Cell Communication and Signaling

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Chemoresistance and the tumor microenvironment: the critical role of cell–cell communication

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Abstract
Resistance of cancer cells to anticancer drugs remains a major challenge in modern medicine. Understanding the mechanisms behind the development of chemoresistance is key to developing appropriate therapies to counteract it. Nowadays, with advances in technology, we are paying more and more attention to the role of the tumor microenvironment (TME) and intercellular interactions in this process. We also know that important elements of the TME are not only the tumor cells themselves but also other cell types, such as mesenchymal stem cells, cancer-associated fibroblasts, stromal cells, and macrophages. TME elements can communicate with each other indirectly (via cytokines, chemokines, growth factors, and extracellular vesicles [EVs]) and directly (via gap junctions, ligand–receptor pairs, cell adhesion, and tunnel nanotubes). This communication appears to be critical for the development of chemoresistance. EVs seem to be particularly interesting structures in this regard. Within these structures, lipids, proteins, and nucleic acids can be transported, acting as signaling molecules that interact with numerous biochemical pathways, thereby contributing to chemoresistance. Moreover, drug efflux pumps, which are responsible for removing drugs from cancer cells, can also be transported via EVs.

Keywords Chemoresistance, Cell–cell communication, Tumor microenvironment, Cancer

Introduction

The tumor microenvironment (TME), the cellular environment in which a tumor exists, consists of tumor cells, surrounding blood vessels, the extracellular matrix (ECM), and other non-malignant cells. However, the ECM also contains signaling molecules that facilitate cell-to-cell communication. It is a well-known fact that the TME includes not only stromal cells, fibroblasts, and immune cells (such as T lymphocytes, B lymphocytes, natural killer T cells, and tumor-associated macrophages [TAMs]) but also pericytes and sometimes adipocytes [1]. Interactions between cancer cells and other cells, as well as molecules released into the TME, play an important role in tumor growth and the suppression of antitumoral immunity [2]. Moreover, in response to evolving environmental conditions, the TME may change over the course of cancer progression, indicating its role in metastasis. It has been proven that stromal cells and fibroblasts can secrete numerous growth factors, such as CXCL12 chemokine, hepatocyte growth factor (HGF), and fibroblast growth factors (FGFs). These factors not only increase the growth and survival of tumor cells but also chemoattract other cells into the TME [3].

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In general, cells can receive environmental cues from transmembrane ligands or intracellular molecular networks. This allows them to adjust to changes through gene expression, cytoskeletal changes, and the secretion of specific molecules. Numerous studies have shown that the complexities of cell–cell communication, especially in the TME, create new opportunities for treating cancer. Cells can communicate using both direct and indirect signaling. Direct cell–cell communication involves intracrine, autocrine, and juxtracrine (e.g., tunneling nanotubes [TNTs] and gap junctions [GJs]) communication, while indirect signaling includes paracrine, synaptic, or endocrine signaling. A multistep sequence of events, which describes most tumors, consists of a pathogenic stimulus followed by chronic inflammation and fibrosis, which creates a pre-cancerous niche and allows the development of a chronic escape strategy. This may induce a cancerous transition of normal cells. Thus, it has recently been suggested that cell–cell communication plays a key role in carcinogenesis, because it is involved in most of the changes following cancerous mutations and may influence its progression [4]. Furthermore, cell–cell communication is becoming a fundamental hallmark of tumor biology and is crucial in the adaptation of cancer cells. Intercellular interactions contribute significantly to the development of chemoresistance, emphasizing their importance as a target for novel therapeutic interventions.

Ongoing research on tumors and treatment targeting has led to the creation of recapitulative disease models and their use as important experimental tools. Anticancer drugs have a high risk of failure in clinical trials, because more than 95% of them do not make it to the market during the drug development pipeline. Therefore, cancer modeling might improve predictions of drug efficacy. Modeling approaches can be divided into 2D and 3D models. The crosstalk between tumor cells and TME components is widely discussed using 2D models through direct cell–cell interactions or paracrine signaling. The 3D approaches mainly include spheroids and organoids. Spheroids can be obtained using gravity-based systems, low-adherence surface systems, or agitation-based systems, while organoids are based on tumor tissues that self-organize and proliferate within a matrix [5].

As described above, the TME includes both tumor cells and non-malignant ones. A heterogeneous cell population of fibroblasts represents the main stromal component of solid tumors. In the TME, fibroblasts become activated and evolve into a phenotype described as cancer-associated fibroblasts (CAFs). In this form, they secrete numerous cytokines and growth factors, mainly transforming growth factor β (TGF-β), but also fibroblast growth factor 2 (FGF-2) and platelet-derived growth factor (PDGF) (Fig. 2). Moreover, CAFs produce not only bioactive molecules, proteins, and ECM but also ECM remodeling mediators. It is known that CAFs play an important role in tumor progression, invasion, and drug resistance to different anticancer compounds. However, it is still unclear whether CAFs directly influence cancer cell invasion or if they remodel the ECM [6]. Finally, exosomes (EXOs) are cargo-carrying multi-vesicular bodies secreted into the extracellular environment. They participate in both autocrine and paracrine signaling pathways in the microenvironment.

Direct intercellular communication

Types of connections and their role in cancer biology

Cells constituting the TME can directly communicate among themselves via GJs, ligand–receptor pairs, cell adhesion, and TNTs (Fig. 1). When cells are in close proximity to each other, they can connect via GJs [7]. GJs are made up of two connexons (hemichannels) that originate from two adjacent cells. Hemichannels are hexamers and consist of connexins (Cxs). Cxs have four transmembrane domains, two extracellular loops, one intracellular loop, and intracellular N- and C-terminal tails. Currently, 21 types of Cxs have been identified. They enable the formation of heteromeric hemichannels and heterotypic GJs, whose functions can be differentiated or overlap [8]. Cxs in the cell can also exist in soluble form in the nucleus or cytoplasm. Cxs channels can localize to the basement membrane, cellular protrusions (e.g., TNTs), or extracellular vesicles (EVs) (e.g., EXOs). Gap junctional intercellular communication (GJIC) enables the transport of small molecules (<1 kilodalton), including ions, metabolites, miRNAs, or some anticancer drugs, between neighboring cells [9]. The function of GJs in cancer progression is complex. Depending on the composition of GJs, tumor factors, and the type of tumor, GJs can contribute to both tumor progression and tumor suppression [11]Kliknij lub naciśnij tutaj, aby wprowadzić tekst. Recent studies show that Cxs can affect cell function through GJIC, signaling involving the C-terminal tail, and through cell-to-cell adhesion. The role of Cxs also depends largely on their level of expression and subcellular localization [10]. Among the Cxs that have the greatest impact on cancer processes are Cx43, which is the best studied of all Cxs, as well as Cx25, Cx26, Cx32, Cx30, Cx31, Cx37, and Cx46 [11]. TNTs and tumor microtubes (TMs) allow the transfer of mitochondria, cellular vesicles, miRNAs, and proteins between cells that are farther apart than those connected by GJs. TNTs are long and thin (50–200 nm) channels formed by F-actin filaments. They can occur both between normal cells (e.g., cardiac myocytes) and between cancer cells, such as in colorectal cancer, bladder cancer, and breast cancer [12]. TMs are larger structures than TNTs. They are composed of Cx43 gap junction proteins and have been shown to promote the

aggressiveness, invasion, and therapeutic resistance of glioma cells [13].

Chemoresistance – glioblastoma multiforme (GBM)

GJs are also associated with GBM resistance to temozolomide (TMZ) therapy [14]. Resistance to this anticancer drug may be related to the presence of O-6-methylguanine-DNA methyltransferase (MGMT). MGMT is an enzyme that transfers a methyl group to the internal residue of the cysteine acceptor, leading to a limitation of the activity of the alkylating agent. Patients without MGMT activity show better sensitivity to TMZ therapy, but over time they often develop resistance anyway, which is independent of MGMT. The mechanisms of this resistance are not completely known, although it has been found to be related to overexpression of epidermal growth factor receptor (EGFR), galectin-1, murine double minute 2, and mutations in the p53 gene [15]. Studies by several groups have shown that increased levels of gap junction protein Cx43 correlate with the resistance of GBM to TMZ [16, 17]. Cx43 is more strongly expressed in GBM tissues than in normal cells [16, 17]. Additionally, TMZ-resistant GBM cells are capable of activating EGFR, which led to the activation of the JNK-ERK1/2-AP-1 axis to induce Cx43 [16]. The use of a C-terminal mimetic peptide (αCT1), which is a selective inhibitor of Cx43 channels, led to the recovery of sensitivity to TMZ treatment in GBM cells deficient in MGMT. Thus, it has been suggested that Cx43 is a potential biomarker for determining the prognosis of patients with MGMT-independent TMZ resistance and that Cx43 inhibitors may have therapeutic applications to reduce chemoresistance [18]. Interestingly, αCT1 may also find use as a therapeutic agent to accelerate wound closure rates, and clinical studies to date have not shown adverse events associated with its use [19]. It has also been observed that targeting GJs, mediated by 1-octanol and CBX, leads to attenuated maintenance of glioblastoma cancer stem cells (CSCs), reduced tumor progression, and increased sensitivity of GBM cells to TMZ [20].

