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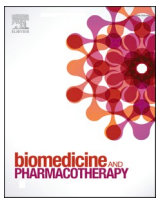

Review

Promising applications of nanotechnology in inhibiting chemo-resistance in solid tumors by targeting epithelial-mesenchymal transition (EMT)

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ABSTRACT

The resistance of cancer cells to chemotherapy, also known as chemo-resistance, poses a significant obstacle to cancer treatment and can ultimately result in patient mortality. Epithelial-mesenchymal transition (EMT) is one of the many factors and processes responsible for chemo-resistance. Studies have shown that targeting EMT can help overcome chemo-resistance, and nanotechnology and nanomedicine have emerged as promising approaches to achieve this goal. This article discusses the potential of nanotechnology in inhibiting EMT and proposes a viable strategy to combat chemo-resistance in various solid tumors, including breast cancer, lung cancer, pancreatic cancer, glioblastoma, ovarian cancer, gastric cancer, and hepatocellular carcinoma. While nanotechnology has shown promising results in targeting EMT, further research is necessary to explore its full potential in overcoming chemo-resistance and discovering more effective methods in the future.

Abbreviations: NP, nanoparticle; EMT, epithelial-mesenchymal transition; MET, mesenchymal-epithelial transition; IL, interleukin; TGF, transforming growth factor; TNF, tumor necrosis factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; HGF, hepatocyte growth factor; CTGF, connective tissue growth factor; EGF, epidermal growth factor; IFN, interferon; PDGF, platelet-derived growth factor; MCP-1, macrophage inflammatory protein 1; RANTES, regulated upon activation normally T-expressed and presumably secreted; VEGF, vascular endothelial growth factor; ANG-2, angiopoietin-2; ANGPTL, angiopoietin-like; siRNA, short interfering RNA; lncRNA, long non-coding RNA; HIF-1, hypoxia-inducible factor-1; mTOR, mammalian target of rapamycin; MAPK, microtubule associated protein kinases; PI3K, Phosphatidylinositol 3-kinase; CSCs, cancer stem cells.

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1. Introduction

1.1. Cancer etiology and pathology

Senescence, demographic expansion, sociodemographic alterations, chronic infections, and a rise in the use of cancer-causing behaviors all contribute to the rising incidence of cancer in the world's population [1]. In 2012, there were 14.1 million newly diagnosed instances of cancer, 8.2 million mortalities from cancer, and 32.6 million individuals surviving with cancer (within five years of diagnosis) around the globe [1]. A pulmonary tumor (1.8 million cases, or 13.0% of the total), breast cancer (1.7 million cases, or 11.9%), and colorectal cancer (1.4 million, 9.7%) were the types of malignancy that were identified the most frequently over the world [1]. The pulmonary (1.6 million deaths, or 19.4% of the total), hepatic (0.8 million deaths, or 9.1%), and stomach tumors (0.7 million, 8.8%) were the most frequent types of cancer that resulted in mortality [1]. Africa, Asia, Central, and South America account for more than sixty percent of the world's newly diagnosed cancer cases, and they also account for seventy percent of the world's cancer-related fatalities. According to predictions derived from the estimations provided by GLOBOCAN in 2012, by the year 2025, there would be significant growth to 19.3 million new instances of cancer diagnosed annually [2–4]. In China in 2015, it was predicted that there were 4292,000 new instances and 2814,000 mortalities from cancer. Of these, the pulmonary tumor was the most frequent cancer and the main reason for cancer-related mortality [5].

It was anticipated that there were 1685,210 new instances of cancer identified in the United States in 2016 and that 595,690 individuals passed away as a result of the condition. Breast cancer, pulmonary and bronchus cancer, prostate tumor, colorectal cancer, bladder cancer, skin melanoma, non-Hodgkin lymphoma, thyroid cancer, renal-pelvis cancer, leukemia, endometrial cancer, and pancreatic cancer were estimated to be the most frequent malignancies in 2016. In 2014, the frequency of individuals surviving beyond a cancer diagnosis achieved approximately 14.5 million. It is anticipated that this number will increase to about 19 million by the year 2024. Approximately $125 billion was spent nationally in the United States on cancer care in 2010, and that number is expected to rise to $156 billion by 2020 [2,3].

