squamous cell carcinoma (ESCC), IL-6 released by CAFs increased the chemoresistance of ESCC to cisplatin by increasing the chemokine receptor CXCR7 expression in tumor cells through the STAT3/NF- κ B axis (117). Similarly, CAFs can release IL-8, promoting chemoresistance to cisplatin in human gastric cancer *via* NF- κ B activation and ABCB1 upregulation (118). CAFs support the chemoresistance of tumor cells by promoting stemness. In colon cancer, Lotti *et al.* showed that CAFs upon the FOLFOX protocol released IL-17 which sustains the reservoir of CD44-positive self-renewing tumor-initiating cells (119). In breast cancer, CAFs secreted soluble factors such as activin A, insulin growth factor (IGF)-1, and leukemia inhibitory factor (LIF), all of which enhanced CSC proliferation and self-renewal *via* the activation of hedgehog signaling (120). Cancer and the tumor microenvironment acquire peculiar metabolic needs switching toward aerobic glycolysis (Warburg effect) (121). In lung carcinoma, EGFR- or MET-expressing cancer cells exhibited an elevated glycolysis activity and increased production of lactate that induced CAFs to secrete large amounts of HGF through an NF- κ B-dependent mechanism. Subsequently, HGF activated MET-dependent signaling and enabled cancer cells to resist tyrosine kinase inhibitors (122). The escape from immune surveillance is a pivotal pro-survival event adopted by cancer cells, and CAFs can directly promote this phenomenon. In fact, in pancreatic cancers, CAFs have been reported to actively switch polarizing macrophages toward the immunosuppressive M2 phenotype by the release of IL-8, the granulocyte-macrophage colony-stimulating factor (GM-CSF), and monocyte chemoattractant protein-1 (MCP-1) (123). In breast cancer, CAFs over-express chitinase-3-like-1 (Chi3L1), a secreted glycoprotein, involved in macrophage recruitment and M2 polarization (124). In fact, genetic *in vivo* ablation of Chi3L1 in fibroblasts reduced tumor growth and macrophage recruitment while enhancing tumor infiltration by T cells.

CHEMORESISTANCE AND EVS

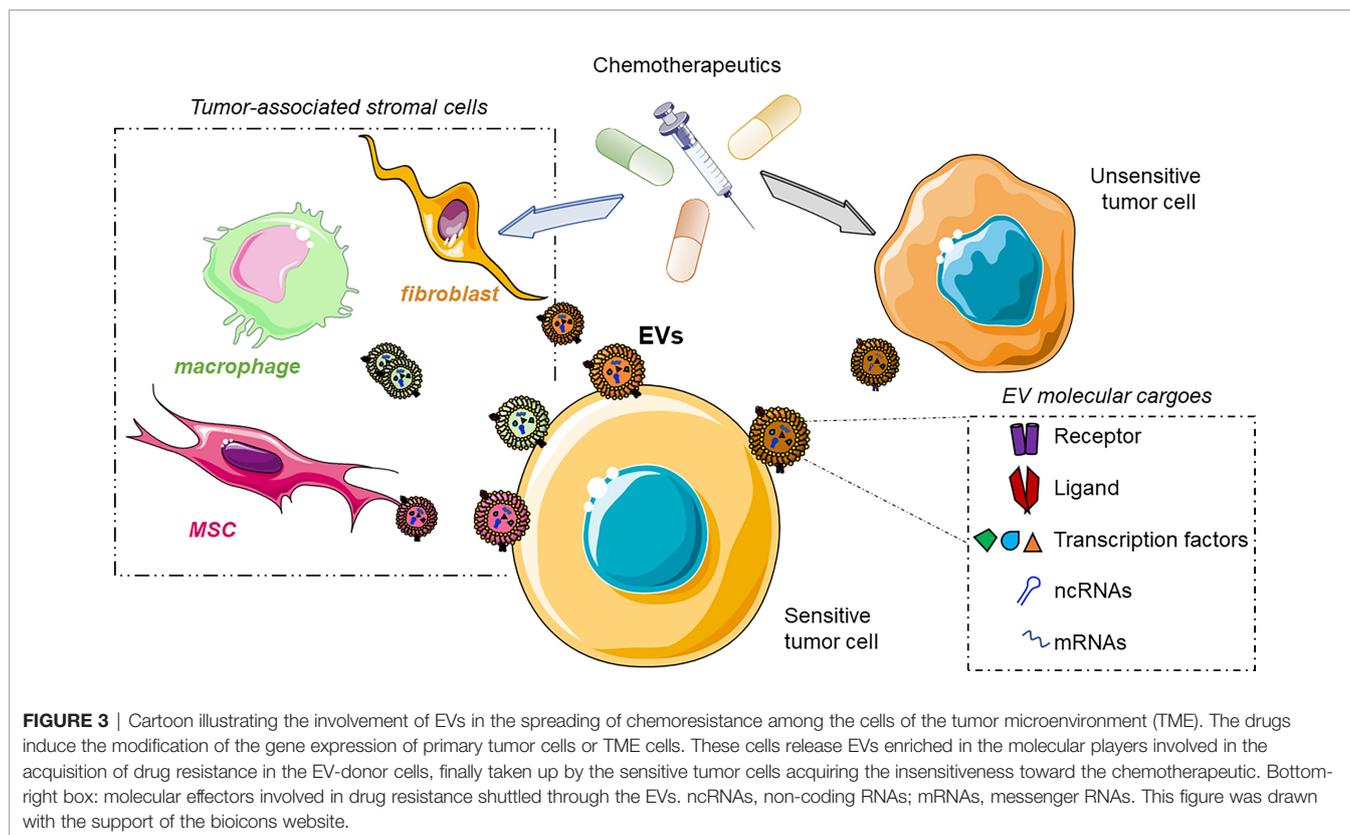
A consistent body of evidence showed that EVs are an invaluable tool for tumor cells for protecting against cytotoxic agents. Generally, EVs sequester and extrude far from the tumor cells a drug, gaining resistance to chemotherapy. Shedden *et al.* measured this feature by the correlation of a “vesicle shedding index” with the sensitivity of breast cancer cells MCF7 for a range of drugs (125). Accordingly, other authors reported that the release of EVs from resistant cells is higher compared to parental sensitive cells in different cancer cell lines, such as ovarian and pancreatic cancers (126, 127). The higher vesiculation allowed to export drugs, allowing the cells to be more resistant. Furthermore, the tumor EVs can be “upgraded” with specialized molecular machinery to more efficiently load drugs inside. Cancer cells, such as MCF7,