Coculturing glioma cells with astrocytes decreased the effectiveness of chemotherapeutic agents such as TMZ, cisplatin, 5-FU, and vincristine (VCR) on cancer cells [21, 22]. Moreover, using a semi-permeable Transwell membrane, it was demonstrated that astrocytes are involved in the protection of glioma cells through physical contact mediated by GJIC. Microarray-based expression profiling identified 699 genes whose expression is altered by the presence of functional GJICs. Among these were genes known to be related to chemoresistance, such as mitogen-activated protein kinase (MAPK), tyrosine-protein kinase, and B cell lymphoma-2 [21]. It has also been observed that targeting GJs, mediated by 1-acetanol and CBX, impairs CSC maintenance, reduces tumor progression, and sensitizes GBM cells to TMZ [20]. Recently, AS602801 was proposed as a new adjuvant chemotherapy drug that may prove effective in the treatment of GBM. AS602801 is a JNK inhibitor that, by blocking GJs between astrocytes and glioblastoma cells and downregulating Cx43, sensitizes cancer cells to VCR and TMZ [22]. It has also been shown that glioma cells can affect neighboring cells through the direct transfer of mature miR-5096 to astrocytes via GJs [23]. Currently, the creation of quadruplicate 3D models based on resected patient tumors may significantly advance our knowledge of the role of the TME in the chemoresistance phenomenon [24].

A study by Osswald et al. showed that astrocytes within gliomas can form multicellular networks and communicate via Cx43 gap junction connections. These microtubes can contribute to resistance to radiotherapy, which is most likely related to the maintenance of calcium homeostasis. A radiotherapy-induced increase in cell calcium concentration leads to cell death. Microtubes formed between astrocytes can distribute small molecules such as calcium across a larger network, reducing calcium concentration to non-lethal levels [25].

Chemoresistance – leukemias

Intercellular communication between hematopoietic stem cells and the bone marrow microenvironment is crucial for both the maintenance of normal hematopoiesis and the development of leukemogenesis. Functional GJ channels occur both between bone marrow stem cells (BMSCs) and between hematopoietic stem and progenitor cells and BMSCs. These connections may contribute to the formation of leukemic niches, which, by providing a source of GJIC-dependent energy, affect proliferation, limit tumor cell apoptosis, increase the risk of relapse, and affect chemoresistance [26]. The use of carbenoxolone (CBX), a GJ-disrupting agent, against a coculture of acute myeloid leukemia (AML) tumor cells and bone marrow mesenchymal stromal cells led to the abrogation of the anti-apoptotic effect of the niche [27]. Direct interactions between AML tumor cells and bone marrow mesenchymal stem cells (BM-MSCs) led to upregulation in leukemic cells of survival pathways such as the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) pathway, which contributes to reduced apoptosis of AML cells [28]. Five different Cxs (Cx26, Cx32, Cx37, Cx43, and Cx45) have been characterized and are present in primary AML cells. Particularly high expression, especially at the most differentiated stages, has been reported for Cx43 and Cx45 [9]. Higher expression of Cx45 on the surface of AML blasts has been linked with altered regulation of the MAPK pathway and the release of the pro-inflammatory cytokines IL-17, TNFα, and IFN. This

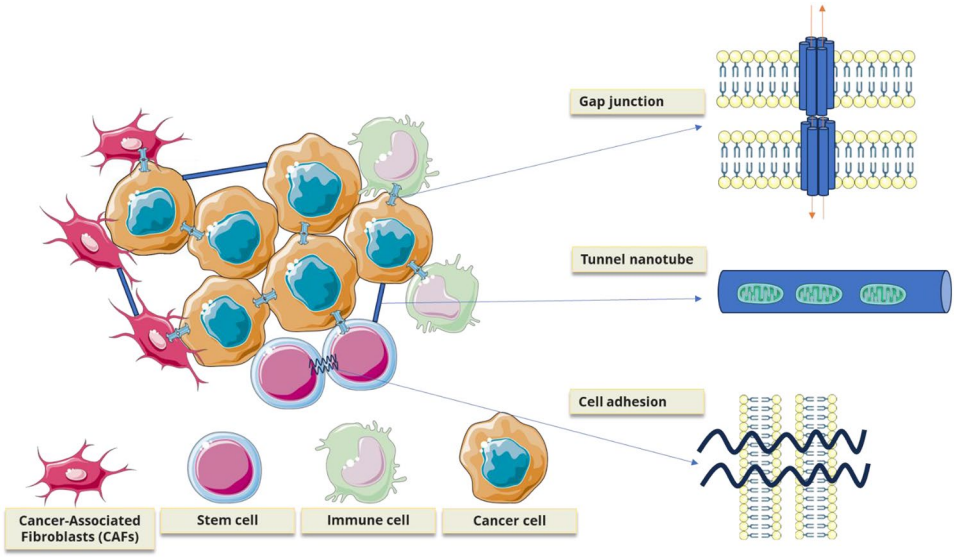

Fig. 1 Scheme of direct intercellular communication within the tumor microenvironment (TME)

can lead to the development of an environment that promotes chemoresistance [26]. It has been shown that AML cells can also directly communicate with each other via Cx25. The use of RNA interference to knockdown Cx25 in models for acute lymphoblastic leukemia (Jurkat and MV4-11 cells) led to increased sensitivity to cytarabine (Ara-C) treatment [29]. Functional Cx43 GJIC between multiple myeloma (MM) cells and BM-MSCs induces the release of IL-6, stromal cell-derived factor (SDF)-1, and IL-10, which is associated with tumor cell proliferation and chemoresistance. Inhibition of Cx43 GJ by non-specific GJ inhibitors, such as heptanol or 18-glycyrrhetinic acid, significantly attenuates CXCL12 secretion by BMSCs and enhances bortezomib-induced MM cell apoptosis [30]. It has also been shown that in the coculture niche system, AML cells take up mitochondria from mouse and human BMSCs [31]. Moreover, CBX-induced disruption of GJ functionality in the leukemic niche leads to reduced oxidative phosphorylation in AML cells, revealing severe perturbations in mitochondrial function [27]. This suggests that mitochondrial transfer may occur via GJs. However, it is important to note that CBX is not a GJ-specific inhibitor, so further analysis of existing and future genetic models modifying Cx expression is required [26].

Chemoresistance – carcinoma

Cell communication mediated by GJs, in which Cxs participates, also significantly influences the breast cancer TME. GJs are involved in both tumor suppression and progression, metastasis, and the survival of treatment-resistant breast CSCs [32]. However, the relationship between GJs and mild resistance is complex. Drug-resistant $HER2^{+}$ cells are Cx43-negative, but their ectopic replacement does not lead to resistance reversal. This suggests that Cx43 plays an intracellular role in the context of multidrug resistance (MDR) [33]. The role of GJIC in breast cancer cell survival makes its components potential therapeutic targets. Preclinical and clinical validation of arsenic trioxide, used in patients to treat acute promyelocytic leukemia, for breast cancer patients would be advisable in this regard [34]. However, it is important to remember that GJs affect numerous functions of cancer cells, and there are reports of GJs improving cancer treatment [32]. Changes in intercellular communication and GJ remodeling affect epithelial-to-mesenchymal transition (EMT). This is a highly dynamic and complex process in which the cell undergoes morphological changes and acquires new functions, such as increased motility, invasiveness, and resistance to anticancer drugs [35]. An increase in Cx26 expression induced EMT through an increase in vimentin and slug expression and a decrease in E-cadherin expression via the PI3K/AKT pathway in a GJIC-independent manner. This correlated with increased chemoresistance of the HCC-827 and PC9 non-small cell lung cancer (NSCLC) cell lines to gefitinib [36]. In contrast, high expression of Cx32 in hepatocellular carcinoma cells from the doxorubicin (Dox)-resistant HepG2 line was associated with upregulation of E-cadherin and downregulation of vimentin. In these cells, an EMT to mesenchymal-to-epithelial transition (MET) was observed with overexpression of Cx32. It has also been suggested that this process limits the ability of HCC cells to migrate, metastasize, and invade [37]. Moreover, decreased expression of Cx43 in colon cancer cells and a correlation between this decrease and poor patient prognosis have been demonstrated. Decreased Cx43-dependent reduction in cell stiffness and increased