1.2. Cancer treatments strategies

Limiting one's exposure to controllable risk factors makes it possible to prevent about sixty percent of all mortalities from cancer. Surgery, radiation therapy, chemotherapeutic approaches, hormone treatment, immunotherapy, and biologically targeted therapy are the primary therapeutic methods utilized in the fight against cancer. Nevertheless, these treatments are only effective if the illness is diagnosed at an initial stage or if they are restricted to specific cancer types (such as leukemia and Hodgkin's lymphomas). Chemotherapy has advanced largely because of our growing understanding of the different cellular and molecular pathways that lead to cancer progression [2,6]. As a result of the difficulty of diagnosing cancer in its early stages, the majority of patients present when the disease has already progressed to an advanced phase, with substantially localized infiltration and metastatic dissemination. These treatments frequently fail when applied to advanced cancers, particularly tumors originating from epithelial tissues, including those found in the lung, colon, breast, prostate, and pancreas [6,7].

Since Goodman and his colleagues pioneered the use of chemotherapy in the management of lymphosarcoma and leukemia at the termination of World War II, the field has progressed a great deal over the past seven decades. Chemotherapy has since become one of the most important clinical methods in cancer management. However, significant resistance and complications have been associated whit therapies as substantial clinical hurdles to an effective cure for cancer. For the greatest cancer cell destruction, chemotherapeutic drugs are administered in conjunction with a maximum tolerable dose because of their narrow safety margins [2,8]. Direct cytotoxic activity, activation of the host immunological reaction, inhibition of the growth processes of tumor cells, and induction of apoptosis are the four methods used to destroy tumor cells [2,8]. There is substantial inter-individual heterogeneity in the pharmacokinetics of most chemotherapeutic medications. As a consequence, the toxicity of these drugs can be unanticipated, and their anticancer effectiveness can differ [4].

1.3. Cancer treatments challenges

The vast majority of patients, nevertheless, do not respond favorably to these treatments (as it mentioned), and they frequently endure severe unintended effects, including diarrhea and hair loss [7]. The fundamental reason for this is due to the fact that the medicine is capable of killing both normal and cancerous cells, but the concentration of the drug within tumor cells is insufficient. Drug resistance and dose-limiting are the two primary obstacles that need to be considered before chemotherapy for cancer patients [2,7].

We are unable to change the fatal nature of cancer, notwithstanding the widespread usage of more than 200 chemotherapeutic medicines (mainly cytotoxic and biologically targeted compounds) in clinical environments. These drugs have only allowed for overall accumulative developments in clinical findings, but this emerges at the cost of tremendous host toxicities [6]. In therapeutic development and implementation, chemotherapeutic medications have had a very low-efficiency rate (~ 5%) so far, which is much lower than medicines in other fields. Alkylating compounds, antimetabolites, anticancer antibiotics, topoisomerase blockers, mitotic inhibitors, corticosteroids, hormones and antagonists, and biologically targeted compounds, including antibiotics, tyrosine kinase blockers, and other pathway inhibitors, are all types of anticancer medicines that can be functionally categorized [6,7,9].

1.4. Overview of Chemo-resistance mechanisms

Apoptosis, mitotic catastrophe, and early aging are three mechanisms by which agents frequently employed in cancer chemotherapy induce cell death. Disruption of DNA or other essential molecules is thought to be a frequent preliminary event after administering the cytotoxic chemicals [10]. This damage is subsequently conveyed by the cellular stress reaction to the stimulation of cellular effector mechanisms in cancerous cells, including the apoptotic pathway[2,10]. Cancer resistance can be widely divided into two types: primary and acquired. These categories are determined by how the tumor reacts to the preliminary treatment. Before any particular intervention, initial drug resistance occurs, while acquired resistance emerges following beginning treatment [11]. Cross-resistance or multidrug resistance (MDR) refers to the development of resistance to numerous structurally dissimilar chemotherapeutic medicines in a subset of patients exposed to a single chemotherapeutic compound over an extended period. At some point during treatment, it is highly likely that most of the patients will acquire resistance to the medication [11–13]. The fundamental processes that contribute to the establishment of cancer drug resistance are complex. These processes include alterations in drug metabolic pathways and transport, mutation amplification or drug targets reactivation, overactivation of alternative mechanisms, interaction with the microenvironment, changed DNA reaction and repairing capacity, genetic rewiring that contributes to deficient cell death and autophagy and their regulatory events, cancer cell-stroma interrelations, the presence of cancerous stem cells, and many more [2,11]. Drug resistance and restricted therapeutic response may both be induced by tumor heterogeneity [13].