overexpress upon doxorubicin exposition the *ABC* genes (encoding for ATP-binding cassette transporters known to confer resistance to multiple drugs) (128). The protein is found not only as a membrane transporter, to extrude drugs from the cytoplasm to the extracellular space, but is also present on the surface of EVs (129). Interestingly, the orientation of the protein on EVs can be reversed (130, 131). This feature allows importing the drugs inside EVs before their release from cells and improves the resistance of cancer cells to chemotherapeutics. Moreover, EVs can dampen the effectiveness of biological drugs. In fact, EVs act as a decoy or antagonist of monoclonal antibody-based therapies.

In the next section, we will discuss the EV-based strategy adopted by cancer cells to overcome chemotherapeutic agents (Figure 3).

MECHANISMS OF DRUG RESISTANCE ACTIVATED BY EV MOLECULAR CARGOES

In recent years, not only the tumor progression and growth but also the response to drugs and the outcome of antitumoral therapies have been associated with the specific effects of EVs, and precise pathways favoring tumor growth and facilitating metastasis have been described (132). For example, EVs are enriched in particular families of non-coding RNAs (microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs)] involved in the epigenetic regulation of gene expression (133). *MALAT1*, a long-non-coding RNA associated with tumor metastasis and invasion in lung cancer and hepatocellular carcinoma (HCC), has also been found to be enriched in EVs from cervical carcinomas and breast cancer cells (134–136). lncRNA *TUC339* is responsible for regulating the proliferation and adhesion of HCC and is shuttled in EVs (137, 138). Through the shuttling of miRNAs, tumor cells can also acquire insensitiveness toward drugs. Yoshida *et al.* described in human biopsies of patients suffering from osteosarcoma (OS) an upregulation of miR-25-3p, negatively correlated with the clinical outcome (139). The same group demonstrated that miR-25-3p silences the Dickkopf WNT signaling pathway inhibitor 3 (DKK3) gene, thus supporting *in vitro* cancer growth and resistance to different chemotherapeutics [methotrexate, cisplatin, doxorubicin, and docetaxel (DOC)]. Similar effects have resembled after direct DKK3 silencing. Finally, miR-25-3p was found in cancer cell-derived EVs. In a similar study, Pan *et al.* confirmed the clinical relevance of EV-mediated drug resistance in OS patients (140). The authors revealed that circulating EVs from 43 OS patients presented the overexpression of the circular RNA circRNA103801 compared to healthy subjects. This EV cargo showed a prognostic value for patients, having an inverse correlation with the overall survival. The authors further investigated that the overexpression of circRNA103801 in human OS cell line MG63 conferred resistance to cisplatin and cells released EVs enriched in the same circRNA. The uptake of these EVs from naïve MG63 and U2OS cells increased the resistance to cisplatin,