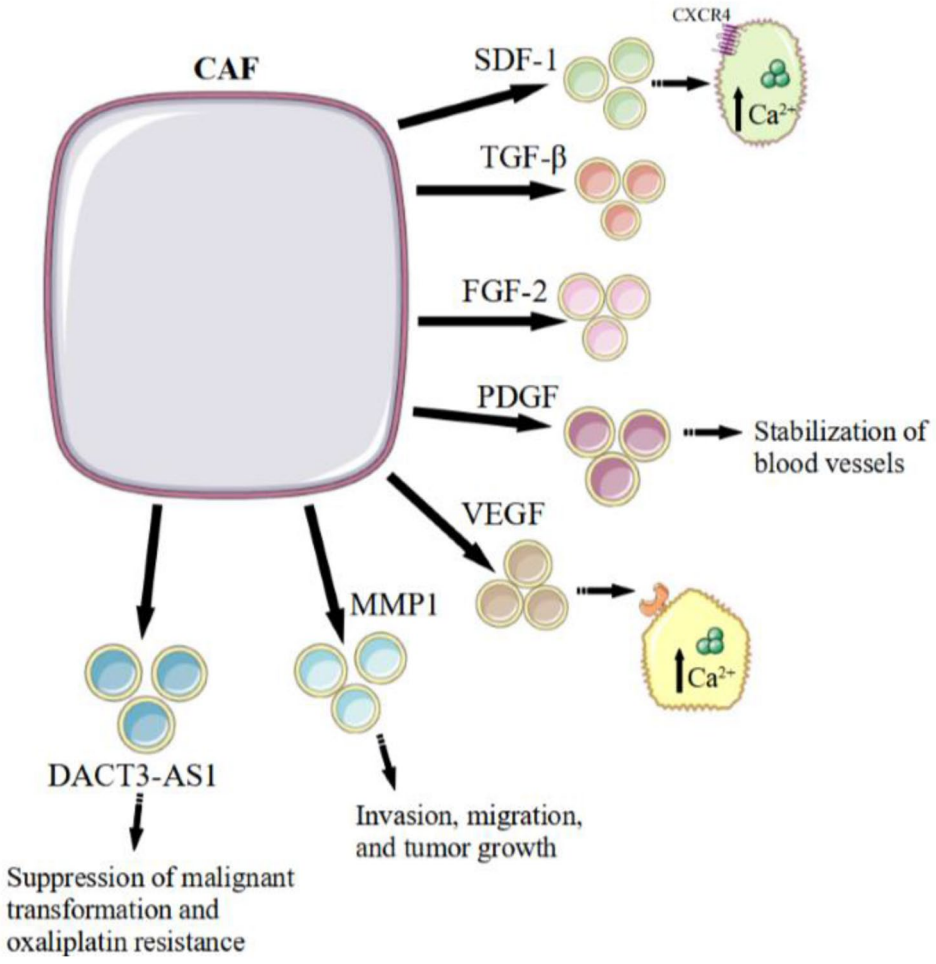

Fig. 2 Stromal cells and fibroblasts secrete numerous growth factors, such as fibroblast growth factors (FGFs), TGF-β, SDF-1, PDGF, VEGF, matrix metalloproteinase-1 (MMP1), and DACT3-AS1. PDGF in the TME leads to the stabilization of blood vessels, while VEGF binds to VEGFR and increases cytoplasmic Ca^{2+} signaling in cancer cells, inducing chemoresistance. Additionally, MMP1 secretion results in invasion, migration, and tumor growth, whereas DACT3-AS1 might suppress malignant transformation and oxaliplatin resistance

cell stemness led to drug resistance. Furthermore, overexpression of Cx43 was associated with increased GJIC and increased sensitivity to 5-FU. These findings suggest that Cx43 may be a potential therapeutic target [38].

Recently, a zinc transporter (ZIP1) present in a subset of CAFs was reported to directly connect lung cancer cells via GJ junctions and influence tumor cell chemoresistance [39]. It was previously shown that unidirectional GJIC formed by Cx43 between NSCLC cells and CAFs led to enhanced tumor progression [40]. However, short-range interactions between fibroblasts and tumor cells have rarely been described, in contrast to long-range interactions. It has been shown that $Zip1^+$ fibroblasts were highly enriched in mouse tumors after treatment with Dox. ZIP1 expression on fibroblasts led to increased production of Cx43 and the formation of functional GJs. $Zip1^+$ fibroblasts were involved in the development of chemoresistance due to Zn^{2+} uptake and translocation into tumor cells. Zn^{2+} transfer from fibroblasts to cancer cells resulted in increased expression of ABCB1 (an MDR protein involved in removing many types of drugs, including Dox, from inside the cell) and chemoresistance. It was suggested that this mechanism is related to AKT kinase. Inhibition of AKT kinase with LY294002 effectively inhibited the upregulation of ABCB1 resulting from Zn^{2+} stimulation [39]. It is possible that ZIPs are also involved in transporting other metals, such as iron and manganese [28]. Importantly, more ABCB1 inhibitors are being investigated for this type of MDR [41].

Indirect intercellular communication

Cytokines, chemokines, and growth factors

Growth factors such as TGF-β and PDGF might be either freely secreted in the TME or delivered via EXOs secreted by CAFs. They take part in both autocrine and paracrine signaling in the TME. Numerous growth factors secreted by stromal cells and fibroblasts are present in Fig. 2.

The TGF-β signaling pathway plays a crucial role in the development of the tumor and regulation of numerous mechanisms such as apoptosis, migration, angiogenesis, proliferation, and invasion [42]. Both overexpression and silencing of this pathway might induce carcinomal changes. Yet, it is the activation of multiple downstream pathways that leads to the remodeling of the ECM. Conditional loss of the TGFβ type II receptor (TRII) in fibroblasts followed by overexpression of HGF attenuates cell proliferation of fibroblasts and nearby epithelial cells. Furthermore, CAFs without TRII might still secrete the growth factor, and consequently, TGFβ-sensitive fibroblasts can further benefit from it. TGFβ also stimulates the expression of SDF-1 in CAFs, which allows a positive feedback loop to be established—SDF-1 has an autocrine effect on CAFs and, consequently, causes the secretion of TGFβ and the activated CAF phenotype [43] (Figs. 2 and 3).

Studies have proven that patients with infiltrative-type gastric cancer have a higher rate of metastasis and recurrence. Based on the proteomics data and immunohistochemical staining results, notable expression of IGFBP7 was shown in this type of gastric cancer. It has been proven that such expression originated mainly in myofibroblastic CAFs and consequently promoted the migration, invasion, and growth of the tumor. Therefore, Hong's study demonstrated that in the TME, tumor-cell-derived TGF-β1 leads to the appearance of the IGFBP7^{+} CAF subgroup. As a result, increased IGFBP7 extracellular secretion accelerates the progression of tumors [44].

Shinagawa et al. carried out a study in which imatinib therapy was used in a colon cancer model. It was proven that imatinib hindered the recruitment of CAFs to the site of the tumor, consequently stopping cancer growth and metastasis [45]. Furthermore, PDGFC and D expression are strongly connected with a poor prognosis in patients with gastric cancer, while PDGF receptor beta (PDGFRβ) is predominantly expressed in diffuse-type gastric cancer stroma. Akiyama et al. conducted a study in which they discussed the impact of stromal reprogramming and combined immunotherapy for patients with fibrotic cancer, and found that combining PDGFRα/β blockade and anti-programmed cell death protein-1 (PD-1) treatment synergistically diminished the growth of fibrotic tumors. They have proven that PDGFRα/β blockade reversed the immunosuppressive microenvironment due to stromal modification and influenced the expression of CXCL1, CXCL3, CXCL5, and CXCL8, which are crucial in polymorphonuclear myeloid-derived suppressor cell recruitment [46].

Numerous studies have proven that calcium signaling is not only an important factor in cancer progression but also influences the TME. Interest in the interplay between CAFs building the TME and Ca^{+} has been growing over the last decade. There can be observed phenotypic changes of cancer cells due to CAF-induced Ca^{2+}-mediated signaling. Prostate CAF TRPA1 might cause an increase in the secretion of VEGF and, consequently, activate VEGFR. Activation of these receptors leads to elevated cytoplasmic Ca^{2+} signaling in the

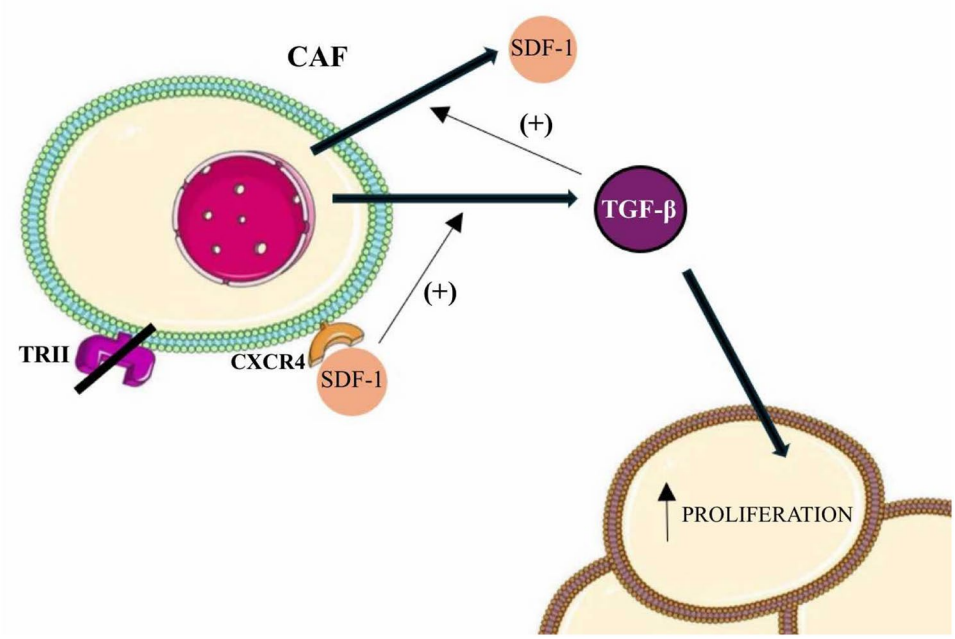

Fig. 3 Despite lacking TRII, CAFs can still secrete growth factors, such as TGFβ, which can induce SDF-1 expression in CAFs. This establishes a positive feedback loop, where SDF-1 triggers TGFβ secretion, maintaining CAF activation

cancerous cells and thus induces chemoresistance [47]. Moreover, the role of this element is crucial in the migration and invasion of breast, endometrial, and colon tumor cells, because CAFs secrete SDF-1, which activates CXCR4 and consequently increases the levels of cytoplasmic calcium [48]. Breast CAFs might also secrete MMP1, which connects with PAR1 and induces Ca^{2+} signaling. As a result, MMP1 induces migration, invasion, and tumor growth in breast cancer cells (Fig. 2) [49].

VEGF and its receptors—VEGFR-1, VEGFR-2, VEGFR-3, neuropilin (NRP)-1, and NRP-2—play an important role in angiogenesis by increasing the expression of numerous growth factors. VEGFs can suppress antigen presentation and stimulate the activity of regulatory T (Treg) cells and TAMs. The EGF and EGFR receptors affect the cell proliferation, differentiation, and migration of cancer cells [50]. Furthermore, another growth factor—placental growth factor (PlGF)—controls angiogenic and inflammatory responses, because it allows the formation of PlGF/VEGF homodimer/heterodimer and VEGF-competitive binding to the VEGF receptors and sFlt-1. Moreover, dysregulation of the insulin-like growth factor (IGF)-axis is involved in the oncogenesis and metastasis of various solid tumors [51].

Chemokines and cytokines are among the therapeutic targets in cancer treatment. There are studies suggesting the influence of the inhibition of VEGF and/or TGF-β pathways on the TME. It is currently being discussed whether such inhibition might convert the immunosuppressive characteristics of the TME into immune-supportive ones. Several studies show that this inhibition might enhance sensitivity to immunotherapy such as PD-1/programmed cell death-ligand 1 (PD-L1) inhibitors [52]. Moreover, targeting the VEGF/VEGFR pathway, including neutralizing antibodies to VEGF or VEGFR and receptor tyrosine kinase inhibitors, has shown significant efficacy in patients with NSCLC [53].

EVs

Characterization, biosynthesis, role in cancer biology

EVs are spherical and membrane-bound vesicles that are secreted into the intercellular space and participate in intercellular communication. Based on their origin and size, they can be divided into three subpopulations: EXOs, microvesicles (MVs), and apoptotic bodies (ABs) [54]. EXOs are single-membrane EVs, ranging from 30 to 150 nm in diameter, that originate from endosomal membranes. MVs are a type of EV that range from 100 nm to 1 μm in diameter and are formed by direct budding outside the cell. ABs, on the other hand, range from 50 nm to 5,000 nm in diameter. They are secreted by dying cells, and their composition differs from EXOs and MVs in that they contain primarily chromatin and intact cell organelles [55]. The biogenesis of EXOs is complex and dynamically controlled. During the first stage, primary endocytic vesicles fuse, leading to the formation of an early endosome (EE). Some of the EEs are returned to the plasma membrane, and some are transformed into multivesicular bodies (MVBs), which are characterized by having several intraluminal vesicles (ILVs) inside. ILVs are secreted into the extracellular space as EXOs after the fusion of MVBs with the cell membrane or fuse with lysosomes and are degraded [56]. Vesicles that bud into the extracellular space from the plasma membrane are sometimes called MVs [57]. The contents of EXOs include numerous proteins (including enzymes, transcription factors, and receptor proteins), amino acids, lipids, DNA, mRNA, and non-coding RNA (ncRNA) (including microRNA [miRNA], long non-coding RNA [lncRNA], and circular RNA [circRNA]) (Fig. 4). Interestingly, the

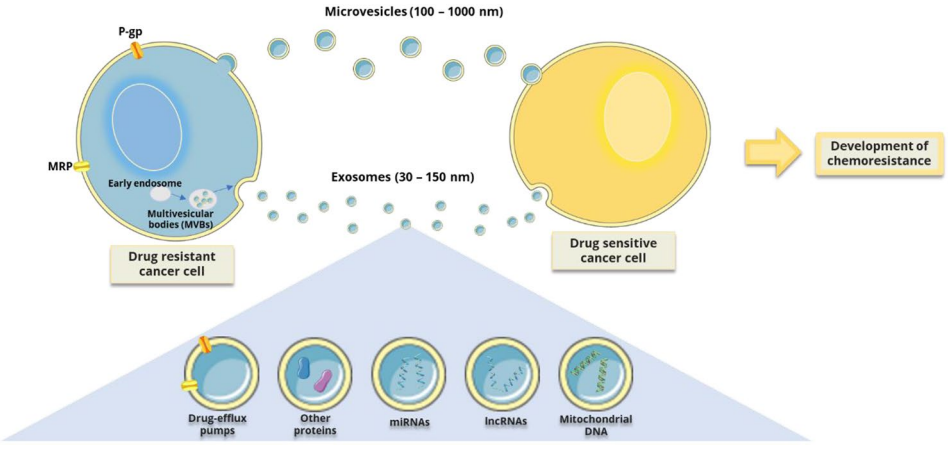

Fig. 4 Scheme of the transport of factors leading to the development of chemoresistance via extracellular vesicles (EVs). Chemotherapy-resistant cells secrete various types of EVs (exosomes and/or microvesicles) into the intercellular space. EVs contain factors leading to the development of chemoresistance in cells previously sensitive to treatment. EVs may contain drug efflux pumps (e.g., P-glycoprotein, multidrug resistance-related protein 1), other types of proteins, microRNA, long non-coding RNA, and DNA (e.g., mitochondrial DNA)

RNA components in EXOs are different from those present in parental cells [56].

The mechanisms underlying the selective sorting of elements transported in EXOs are not fully understood. However, both endosomal sorting complexes required for transport (ESCRT) and ESCRT-independent mechanisms are involved [58]. Recent studies have found that cisplatin-resistant ovarian cancer cells have higher numbers of ILVs, MVBs, and ESCRT components than cisplatin-sensitive ovarian cancer cells. The secretion of MVBs as EXOs and their degradation are dependent on Ras-associated binding (RAB) GTPases. Interestingly, silencing Rab-27 A in chemoresistant ovarian cancer cells restored normal lysosomal function, led to an increase in their sensitivity to treatment, and reduced the number of secreted EVs [59]. Intercellular communication via EXOs is crucial for numerous physiological and pathological processes. Moreover, numerous studies have shown that cancer cells produce more EXOs compared to normal cells and that the proteins responsible for their biogenesis and secretion are upregulated in various cancers. EVs are particles that are released from cells into the extracellular space under both pathological and normal conditions. It is well-established that cancer cells secrete more EVs compared to non-cancerous cells and that, intriguingly, several proteins involved in EV biogenesis and secretion are upregulated in various tumors. Recent studies have revealed that EVs facilitate interactions between cancer cells and their microenvironment and play a substantial role in tumor growth. EVs are involved in several aspects of cancer progression, including angiogenesis, organotropism, pre-metastatic niche formation, metastasis, and chemoresistance. Consequently, inhibiting EV release from cancer cells and the surrounding TME has been proposed as an ideal strategy for treating cancer and associated paraneoplastic syndromes. Recently, EVs have shown immense benefits in preclinical settings as novel drug delivery vehicles. This review provides a brief overview of the role of EVs in various hallmarks of cancer, focusing on (i) strategies for cancer treatment by therapeutically targeting the release of tumor-derived EVs and (ii) EVs as valuable drug delivery vehicles. Additionally, we outline the drawbacks of existing anti-cancer treatments and the future prospects of EV-based therapeutics [60]. Tumor-derived EXOs participate in the transfer of functional biological cargoes that, through the activation of various signaling cascades, are involved in the processes of tumor transformation, proliferation, progression, metastasis formation, immune escape, and chemoresistance. EVs determine the development of chemoresistance as well as resistance to immunotherapy, radiotherapy, and targeted therapy by delivering molecules that affect the efflux of anticancer drugs, alter the activity of numerous signaling pathways such as PTEN and PI3K/Akt, control cell metabolism, and affect autophagy or cancer stemness [61]. Furthermore, EVs modulate interactions not only between cancer cells but also between cells forming the TME, which contributes to TME remodeling, niche formation, and treatment resistance [62] (Fig. 5).

Analysis of EXO and MV subpopulations isolated from ovarian cancer cells showed that EVs can activate fibroblasts to form CAFs, affecting their proliferation, invasiveness, and enzyme expression. The EXO-like subpopulation likely plays a more significant role in this process, indicating that different EV subpopulations have distinct functions [63]. Research has consistently shown that intercellular communication via EVs contributes to chemotherapy resistance in various cancers, including

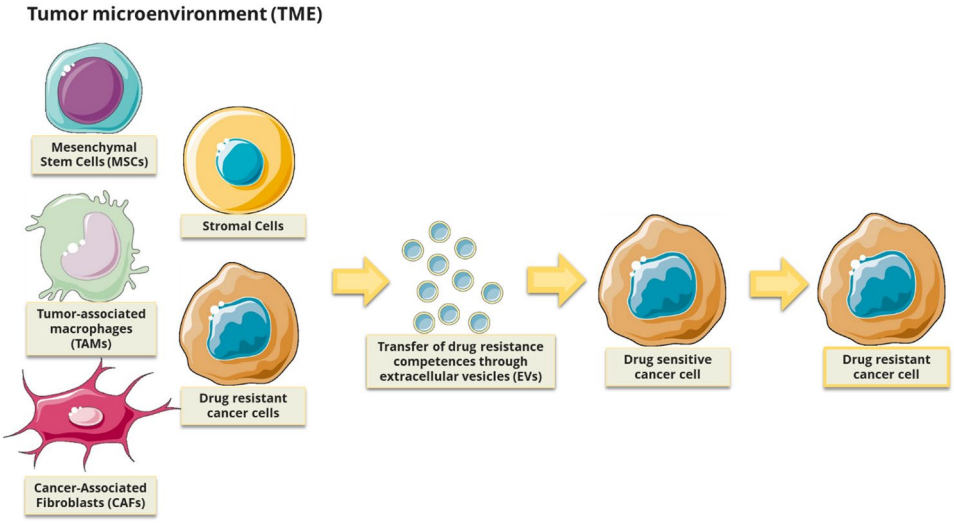

Fig. 5 Scheme of the transport of drug-resistant competencies by EVs spreading from different cell types constituting the TME

ovarian, breast, genitourinary, pancreatic, colorectal, lung, melanoma, and osteosarcoma [61].