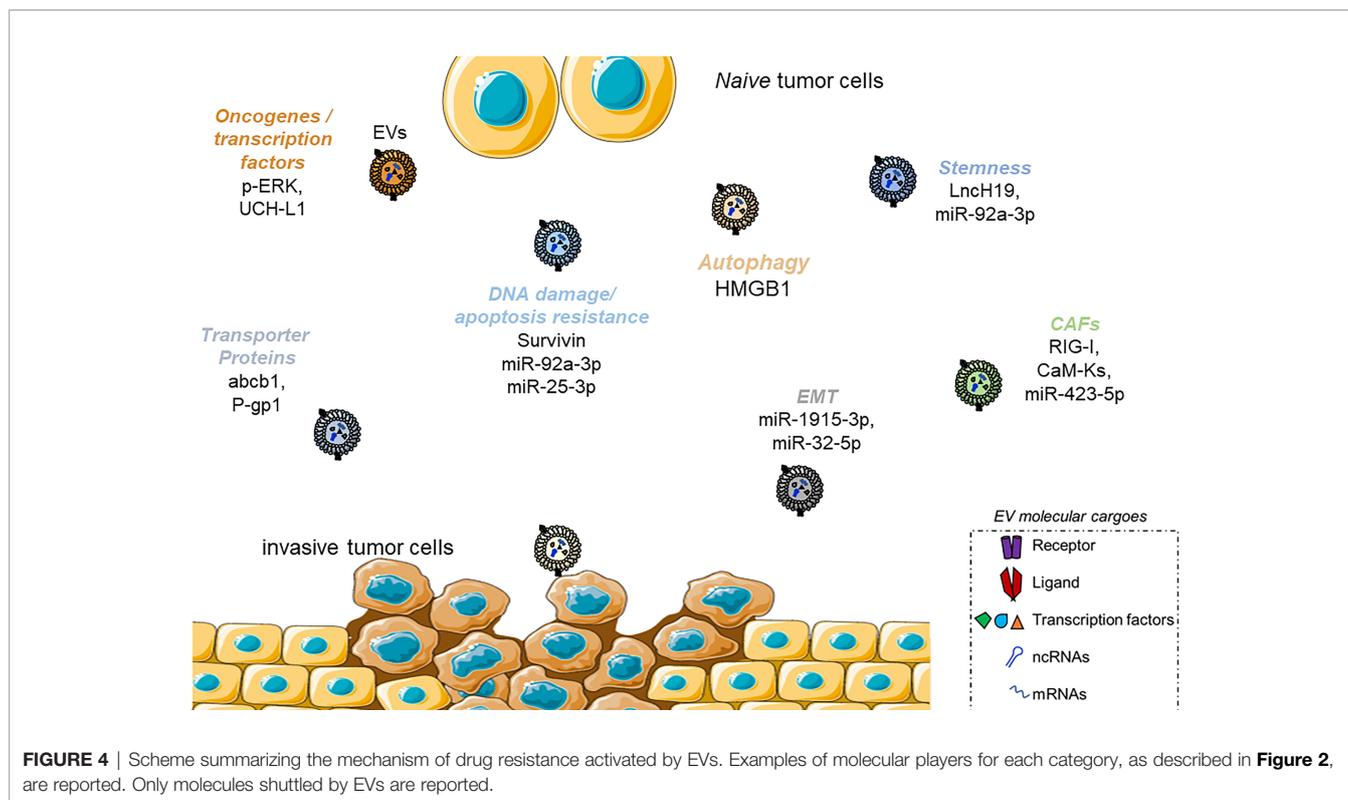


upregulating the expression of P-gp and multidrug resistance protein 1 (MRP1). Takahashi et al. showed that HCC protects from sorafenib-induced apoptosis and cytotoxicity through the release of EVs enriched in *Linc-ROR*, via a TGF β -CD133 axis (33). Exosomal miR-222 is responsible for the resistance to tamoxifen in MCF7 cells, suppressing p27 and estrogen receptor (ER) alpha expression (141). In the next paragraph, we will deeply focus on some EV-based mechanisms specifically interfering with some of the most important chemotherapeutics used for fighting cancers (Figure 4).