Proteins and drug efflux pumps transported by EVs

One of the main reasons for failure in the treatment of malignant tumors is the presence of the MDR phenotype. ATP-binding cassette (ABC) transporters are closely associated with the development of MDR, enabling the active pumping of various substances, including drugs, from cells into the extracellular space. More than 40 ABC transporters have been identified in humans, with at least 11 of them involved in MDR. Major ABC transporters associated with MDR include P-glycoprotein (P-gp), MDR-associated proteins (MRPs), and breast cancer resistance protein (BCRP/ABCG2) [64]. EVs are involved in transporting both functional ABC transporters and proteins and nucleic acids between cells, which affects their expression and activity [61]. EXOs isolated from multidrug-resistant MG-63DXR30 osteosarcoma cells were able to be engulfed by sensitive parental cells and induce a Dox-resistant phenotype in these cells by delivering MDR-1 and P-gp mRNAs [65]. Similarly, ovarian cancer cells from the treatment-resistant A2780/PTX cell line were able to produce and release P-gp-containing MVs, which led to the development of a 5-fold poorer response to treatment with adriamycin (ADR) and paclitaxel among initially treatment-sensitive cells [66]. It has also been reported that EXOs may participate in the delivery of P-gp from drug-resistant breast cancer cells to sensitive cells, thereby leading to the development of resistance to docetaxel treatment [67]. Recently, it was reported that ABCB4 could be transported via EXOs from glioma stem cells to differentiated glioma cells and induce TMZ resistance there [68]. Nuclear factor erythroid 2-related factor 2 (Nrf2), on the other hand, has been shown to influence the resistance of colon cancer cells to oxaliplatin treatment. Incubation of EXOs from the resistant LS174T/R line that contained Nrf2 with cells from the treatment-sensitive LS174T/S line conditioned increased P-gp expression in these cells [69]. MDR has also been shown to be associated with transient receptor potential (TRP) channels, which are among the Ca^{2+} permeable ion channels [70]. It has been observed that TrpC5 can be transferred via EXOs from chemoresistant breast cancer cells to chemosensitive cells, thereby leading to their acquisition of resistance to treatment with ADR. Acquisition of TrpC5 by the cell results in the generation of a functional Ca^{2+} transport channel, which is associated with the activation of signaling pathways and leads to the production of P-gp/ABCB1 [71]. A correlation was also demonstrated between TrpC5 and the CaMKKβ/AMPKα/mTOR pathway-dependent cytoprotective autophagy of breast cancer cells [72]. Moreover, circulating EXOs in the peripheral blood contained TrpC5, and their number was associated with TrpC5 expression in breast cancer cells and the development of chemoresistance [73]. EVs can also carry many other proteins affecting various signaling pathways, cell metabolism, and the TME [62]. For example, in a cell apoptosis assay, it was shown that EXOs (Exo/R) produced by a 5-FU-resistant colon cancer cell line (RKO/R) compared to EXOs (Exo/P) produced by the parental RKO/P cell line significantly promoted cell survival. It was suggested that this effect was due to p-STAT3 present in the EXOs, which was expressed in both the nucleus and cytoplasm of RKO/R cells but not in the nucleus of RKO/P cells. Moreover, the use of a STAT3 protein inhibitor and EXOs to treat recipient cells allowed the abrogation of 5-FU-induced resistance to Exo/R. The molecular mechanism of this resistance is most likely related to inhibition of the caspase cascade [74]. In turn, plasma gelsolin (pGSN) transported by EXOs plays a role in the formation of chemoresistance in ovarian cancer cells and the disruption of immune surveillance. Resistance to cisplatin treatment is related to the induction of $CD8^+$ T-cell apoptosis and the promotion of glutathione (GSH) production [75, 76]. pGSN was more strongly expressed and secreted in cells resistant to anticancer treatment than in chemosensitive counterparts. Increased pGSN expression also correlated with poorer patient survival [77]. More recently, pGSN has been reported to act as an inhibitor of the anti-tumor effects of M1 macrophages. Treatment-resistant ovarian cancer cells secreted more pGSN-containing small EVs (sEVs). The pGSN taken up by M1 macrophages, on the one hand, activated caspase-3 leading to apoptosis and, on the other hand, was associated with a secondary response in which TNFα and iNOS production was reduced. Taken together, these two effects led to an impaired ability of M1 macrophages to kill cancer cells [78]. Moreover, total pGSN/sEV-pGSN proved to be the best predictor of the efficacy of anticancer treatment, outperforming such biomarkers as CA125, total pGSN, and sEV-pGSN [79]. Upregulation of DNA methyltransferase 1 (DNMT1) also led to increased chemoresistance of ovarian cancer cells to cisplatin treatment. Coincubation with EXOs containing DNMT1 stimulated endogenous expression and resulted in host cell resistance to cisplatin cytotoxicity. Reversal of this effect was possible by using the EXO inhibitor GW4869, indicating the potential of using such inhibitors in combination with cisplatin in cisplatin-resistant patients [80]. It was also shown that EXOs derived from ovarian cancer cell lines that were cultured under hypoxia contained more potent oncogenic proteins STAT3 and FAS. Hypoxia also conditioned an increase in the number of secreted EXOs due to an increase in Rab27 activity and a decrease in Rab7, LAMP1/2, and NEU-1 activity [81]. PDGFRβ transport in EVs derived from melanoma cells with a BRAF mutation

to cells sensitive to BRAF inhibitor treatment led to the development of a treatment-resistant phenotype in previously sensitive cells [82]. In contrast, EXO-mediated transport of acid sphingomyelinase was associated with the development of resistance to melphalan or bortezomib treatment among MM cells [83]. Recently, Xenopus kinesin-like protein 2 (TPX2), which is a microtubule-associated protein with an important role in mitosis and spindle formation, has been shown to play a key role in docetaxel chemoresistance [84]. Overexpression of TPX2 in NSCLC cells led to the development of chemoresistance by increasing β-catenin and C-myc accumulation, while excess TPX2 was packaged into vesicles and transported to neighboring cells, resulting in decreased sensitivity to treatment [84]. Recently, the involvement of VEGFA carried by EXOs derived from chemoresistant CAFs (R-CAF) in promoting cisplatin resistance among colorectal cancer cells has also been proposed. VEGFA was highly expressed in R-CAFs and EXOs derived from them, and their delivery to colon cancer cells from the HT29 lineage affected their viability, angiogenesis, and resistance to treatment [85]. Exosomal PD-L1 was positively correlated with chemoresistance in patients with esophageal squamous cell carcinoma. EXOs from the paclitaxel-resistant EC-9706 cell line decreased the sensitivity to treatment of the initially sensitive EC-9706 cell line, most likely through regulation of the STAT3/miR-21/PTEN/Akt axis. Furthermore, PD-L1 may increase miR-21 expression [86].

ncRNA transported by EVs

ncRNA found in EVs plays an important role in many physiological and pathological processes occurring in the human body. ncRNAs (miRNAs, small interfering RNAs [siRNAs], circRNAs, antisense RNAs, piwi-interacting RNAs, and lncRNAs) are classified as functional RNAs that also play a key role in tumorigenesis, cancer progression, and chemoresistance formation. Currently, by far the most studied exosomal ncRNA subtypes are miRNA and lncRNA [87]. miRNAs post-transcriptionally regulate several genes through complementary pairing and affect mRNA expression in target cells. In turn, circRNAs and lncRNAs influence miRNAs (acting as their sponges), which in turn indirectly influence the expression of proteins [88]. In recent years, several scientific papers have shown that ncRNA-containing EVs are involved in many key TME processes that mediate metastasis and chemoresistance. Numerous papers have shown that ncRNA-containing EVs derived from chemoresistant cells can induce such resistance in cells that were previously sensitive to treatment [61]. Exosomal ncRNAs can also serve as biomarkers for predicting treatment response and detecting chemoresistance emerging after treatment initiation. Moreover, many ncRNAs are potential targets for therapy to overcome treatment resistance [89].