Platin (Platinum-Based Drug) Resistance by EV Molecular Cargoes

Platins are coordination complexes of platinum having a mainly alkylating activity on DNA, acting as intrastrand, interstrand, or DNA-protein crosslinks (142). An interesting study from Weinman *et al.* clarifies the correlation between EVs and drug resistance in a spontaneous canine model of OS (143). Based on the lag time between amputation and the start of adjuvant carboplatin treatment (good, disease-free interval >300 days; poor, disease-free interval <100 days), the animals have been divided into two cohorts and the protein profile of circulating EVs was run by mass spectrometry. The proteomic profile identified that tetranectin (TN) is decreased in the poor prognosis group and can be used as the most reliable biomarker. TN, a member of the C-type lectin family, shows a proteolytic activity. In the bone, TN has a crucial role in mineralization during osteogenesis and in extracellular matrix

stiffness. Accordingly, the genetic loss of TN causes extracellular matrix softening and skeletal deformities (144). In a mouse model of CRC, LncH19-enriched EVs have been revealed to be promoters of oxaliplatin resistance. LncH19-EVs are released by CAFs and uptake by CRC cells SW480. Inside target cells, H19 activated the β -catenin pathway via acting as a competing endogenous RNA sponge for miR-141, an inhibitor of the cancer stemness. The overexpression of H19 was also confirmed in CRC patient samples at different tumor node metastasis stages (145). Lin and colleagues found that carnitine palmitoyltransferase 1A (CPT1A) was more highly expressed in colon cancer tissues than in noncancerous tissues and confirmed that CPT1A was increased by oxaliplatin stimulation in human colon cancer cell lines HCT116 and SW480. Silencing RNA could reverse the sensitivity of drug-resistant colon cancer cells to oxaliplatin (146). An elegant study showed in CRC cells the role of the antisense-RNA PGM5-AS1 in oxaliplatin resistance. Comparing tumor biopsies and perineoplastic tissues from patients, the authors found PGM5-AS1 as the second most downregulated ncRNA. In oxaliplatin-resistant SW480 cells, the downregulation of PGM5-AS1 is accompanied by the upregulation of the transcription repressor growth factor independent 1B (GFI1B). Further experiments demonstrated that GFI1B suppresses the expression of non-coding antisense RNA PGM5-AS1, which acts as a sponge for has-miR-423-5p to upregulate the expression of Nucleoside Diphosphate Kinase 1, NME1, and EVs can be involved in the intercellular exchange of the member of these pathways, contributing to resistance to



oxaliplatin (147). Another miRNA involved in CRC was reported by Xiao *et al.* They found that the exosomal delivery of miR-1915-3p can improve the chemotherapeutic efficacy of oxaliplatin in CRC cells by suppressing the expression of 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 (PFKFB3) and ubiquitin carboxyl-terminal hydrolase 2 (USP2) and inducing the expression of E-cadherin (148). Another study showed the involvement of circRNAs in the EV-based resistance to the FOLFOX regimen (oxaliplatin, 5-fluorouracil, folic acid) in CRC patients (149). A microarray profiling of exosomal circRNAs in FOLFOX-resistant HCT116 colon cancer cells identified 105 upregulated and 34 downregulated circRNAs compared to parental cells, with hsa_circ_0000338 being the most upregulated. Finally, the drug resistance can be transferred from resistant cells into sensitive cells *via* the uptake of exosomes. As reported in the previous paragraph, cancer cells can take advantage of CAF to acquire chemoresistance. Indeed, it

has been shown that EVs from CAFs sustain chemo- and radio-resistance to the cisplatin of breast cancer MDA-MB-231 cells by activating retinoic acid-inducible gene I (RIG-I), the signal transducer and activator of transcription (STAT) 1, and NOTCH3 pathways (150). These studies are summarized in **Table 1**.

Antimetabolite Resistance by EV Molecular Cargoes

5-fluorouracil (5-FU) is an antimetabolite working as a thymidylate synthase inhibitor, finally depleting the cells of the pyrimidine thymidylate, a nucleotide pivotal for DNA replication (151). Although 5-FU is the first-choice drug for cancer treatment, its efficiency is limited by the acquisition of an innate or acquired resistance. Zhao *et al.* showed that circ_0000338 is upregulated in 5-FU-resistant CRC both *in vitro* and *in vivo* as well as in CRC patients (152). The authors

TABLE 1 | Resistance to platins mediated by EVs.

Drug	Cancer Type	EV Cargo	Effects	Refs
Cisplatin	Osteosarcoma patients and <i>in vitro</i>	miR-25-3p	Inhibition of DKK3	(139)
Carboplatin	Osteosarcoma, spontaneous canine tumor	Tetranectin	Unreported	(143)
Oxaliplatin	CRC, <i>in vivo</i> and <i>in vitro</i>	LncH19-EVs	Sponge for miR-141 and β -catenin activation	(145)
Oxaliplatin	CRC <i>in vivo</i>	GPT1A	Unreported	(146)
Oxaliplatin	CRC <i>in vitro</i>	PGM5-AS1	Sponge for miR-423-5p and upregulation of NME1	(147)
Oxaliplatin	CRC <i>in vitro</i>	miR-1915-3p	Suppression of PFKFB3 and USP2	(148)
Oxaliplatin (FOLFOX)	CRC patients, <i>in vitro</i>	circ_0000338	Unreported	(149)
Cisplatin	Breast cancer, <i>in vitro</i>	EVs from CAF, unreported	Activation of RIG-I, STAT1, and NOTCH3	(150)

revealed that exosomes containing circ_0000338 are delivered from resistant to sensitive cells and confirmed that circulating EVs in CRC patients were enriched in circ_0000338. Further experiments revealed miR-217 and miR-485-3p as the target miRNAs of circ_0000338. Particularly, miR-217 induces tumor suppression by targeting downstream genes such as astrocyte elevated gene-1 (AEG-1), mitogen-activated protein kinase (MAPK), and zinc finger E-box binding homeobox 1 (ZEB1). On the other part, miR-485-3p counteracts CRC development, inhibiting the targeting protein for Xklp2 (TPX2). Runbi Ji *et al.* showed that EVs from human mesenchymal stem cells (MSCs) isolated from the umbilical cord promoted the 5-FU resistance of gastric cancer both *in vitro* and *in vivo* (153). In fact, the exposition to MSC-EVs induced in gastric cancer cells HGC-27, MGC-803, and SGC-7901 the activation of calcium/calmodulin-dependent protein kinases (CaM-Ks) and Raf/MEK/ERK kinase pathways, culminating in the upregulation of MDR, multidrug resistance-associated protein (MRP) and lung resistance-related protein (LRP), and finally, insensitiveness to apoptosis induced by 5-FU. In another study, miR-92a-3p expression in the circulating EVs of CRC patients has been demonstrated to be correlated with metastasis to the liver and chemoresistance to 5-FU (154). The main players in this context were CAFs, exhibiting the upregulation of miR-92a-3p, compared to normal fibroblasts, delivered in the surrounding by EVs. Once uptaken by cancer cells, miR-92a-3p-EVs induced the stemness, EMT, metastatization, and 5-FU resistance of cancer cells both *in vitro* and *in vivo*. Finally, F-Box and WD Repeat Domain Containing 7 (FBXW7) and Modulator of Apoptosis 1 (MOAP1) were identified as the main targets of miR-92a-3p. Consistently, CRC biopsies resulted to being enriched in miR-92a-3p and depleted in FBXW7 and MOAP1. Colon cancer cells exposed to 5-FU are also able to increase angiogenesis (155). Upon exposition to 5-FU, cancer cells HCT-15 released EVs enriched in growth/differentiation factor 15 (GDF15), which binds the TGF- β III receptor. The activation of the receptor induces the suppression of Smad signaling and the upregulation of periostin in endothelial cells, culminating in the increase of angiogenesis. In HCC, Fu and colleagues found that HCC cells Bel7402 resistant to 5-FU produce EVs enriched in miR-32-5p shuttled to sensitive parental cells, in which it induces a decrease in PTEN and the activation of the PI3K/Akt, triggering EMT, angiogenesis, and finally, chemoresistance (156). Lastly, the relevance of miR-32-5p and PTEN in human HCC samples was investigated, confirming a negative correlation between them. This evidence is summarized in **Table 2**.