miRNAs transported by EVs The role of miR-21, miR-222, and miR-155 in chemosensitivity has been particularly documented, with their widespread presence demonstrated in breast cancer, colorectal cancer, ovarian cancer, and patients with diffuse large B-cell lymphoma [90]. miR-21 acts on a variety of genes that influence numerous intracellular signaling pathways, which can induce chemoresistance, modify cellular metabolism, facilitate drug detoxification, and increase genome instability. In recent years, some methods to reduce miR-21 downregulation have been proposed, but much research is still needed to determine the best strategy for reversing chemoresistance [91]. Exosomal miR-21 derived from hypoxic NSCLC cells promotes chemoresistance by downregulating phosphatase and tensin homolog (PTEN) [92]. Another study has shown that nicotine can induce miR-21-3p, which, due to negative regulation of FOXO3a, is associated with a reduced response of lung cancer cells to treatment with cisplatin or docetaxel. Furthermore, knockdown of miR-21-3p re-sensitizes lung cancer cells to treatment, making it possible to use this phenomenon as a new treatment strategy for patients with chemoresistant lung cancer [93]. Recently, hypoxia was shown to also stimulate CAFs to secrete more miR-21-rich EVs, which was associated with the activation of the miR-21/RAS/ATK/extracellular signal-regulated kinase (ERK) pathway in pancreatic cancer cells and the development of their resistance to gemcitabine treatment [94]. High expression levels of miR-21 may also increase the proliferation, invasion, and migration capacity of ovarian cancer cells. Moreover, higher expression of miR-21 was observed in SKOV3/DDP cells (cisplatin-resistant) compared to cisplatin-sensitive SKOV3 cells [95]. Treatment of SKOV3 cells with EXOs isolated from SKOV3/DDP led to inhibition of the alpha 1 subunit of pyruvate dehydrogenase E1, which was associated with reduced cell apoptosis and glycolysis [96]. Additionally, the role of miR-21 in ovarian cancer cell resistance may be influenced by interactions with CD44v6 and P-gp [95]. miR-21 has also been observed to play an important role in the polarization of M2 macrophages, which also contributes to the development of chemoresistance in ovarian cancer cells. Moreover, the prognosis of patients with increased expression of M2 macrophages and decreased expression of M1 macrophages is worse [97]. Recent studies highlight the role of miR-6836 in promoting resistance of epithelial ovarian cancer cells to cisplatin treatment through the DLG2-YAP1 signaling pathway [98]. Moreover, it was reported that overexpression of miR-296-3p in EVs secreted by CAFs closely correlates with the progression and chemoresistance of ovarian cancer cells, making them poten-

tially useful for diagnosis or as a therapeutic target [99]. MiR-21 is also implicated in the development of chemoresistance in breast cancer cells. It has been discovered that Dox treatment affects MSCs and the EXOs they produce, whereas miR-21-5p expression increases. MSC-derived EXOs induce chemoresistance in breast cancer cells via the *S100A6* gene. Moreover, inhibition of miR-21-5p expression in MSCs and EXOs abolished Dox resistance [100]. miR-21-5p also suppresses the sensitivity of HCC cells to cisplatin treatment by targeting the FAS ligand [101]. miR-222 can reduce the response of breast cancer cells to ADR treatment through the PTEN/Akt/p27 kip1 signaling pathway. This effect can be reversed by LY294002, an inhibitor of ADR [102]. Exosomal miR-222 can also induce M2 macrophage polarization [103]. It has been shown that treatment with cisplatin in combination with anti-miR-221/222 may lead to increased treatment effectiveness [104]. HCC chemoresistance has also been linked to miR-222. GAS5-mediated sponging of this miRNA was associated with improved cell sensitivity to cisplatin [105]. Overexpression of miR-21-5p and miR-15a-5p in patients with AML was associated with reduced apoptosis induced by treatment with daunorubicin or Ara-C. This effect was shown to be due to the targeting of these miRNAs to three proapoptotic genes: targeting programmed cell death factor 4 (PDCD4), ARL2, and BTG2 [106]. Treatment of pancreatic ductal adenocarcinoma (PDAC) with gemcitabine may cause chemotherapy resistance associated with aberrant expression of multiple miRNAs, including miR-21. Moreover, miRNA-21 may play a role in PDAC mesenchymal transformation, making it a possible biomarker of aggressiveness in this cancer [107]. Zhang et al. recently synthesized a stimuli-responsive poly(beta-aminoester) (PBAE)-based polymeric nanoparticle (miR-21i@HA-Gem-SS-P12) that can co-deliver miR-21 siRNA (co-delivered miR-21 modulator) and gemcitabine. It showed improved tumor inhibition in PDAC in vitro and in vivo due to the synergism of gemcitabine and miRNA-21i. Additionally, gemcitabine's cargo release was associated with the effects of increased reduction stimuli in TME on disulfide bonds that couple the chemotherapeutic to PBAE [108]. Each year, numerous new papers describe new miRNAs involved in the development of chemoresistance. Recent studies suggest significant involvement of miRNAs such as miR-21, miR-155, miR-27, miR-365, miR-494, miR-375, and miR-145 in the development of oral cancer chemoresistance. Expression of miR-375 is associated with upregulation of rearranged L-myc fusion and downregulation of centriolar protein B, while lack of miR-27 is associated with expression of nucleophosmin 1 [109]. Previously, bioinformatics analyses also showed a correlation between miR-21-5p-enriched EXOs and metastasis, chemoresistance, and poor survival of oral squamous cell carcinoma patients. Additionally, increased activity of EXOs derived from CSCs positively correlated with increased regulation of PI3K, STAT3, and TGF and was associated with the transformation of the gingival fibroblasts phenotype into the CAF phenotype. Interestingly, these effects were inhibited by treatment with ovatodiolide, which is a biologically active component of *Anisomeles indica* [110]. Recent studies have highlighted the role of EVs transporting tumor cell-derived miR-210 into biliary tract cancer cells in the development of resistance to chemotherapy. miR-210 acts by specifically reducing RECK expression [111]. Transport of miR-301b-3p via EVs from mesenchymal stem cells (MSCs) to gastric cancer cells has also been described. miR-301b-3p promoted cancer cell chemoresistance by inhibiting thioredoxin interacting protein [112]. Moreover, it was observed that EV-transferred miR-31-5p induced chemoresistance in pancreatic cancer cells both by affecting the LATS2 pathway in cancer cells and by affecting the Hippo pathway in pancreatic stellate cells (PSCs). PSCs, in response, produced SPARC protein, which in turn stimulated ERK signaling in pancreatic cancer cells. Additionally, it was observed that higher expression of miR-31-5p in the tissue matrix of patients was associated with their shorter survival [113]. Furthermore, it has been shown that miR-432-5p-containing EXOs produced by CAFs present in the TME of prostate cancer are associated with the inhibition of ferroptosis via the effect on ChaC glutathione-specific gamma-glutamylcyclotransferase 1 and thus influence the development of chemoresistance [114]. It was also reported that miR-34a-5p could be transferred from Dox-resistant to treatment-sensitive breast cancer cells and induce chemoresistance in them by affecting NOTCH1 expression. Breast cancer is the most common cancer among women. ADR, also known as Dox, is a commonly used chemotherapeutic agent for breast cancer patients, however, the susceptibility of tumor cells to develop resistance to Dox has severely limited its clinical use. One new promising therapeutic target for breast cancer patients is EXOs. The objective of this study was to investigate the role of EXOs in regulating Dox resistance in breast cancer. In this study, the EXOs from both types of cells were extracted by differential centrifugation. The effect of EXOs on drug resistance was assessed by laser confocal microscopy, MTT assay, and qRT-PCR. The miRNA was transfected into cells using Lipofectamine 2000, which was then evaluated for downstream genes and changes in drug resistance. EXOs from MCF-7 cells (MCF-7/exo) and MCF-7/ADR cells (ADR/exo) were effectively extracted. The ADR/exo was able to endocytose MCF-7 cells and make them considerably more resistant to Dox. Moreover, a significant difference in miR-34a-5p expression was observed in MCF-7/ADR and ADR/exo compared to MCF-7 and MCF-7/exo. Among the miR-34a-5p target genes, NOTCH1 displayed

a clear change with a negative correlation. Additionally, when miR-34a-5p expression was elevated in MCF-7/ADR cells, the expression of miR-34a-5p in ADR/exo was also enhanced alongside NOTCH1, implying that EXOs may carry miRNA into and out of cells and perform their function. In conclusion, EXOs can influence Dox resistance in breast cancer cells by regulating miR-34a-5p/NOTCH1. These findings provide novel insights for research into the causes of tumor resistance and the enhancement of chemotherapy efficacy in breast cancer [115]. Reprogramming the secretory profile of secreted EVs could significantly contribute to overcoming treatment resistance. Recently, it was shown that alpha-hederin can sensitize paclitaxel-resistant NSCLC cells by inhibiting the TGFβ/SMAD2 pathways and reprogramming the activity of some miRNAs. Alpha-hederin increased the EV-mediated secretion of some types of miRNAs, including miR-21-5p, miR-23a-3p, and miR-125b-5p, which also led to changes in TGFβ/SMAD activity [116].