Doxorubicin Resistance by EV Molecular Cargoes

Doxorubicin (DXR), also known as Adriamycin (ADR), is an anthracycline antibiotic with antineoplastic activity, isolated from the bacterium *Streptomyces peucetius* var. *caesius*, acting as intercalating base pairs in the DNA helix (157). Additionally, DXR inhibits topoisomerase II. DXR also forms oxygen free radicals, resulting in cytotoxicity secondary to the lipid peroxidation of cell membrane lipids. Primary human OS cells MG63 treated with DXR increased their expression of P-gp1. Consistently, EVs from DXR-treated MG63 presented with higher levels of both the ABCB1 transcript and P-gp-encoded protein expression, which can be transferred to untreated MG63 cells, conferring their drug resistance (158).

Breast cancer cells MCF7 treated with ADR showed a high level of UCH-L1 and phospho-ERK, involved in the overexpression of ABCB1, compared to control cells. EVs from ADR-resistant MCF7 conferred to *naïve* MCF7 cells reduced sensitivity to ADR and increased p-ERK and P-gp1 levels (159). Interestingly, circulating EVs from breast cancer patients were positive for UCH-L1 and show an inverse correlation with response to treatment. MCF-7 exposed to ADR and DOC increased both cellular and exosomal miR-222, an inhibitor of phosphatase and tensin homolog (PTEN) gene, a tumor suppressor that negatively regulates the synthesis of phosphatidylinositol trisphosphate and the Akt signaling (141). Upon the uptake of these EVs, interstitial M2 macrophages underwent activation and polarization to support cancer cells. Accordingly, miR-222 has also been found in EVs from the plasma and tissue of chemoresistant patients (141). The overexpression of glutathione-S-transferase P1 (GSTP1, a phase II-metabolizing enzyme that detoxifies chemicals by conjugating with glutathione) is a described tool for cancer cells for counteracting chemotherapeutics like ADR. Yang *et al.* found that this enzyme is present in EVs from ADR-resistant MCF7 and, accordingly, in the sera of chemoresistant patients (160). A study conducted on HCC cells reported the role of long non-coding RNA linc-VLDLR in resistance toward DXR. Linc-VLDLR promoted the expression of the PCNA and ABCG2 genes, and the EV-mediated transfer of linc-VLDLR can result in the chemoresistance of HCC (161). **Table 3** summarizes these studies.

Taxane Resistance by EV Molecular Cargoes

Taxanes are diterpenes firstly isolated from the plants of *Taxus* spp. Taxanes work as microtubule-stabilizing drugs, inhibiting

TABLE 2 | Resistance to antimetabolites mediated by EVs.

Drug	Cancer Type	EV Cargo	Effects	Refs
5-FU	CRC patients and <i>in vitro</i>	circ_0000338	Repression of miR-217 and miR-485-3p upregulation of AEG-1, MAPK, ZEB1, and TPX2	(152)
5-FU	Gastric cancer patients and <i>in vitro</i>	EVs from MSCs	Upregulation of CaM-Ks, ERK, MDR, MRP, and LRP	(153)
5-FU	CRC patients <i>in vitro</i>	miR-92a-3p from CAFs	Downregulation of FBXW7 and MOAP1	(154)
5-FU	CRC <i>in vitro</i>	GDF15	Suppression of Smad and upregulation of periostin in target endothelial cells	(155)
5-FU	HCC patients and <i>in vitro</i>	miR-32-5p	Downregulation of PTEN and activation of EMT	(156)

5-FU, 5-fluorouracile.

TABLE 3 | Resistance to doxorubicin (DXR) mediated by EVs.

Drug	Cancer Type	EV Cargo	Effects	Refs
DXR	Osteosarcoma, <i>in vitro</i>	P-gp1	Transfer of mRNA and protein of MDR in sensitive cells	(158)
DXR	Breast cancer, patients and <i>in vitro</i>	UCH-L1 and p-ERK	Increase of ABCB1	(159)
DXR	Breast cancer, patients and <i>in vitro</i>	miR-222	Suppression of PTEN in M2 macrophage	(141)
DXR	Breast cancer patients and <i>in vitro</i>	GSTP1	Enhancement of detoxification pathway	(160)
DXR	HCC <i>in vitro</i>	Linc-VLDLR	Upregulation of PCNA and ABCG2	(161)

the depolymerization of microtubules during cell division (162). PTX, DOC, and cabazitaxel are widely used for the treatment of many different cancers. Exposure to the DOC of MCF7 cells induced the expression of P-gp1. Moreover, EVs from DOC-treated MCF-7 expressed higher levels of P-gp compared to EVs from *naïve* MCF-7, and the incubation with DOC-MCF7 EVs reduced the cell apoptosis of *naïve* MCF-7 (163). In another study, breast cancer cells MDA-MB-231 exposed to PTX specifically released EVs enriched in survivin, an inhibitor of apoptosis (164). The survivin-enriched EVs exerted protective effects on drug-sensitive fibroblasts and SKBR3 cells when exposed to PTX. Shan *et al.* described the role of CAF-EVs in the taxane resistance of prostate cancer cells. CAFs released EVs enriched in miR-423-5p, which is internalized inside prostate cancer cells LNCAP, 22RV-1, and C4 suppressing GREM2 [encoding for the gremlin2 protein inhibitor of bone morphogenetic protein (BMP) family members] and increasing TGF- β , overall leading to a reduced sensitivity to taxanes (165). These results are reported in **Table 4**.

Biological Drugs by EV Molecular Cargoes

Monoclonal antibodies are the newest frontier of anticancer drugs. A deeper knowledge of cancer biology and molecular profile allows to precisely target a specific member of pivotal pathways for cancer growth. Unfortunately, tumors can find a strategy to also counteract these agents. Cetuximab is a humanized mouse monoclonal antibody against the EGFR. Zhang *et al.* showed that EVs derived from cetuximab-resistant RKO colon cancer cells induced cetuximab resistance in cetuximab-sensitive Caco-2 cells. RKO cells and RKO-EVs resulted in depleted PTEN and enriched phospho-Akt, and the EV effects were abrogated by the Akt inhibitor LY294002 (166). In another study, circulating EVs from patients suffering from CRC have been exploited as a predictive biomarker for the response to cetuximab (42). In particular, circulating EVs from metastatic and chemoresistant subjects resulted in enriched lncRNA urothelial carcinoma-associated 1 (UCA1). *In vitro* experiments revealed that exosomes from cetuximab-resistant Caco-2 cells can transmit drug UCA1 and resistance to sensitive

parental cells. Epidermal growth factor receptor 2 (HER2)-positive tumors can be targetable with the monoclonal antibody trastuzumab. Disappointingly, tumor cells can neutralize trastuzumab by EV release, *via* a decoy-like system. HER2-positive breast cancer cells BT474 and SKBR3 release HER2-positive EVs able to bind trastuzumab, while EVs from triple-negative cells MDA-MD-231 do not. On this basis, SKBR3 cells treated with autologous EVs were less sensitive to the effect of trastuzumab since EVs sequester trastuzumab, reducing the efficacy of the chemotherapy against the primary tumor (167). Finally, circulating EVs from HER2-positive breast cancer patients at an early stage showed lower binding to trastuzumab compared to EVs from patients with advanced disease. Rituximab is a monoclonal antibody against CD20, a standard in the management of malignant B-cell lymphoma (168). Aung *et al.* showed that leukemic cells released CD20-enriched EVs intercepting rituximab, thus protecting cancer cells from the complement-dependent cytotoxicity induced by rituximab (169). Lubin and colleagues reported that neuroblastoma cells released programmed death-ligand 1 (PD-L1)-EVs that bind to PD-1 on the surfaces of cytotoxic T cells, preventing the targeting of tumor cells and finally allowing immune evasion (170). Other authors described that the response to pembrolizumab (an anti-PD-1 antibody) in patients suffering from melanoma can be reduced by EVs (171). After treatment with pembrolizumab, melanoma cells released EVs enriched in PD-L1, which suppresses the proliferation of cytotoxic T cells and facilitates the immune evasion of tumor cells, counteracting the efficacy of pembrolizumab. **Table 5** summarizes these studies.

DISCUSSION

EVs are nowadays reported to be responsible for sustaining many aspects of tumor biology. Cancer recurrence and metastatization are the main clinical challenges to offer to patients a perspective of a free-disease lifespan or at least a lifetime with a steadied cancer. Resistance to therapies is one of the causative agents of those challenges. Many mechanisms are

TABLE 4 | Resistance to taxanes mediated by EVs.

Drug	Cancer Type	EV Cargo	Effects	Refs
Docetaxel	Breast cancer, <i>in vitro</i>	P-gp	Expression of functional P-gp	(163)
Paclitaxel	Breast cancer, <i>in vitro</i>	Survivin	Inhibition of apoptosis	(164)
Taxanes	Prostate cancer, <i>in vitro</i>	miR-423-5p from CAF-EVs	Inhibition of GREM2 and increase of TGF- β in cancer cells	(165)

TABLE 5 | Resistance to biological drugs mediated by EVs.