lncRNAs transported by EVs In recent years, there have been numerous reports that lncRNAs influence the development of chemoresistance in various types of cancer cells [61]. The lncRNA named small nucleolar RNA host gene 7 (SNHG7) has been detected in EXOs from docetaxel-resistant lung adenocarcinoma cells. It is also possible to transfer SNHG7 via these EVs to parental lung adenocarcinoma cells, which, in turn, is associated with the development of chemoresistance. SNHG7 induces autophagy through the recruitment of human antigen R and polarization of M2 macrophages by stimulating the PI3K/AKT signaling pathway. Functional assays have proven that silencing SNHG7 leads to increased sensitivity of lung adenocarcinoma cells to chemotherapy and a reversal of M2 macrophage polarization, making it a potential therapeutic target [117]. NSCLC tumors resistant to cisplatin treatment showed higher SNHG7 expression than tumors sensitive to such treatment [118]. SNHG7, via miR-34a sponging, also mediates breast cancer chemotherapy resistance [119]. Furthermore, drug susceptibility analysis and in vitro experiments also suggest the involvement of SNHG7 in the formation of chemoresistance in colon adenocarcinoma [120]. Moreover, lung cancer cell-derived EXOs enriched in FOXD3-AS1 promote the proliferation, invasion, and resistance of lung cancer cells to 5-FU through expression of ELAVL1 and activation of the PI3K/Akt pathway in cells of lineages that previously showed no chemoresistance [121]. Another lncRNA carried by EVs, APCDD1L-AS1, confers resistance to 5-FU in oral squamous cell carcinoma cells through the miR-1224-5p/NSD2 axis [122]. Autophagy and consequently chemoresistance to docetaxel can also be regulated by exosomal LOC85009. This is another lncRNA that may become a target for reversing docetaxel resistance [123]. Also involved in docetaxel resistance is lincROR, a lncRNA that stabilizes the structure of the MYH9 protein, which translates into activation of the β-catenin/HIF1α pathway. LincROR can be transported via EXOs to prostate cancer cells, where it induces immunity [124]. One of the biggest problems encountered during the treatment of triple-negative breast cancer (TNBC) is the developing resistance of tumor cells to docetaxel. LINC00667 levels have recently been observed to be higher in EXOs derived from docetaxel-resistant TNBC cells than in EXOs derived from cancer cells that are sensitive to this chemotherapeutic agent. Furthermore, exosomal LINC00667 could induce chemoresistance to docetaxel in cells previously sensitive to it, as a result of miR-200b-3p/Bcl-2 axis regulation [125]. Additionally, MALAT1 transported by breast cancer cell-derived EVs may accelerate cellular metastasis and the development of chemotherapy resistance by affecting the VASP/Rap1 signaling axis [126]. Moreover, it was observed that M2-polarized TAMs could secrete MALAT1-enriched EXOs into the gastric cancer microenvironment. This was associated with the activation of β-catenin and HIF-1α signaling pathways and the promotion of cancer cell progression [127]. It was also shown that hypoxia of the TME in breast cancer led to increased secretion of EVs by CAFs. EVs affected breast cancer cells by delivering lncRNA H19, which recruited DNMT1. This led to decreased expression of miR-497 and the development of chemoresistance, as well as the promotion of metastasis and cell growth [128]. Recently, a novel lncRNA, CAC-Clnc, was identified that promotes chemoresistance in colorectal cancer cells. Interestingly, determining the level of exosomal CACClnc in the plasma of patients who are to undergo chemotherapy for colorectal cancer may prove useful in predicting the effectiveness of treatment [129]. Additionally, lnc-FAL1 promotes colon cancer resistance to oxaliplatin-based treatment. It is produced in CAFs and transported to cancer cells via EVs [130]. Overexpression of lncRNA small nucleolar RNA host gene 11 (SNHG11) was observed in bevacizumab-resistant colon cancer tissues and cells. SNHG11 was also present in EXOs, by which it could promote chemoresistance in subsequent cells by modulating miR-1207-5p and ABCC1 in them. In vivo silencing of SNHG11 abrogated bevacizumab resistance [131]. Recently, CAF-derived EXOs were shown to promote anticancer therapy resistance and EMT of colon cancer cells by transporting LINC00355. These processes were associated with the inhibition of miR-34b-5p expression by LINC00355 and the consequent increase in CRKL expression (a target gene of miR-34b-5p) [132]. An interesting example of a lncRNA carried by EVs is HOTAIR. HOTAIR is present in serum-derived EVs from patients with GBM. Co-culture with GBM cells facilitated cell proliferation, led to the development of more malignant

phenotypes, and was associated with the development of TMZ resistance. Increased levels of HOTAIR were associated with decreased levels of miR-526b-3p and increased levels of EVA1 [133]. Recently, it was reported that the lncRNA myocardial infarction-associated transcript, contained in cancer cell-derived EXOs, can mediate the formation of esophageal cancer cell resistance to paclitaxel through activation of the TAF1/SREBF1 axis [134].

TME cells secreting EVs

Communication between the cells in the TME is a complex and dynamic system. Numerous pathways are involved in the processes of both cancer development and MDR. EVs are one of the most crucial parts of communication interactions and, therefore, different cells producing them are the main subject of many recent studies [135, 136].

MSCs MSCs are a group of non-hematopoietic pluripotent stem cells with high self-renewal and multidifferentiation abilities, which might, therefore, induce MDR. Karnoub et al. conducted a study in which they demonstrated that bone-marrow-derived human MSCs greatly increased cancer cells' metastatic potency [137].

However, there are studies that suggest MSCs as a therapeutic target. In in vivo models, MVs from BM-MSCs in *Helicobacter pylori*-associated gastric cancer promoted tumor growth and metastasis in subcutaneous xenograft tumors (all with a significance level of $P<0.05$). Notably, the protein THBS2 exhibited a significant upregulation after *H. pylori* treatment in BMSC-derived MVs ($P<0.05$). Depletion of the THBS2 gene reduced the tumor-promoting capabilities of BMSC-derived MVs in the context of an *H. pylori* infection, both in vitro and in vivo [138]. The secretions of TNBC cells have the capability to trigger a pro-inflammatory response in human adipose-derived MSCs (hADMSC). However, the Gonzalez-Suarez study has proven a therapeutic effect of the green tea polyphenol epigallocatechin-3-gallate (EGCG), because the addition of EGCG significantly modified EVs' genetic material at low oxygen tension. EVs derived from EGCG-treated MDA-MB-231 cells (EGCG-EVs) exhibited decreased levels of CCL2 and IL-1β, while promoting higher expression of CXCL8 and IL-6. These EVs activated CHK-2, c-Jun, AKT, and GSK-3β signaling pathways in hADMSC, but EGCG-EVs specifically diminished the latter two pathways, along with serum starvation-induced senescence markers p21 and β-galactosidase. Notably, EGCG treatment led to a reduction in the mitochondrial content within EVs derived from TNBC cells [139].

A recent study regarded a potential mechanism through which EV-encapsulated NEAT1, derived from adipose-derived MSCs (ADSCs), could contribute to gemcitabine resistance in pancreatic cancer. EVs derived from ADSCs containing NEAT1 promoted pancreatic cancer cell proliferation, migration, and gemcitabine resistance in vitro, and enhanced tumorigenicity in vivo by inhibiting miR-491-5p and SOCS3, while upregulating Snail. Therefore, these outcomes create a new possible strategy for addressing gemcitabine resistance in pancreatic cancer. However, further research is essential to address this potential therapeutic target [140].

Stromal cells According to a study carried out by Mirjam et al., stromal cells might play an important role in expanding breast cancer cell subpopulations, which induce not only resistance to therapy but also tumor growth. Stromal cells are believed to excrete EVs, which lead to the activation of intracellular pathways and, as a consequence, induce MDR among breast cancer cells [141]. Moreover, there are studies suggesting the influence of EVs derived from bone marrow stromal cells on the bortezomib resistance of MM. The study by Tu et al. has shown that clathrin- and caveolin-dependent endocytosis, along with macropinocytosis, were the primary pathways through which sEVs facilitated communication between bone marrow stromal cells and MM cells. Inhibition of endocytosis mitigated the sEV-induced decrease in chemosensitivity to bortezomib, thereby augmenting its effectiveness against MM [142].

CAFs CAFs, one of the cell types in the TME, play a crucial role in promoting tumor growth and metastasis. Not only can they alter the structure of the ECM and encourage EMT, but they can also interact with cancer cells and other stromal cells by releasing growth factors, cytokines, chemokines, and EXOs [143, 144]. A recent study carried out by Chang has demonstrated significant effects of CAFs in promoting leucine-rich repeat-containing G-protein coupled receptor 5 (LGR5)-marked liver tumor-initiating cells (TICs) and has shown the influence of the TME on stem cell-related therapy. Thus, it seems possible to combine CAF-targeted and tumor stem cell-targeted therapy in treating liver cancer. They used a co-culture organoid model, consisting of murine liver tumor $LGR5^+$ TICs and CAFs in 3D co-culture, to investigate their mutual interaction. Their results also revealed notably larger sizes and numbers of formed organoids when $LGR5^+$ cells were co-cultured with CAFs, both in cell–cell contact and paracrine signaling in vitro, compared to $LGR5^+$ cells alone. Furthermore, CAF-mediated promotion of tumor formation, growth, and metastasis was decreased after a specific knockout of LGR5-expressing cells [145]. The activation of CAFs plays a crucial role in tumor progression and might be caused by cancer-derived EVs. Louback conducted a study on breast cancer cells and focused on EV secretion and its effect on CAFs. It turned out that ASA

reduced the distribution of EVs secreted by MDA-MB-231 tumor cells. Furthermore, fibroblasts stimulated with EVs derived from MDA-MB-231 treated with ASA (EV-ASA) had decreased expressions of alpha-smooth muscle actin and matrix metalloproteinase-2. Invasion assays with a 3D fibroblast spheroid model revealed reduced MDA-MB-231 invasion toward fibroblast spheroids pretreated with EV-ASA compared to spheroids with EV-CTR-stimulated fibroblasts. The authors of this research suggest that ASA might partially inhibit the stimulation of CAFs by EVs, because ASA might interfere with tumor communication by diminishing EV secretion by breast tumor cells and also by stimulating fibroblasts to become CAFs [146].

A recent study has proven the crucial role of DACT3-AS1 (antagonist of beta-catenin3 antisense1) in gastric tumor development. Not only does DACT3-AS1 suppress cell proliferation and migration of cancer cells, but it also reduces invasion by targeting the miR-181a-5p/sirtuin 1 axis. DACT3-AS1 is transmitted from CAFs to gastric cells mainly via EXOs. It is found to have a suppressive influence on malignant transformation and oxaliplatin resistance. Moreover, it could be used for the treatment of gastric cancer (Fig. 2) [147]. Another recent study indicates that CAF-derived miR-146a-5p can lead to stemness and increased chemoresistance in urothelial bladder cancer (UBC). CSCs are crucial in both chemoresistance and recurrence of numerous cancer types, including UBC. Overexpression of miR-146a-5p in CAFs led to CAF-to-UBC cell interactions and cancer stemness and thus created chemoresistance to treatment with gemcitabine and cisplatin. Exosomal miR-146a-5p might be used as a biomarker of UBC recurrence and as a potential therapeutic target [148]. Furthermore, EXOs derived from CAFs in PDAC have been proven to promote chemoresistance in PDAC cells following gemcitabine treatment. miR-3173-5p derived from CAF EXOs sponged ACSL4 and inhibited ferroptosis after uptake by cancer cells, thereby maintaining communication with cancer cells. Furthermore, this pathway might be a promising target for gemcitabine resistance in pancreatic cancer [149].

Macrophages Macrophages are the largest noncancerous cell population within the TME. They can be divided into two subtypes: M1 macrophages, which have antitumor properties, and M2 macrophages, which exhibit pro-tumor functions. In the context of the cancer stroma, resident macrophages are known as TAMs, usually of the M2 phenotype. They play key roles in regulating cancer drug resistance. EVs originating from TAMs are responsible for mediating cancer drug resistance. For instance, TAMs convey miR-27a-3p, miR-22-3p, and miR-221-3p to glioblastoma stem cells via EXOs. This transfer induces resistance to radiotherapy by targeting CHD7 and modulating the RelB/P50 and STAT3 pathways, ultimately triggering a shift from a proneural to a mesenchymal state [150]. Additionally, exosomal miR-365 from TAMs contributes to gemcitabine resistance in PDAC by increasing the pool of nucleotide triphosphates and inducing the expression of the enzyme cytidine deaminase. Moreover, miR-222-3p-containing M2 macrophage-derived EVs increase chemoresistance in pancreatic cancer due to TSC1 inhibition and activation of the PI3K/AKT/mTOR pathway [151]. Furthermore, miR-223 and miR-21 contained in TAM-derived EXOs might cause cisplatin resistance in gastric cancer and ovarian cancer, respectively [152, 153].

Other cell types The relationship between Tregs and exosomal miRNAs seems to be unknown; however, results from a recent study demonstrate that tumor-secreted miR-208b might promote Treg expansion by targeting PDCD4. Furthermore, it can relate to lower oxaliplatin-based chemosensitivity in colorectal cancer. Thus, exosomal miR-208b might be used as a predictive biomarker for oxaliplatin-based therapy response, as well as a potential immunotherapeutic target [154].

Adipocytes might also excrete EXOs, which could lead to cancer drug resistance. EXOs collected from MM adipocytes were found to protect MM cells from chemotherapy-induced apoptosis. Raised levels of lncRNA in MM cells were related to worse outcomes in patients, as MM cells promoted lncRNA packaging into adipocyte EXOs by METTL7A-mediated lncRNA m6A methylation [155].

Microbiome effects on cancer chemoresistance

The human microbiome, understood as the totality of microorganisms inhabiting the human body, plays a key role in many physiological as well as pathological processes. The microbiome, particularly the gut microbiome, influences the development and course of many diseases, including cancer. The composition of the microbiome can affect the TME and modulate the proliferation, invasiveness, metastasis, and response to treatment of cancer cells [156, 157]. It has been shown that bacteria, especially *Gammaproteobacteria*, can affect gemcitabine metabolism. By possessing the appropriate isoform of the bacterial enzyme cytidine deaminase, intratumor bacteria can convert this chemotherapeutic agent to its inactive form, which may have implications for the development of PDAC chemoresistance to gemcitabine treatment [158]. Colorectal cancer can be colonized by colibactin-producing *Escherichia coli* (CoPEC) [159, 160]. Infection of colon cancer cells with CoPEC was associated with the production of a highly glycerophospholipid microenvironment with reduced immunogenicity, which

enabled cancer cells to generate sufficient energy to survive chemotherapy. Tumor cells could be sensitized to treatment by using an acyl-CoA synthase inhibitor [159]. Moreover, CoPEC-infected colon cancer cells produced a senescence-associated secretory phenotype, resulting in increased resistance to treatment of both infected and uninfected cells. CoPEC infection was also associated with the emergence of chemoresistant CSCs [160]. It was also observed that *Fusobacterium (F.) nucleatum* was abundant in colorectal cancer patients who had relapsed after treatment. Moreover, *F. nucleatum* was shown to promote chemoresistance in cells by modulating Toll-like receptor 4 (TLR4) signaling, which in turn led to activation of the autophagy pathway [161]. Importantly, the effect of *F. nucleatum* on colorectal cancer tumorigenesis could be inhibited by a TLR4 antagonist, indicating a potential role for TLR4 as a therapeutic target [162]. *F. nucleatum* could also induce colorectal cancer cell resistance to oxaliplatin treatment by inhibiting ferroptosis. The E-cadherin/β-catenin/TCF4 pathway has been shown to be associated with excessive glutathione peroxidase 4 production by *F. nucleatum* and consequent inhibition of ferroptosis [163]. Furthermore, it was recently reported that EVs derived from *F. nucleatum* may be associated with oral cancer metastasis and activate autophagic flow [164]. In contrast, another study showed that EVs from *Aggregatibacter actinomycetemcomitans* and *F. nucleatum* reduced the proliferation of metastatic oral squamous cell carcinoma cells and induced apoptosis [165].

Drug-induced tumor heterogeneity

Another important factor that might lead to MDR is intra-tumor heterogeneity. Resistance might result from the Darwinian selection of preexisting cell states, where epithelial or mesenchymal properties are increased or acquired through epigenetic adaptation (EMT). Notably, a preexisting poised chromatin state serves as a foundation for cellular reprogramming driven by epigenetic plasticity during the evolution of tumors induced by drugs [166]. In a recent study, the treatment of leukemic mice with triazene compounds (TZC) in vivo significantly increased the immunogenicity of leukemia cells. This phenomenon, known as drug-induced xenogenization, occurs through point mutations that generate strong tumor neoantigens – drug-induced neoantigens. These immunogenic mutations result from TZC-dependent methylation of O6-guanine in DNA, a process that is inhibited by the DNA repair protein MGMT [167]. Furthermore, metabolic reprogramming involves key metabolic alterations associated with amino acids and acetylated derivatives of amino acids [168]. Amino acids are known to be regulatory components of important metabolic cascades, signaling pathways, and gene expressions [169]. One of the crucial adaptations of cancer cells is increased glycolysis and lactate production to meet heightened energy demands, known as the Warburg effect [170]. Importantly, the Warburg effect persists after the formation of malignant tumor phenotypes. It is known to have constitutive expression mediated by mutations or epigenetic modifications, providing a robust selective survival advantage for primary and metastatic lesions [171]. Thus, targeting cancer-associated metabolic pathways seems to be a promising treatment method to use alongside traditional chemotherapy agents.

Conclusions

Understanding the communication between TME-forming cells is crucial for understanding the mechanisms that lead to cancer progression, metastasis, and chemoresistance. In recent years, significant progress has been made in understanding this environment through the use of 3D models of various cancer tumors and artificial intelligence-based methods [172]. Nevertheless, we are still far from thoroughly characterizing the TME and the communication between its components. We know that both direct intercellular communication and indirect intercellular communication have a significant impact on the formation of resistance to anticancer treatment [7]. Furthermore, the role of not only communication between cancer cells themselves but also communication involving cells such as CAFs, MSCs, macrophages, or stromal cells is emphasized. Literature data on direct intercellular communication within the TME and its relevance to chemoresistance are far scarcer than those that address indirect intercellular communication. GJ connections are important in the formation of chemoresistance in AML to methotrexate and other anticancer drugs [28] and in the formation of resistance in GBM to treatment with TMZ [14]. The involvement of Cxs in the acquisition of chemoresistance by breast and lung cancer cells seems interesting. It should be noted here that the influence of Cxs on the TME is complex and is most likely due to both the formation of functional GJ-type junctions and the role of Cxs as signaling molecules acting on various biochemical pathways, such as the PI3K/AKT pathway [32, 36]. Nowadays, the attention of the scientific world is particularly directed toward indirect intercellular communication, especially communication via EVs. Within these structures, lipids, protein elements, and nucleic acids can be transported. On the one hand, the proteins transported by EVs, which are part of the ABC, SLC, and P pump families, can promote the removal of drugs from cancer cells. On the other hand, EVs can contain various signaling molecules, such as miRNAs and lncRNAs, which can induce cancer tumor chemoresistance by acting on various biochemical pathways [62, 91]. It is now

known that EVs influence the formation of resistance within most cancers, including ovarian cancer, breast cancer, urothelial carcinomas, pancreatic cancer, colorectal cancer, lung cancer, melanoma, and bone cancers [61]. Compounds within EVs represent promising therapeutic targets and can be used as biomarkers of chemoresistance, tumor progression, and recurrence [60]. Future clinical strategies may focus on targeting EVs or inhibiting key signaling molecules involved in cell–cell communication within the TME. For example, therapies that block EV formation or release, or disrupt GJ communication could potentially prevent the transfer of chemoresistance factors between cells, thereby enhancing the efficacy of existing treatments. Clinical trials exploring these targeted approaches are essential to validate their potential in overcoming chemoresistance [10, 173–175]. Recently, numerous new signaling molecules, especially various miRNAs, have been successfully linked to chemoresistance [62]. It is certainly necessary to continue the search for lipids, proteins, and nucleic acids carried by EVs that influence resistance formation to anticancer treatments because they may become future targets for overcoming this resistance. With dozens of new reports published annually on molecules transported by EVs that have a role in chemoresistance, there is a need for ongoing reviews to update our knowledge about the link between TME and chemoresistance.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Competing interests

The authors declare no competing interests.

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