Drug	Cancer Type	EV Cargo	Effects	Refs
Cetuximab	CRC, <i>in vitro</i>	p-Akt	Depletion of PTEN	(166)
Cetuximab	CRC patients and <i>in vitro</i>	UCA1	Unreported	(42)
Trastuzumab	Breast cancer patients and <i>in vitro</i>	HER2	Neutralizing trastuzumab	(167)
Rituximab	B-cell lymphoma, <i>in vitro</i> and patients	CD20	Neutralizing rituximab	(168, 169)
Pembrolizumab	Melanoma patients and <i>in vitro</i>	PD-L1	Neutralizing pembrolizumab	(171)

described to drive chemoresistance, and, of note, they frequently overlap, making it virtually impossible to counteract once activated. EVs are recently indicated as a further mechanism supporting chemoresistance. By the means of EVs, insensitive cancer cells can educate sensitive cognate cells, shuttling directly a functional molecular apparatus. On this basis, EVs gain clinical interest as a manageable biomarker of cancer aggressiveness and predisposition to chemoresistance, becoming a promising liquid biopsy.

Moreover, EVs also offer a new strategy to fight cancer *via* the inhibition of the release or the interaction of EVs with target cells. Unfortunately, some issues dampen the use of EVs in clinical and therapeutic management. In fact, while in basic and preclinical studies, the key involvement of EVs is incontrovertible, these results are dampened in patients and not completely reproducible, mostly comparing *in vitro* studies with human trials. A reason for that can be the use of different procedures adopted to isolate EVs since a universal consensus is still lacking on this aspect. It is nowadays reported that the specific isolating procedures can enrich protein contamination (i.e., lipoproteins or protein aggregates), and certain EV subpopulations, in turn, selecting a particular molecular cargo not strictly linked to the real biological condition, making it hard to extrapolate a comprehensive and objective interpretation.

Nevertheless, many authors are exploiting the use of natural or modified EVs as a drug delivery system. A successful and effective encapsulation of chemotherapeutics has been reported for DXR, cisplatin, and methotrexate in EVs from lung (human A549 cells), hepatocarcinoma (murine H22 cells), and breast (human MCF-7 cells) cancer cells. The efficacy has been demonstrated *in vitro* in animal models and in a clinical trial (patients suffering from stage IV lung carcinoma) (172). Paclitaxel was also loaded in EVs from human prostate cancer cells (LNCaP and PC-3 cells) (173). Murine macrophage RAW 264.7 cells were tested as a source of EVs for loading DXR targeting lung and colon (both *in vitro* and in animal models) cancers (174, 175). Similarly, EVs from RAW 264.7 packaged with DXR were effective in H22 tumor-bearing mice (144). Primary murine osteoblast-EVs have been loaded with dasatinib and successfully mitigated exacerbated osteolysis *in vivo* (18).

This is a very stimulating and active field since EVs offer many advantages in drug administration compared to the classical or liposomal formulation. The naturally occurring EV composition can confer very selective tropism to a specific tissue or cell, as well as present a higher biologic activity due to the ability to convey complex molecular machinery to the targets sustaining the required therapeutic effect. Moreover, natural EVs can be engineered for acquiring further or better properties (175).

As discussed above, several issues still curb the possibility to produce EVs for therapeutic use, mainly because the option to produce EVs under Good Manufacturing Process conditions is still lacking, although many efforts are leading in this direction. In this sense, all the key unit operation and process steps are under consideration for standardization and assessment for EV safety and de-risking, considering and not limited to the following: choice and characterization of the cell source, isolation methods, drug-loading methods (loading efficacy/cost ratio for large-scale production), the eradication of potential contaminants and impurities, best formulation, and the shelf life of final EV products. The recent case of a public safety notification on exosome products from the Food and Drug Administration for a group of patients in Nebraska, who have experienced adverse effects from the administration of improper EVs, is an exemplificative of the urgency to have regulatory monitoring about the use of EVs for human health (<https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/public-safety-notification-exosome-products>). The increasing availability of new analytical techniques is predictable to provide new insights into the distinctiveness of EVs and may unlock the full potential of EVs for clinical management.

AUTHOR CONTRIBUTIONS

SP: Conceptualization, Literature Review, Visualization, Writing—Review and Editing. AV: Coordination, Writing—Original Draft. RS: Supervision, Writing—Review and Editing. AC: Conceptualization, Literature Searching and Critical Review, Writing—Original Draft. All authors have read and approved the final manuscript.

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