1.5. New approaches for cancer therapy by using nanotechnology

The growing number of publications documenting the nanocarriers for drug delivery demonstrates that nanomedicines have been an extremely active field [14]. Passive and active targeting are two ways the nanotechnology-based new drug delivery system (DDS) can circumvent the mentioned shortcomings of chemotherapeutic medications. Their larger surface area to volume ratio, size, morphology, charge, and composition are principally responsible for their efficacy as chemotherapeutic drug carriers in managing cancer [15]. The phenomenon, known as "passive targeting," describes how certain sizes of drug-loading particles tend to concentrate in tumor tissue much more than in normal tissues [16]. Because of their nanoscale size, NPs can selectively accumulate within tumors by taking advantage of the increased permeability and retention effect (EPR) typical of malignancies [16]. The abnormal pathophysiological properties of tumors form the foundation of EPR. The extravasation of NPs from the bloodstream into the tumor instead of the neighboring normal tissues is caused by the existence of malformed, fenestrated blood vessels and decreased lymphatic outflow [14,16]. This prevents the NPs clearance, resulting in their retention in the tumor site. To put it another way, the increased permeability of the tumor vasculature renders it simpler for massive compounds and NPs to penetrate the tumor [16]. NPs can accumulate in tumor sites because they lack adequate lymphatic outflow. It is common practice to alter the size or form of the NPs in question to facilitate increased passive accumulation at the tumor site [16]. Only 1% of non-therapeutic medicines are detected in tumors, making passive targeted administration an ineffective method for drug delivery [16,17]. Alternatively, suppose the NPs cannot be targeted passively. In that case, they can be targeted actively by conjugating them to targeting ligands (such as antibodies or peptides), which can subsequently be applied externally to where they are needed. Ligand-conjugated NPs are not only able to accumulate in the tumor's interstitial space, but also receptor-mediated endocytosis results in the NPs internalization, allowing for the delivery of targeted medications to be further enhanced [14,16,17]. Potentially enabling the cell-specific destruction of both primary tumor cells and metastatically disseminated circulating cancer cells, active targeting has greater capability than passive targeting techniques. As a good complimentary method to EPR, active-targeting NPs are presently encouraged to boost Nano medicines' effectiveness even more. To respond to various stimuli, stimulus-regulated NPs systems have been developed [16]. The stimuli may be specific to the diseased region (internal stimuli), and stimuli-regulated releasing NPs devices are created by incorporating compounds reacting to inappropriate pH, temperature, and redox circumstances, as well as the specific biological molecules overexpression. External stimuli, including light, ultrasound, and microwaves, can potentially affect the NPs systems. These nanomedicines are fundamentally multi-component systems that include well-defined nanostructures as delivery platforms, one or more pharmaceuticals as a curative ingredient, and bioactive compounds to prolong the nanomedicine's half-life and encourage aggregation at the target location. As a result, the multi-component system has the potential to raise the efficient concentration of chemotherapeutic medications within tumor cells while simultaneously lowering the likelihood of drug resistance.

This study aimed to investigate current advancements in nanotechnology that restrict chemo-resistance by targeting epithelial-mesenchymal transmission. More specifically, this work sought to investigate developing approaches targeting chemo-resistance in solid tumors.

2. Epithelial-mesenchymal transition (EMT) mechanism

EMT denotes a cellular metamorphosis wherein cells relinquish their epithelial attributes and acquire mesenchymal characteristics. This phenomenon has been demonstrated to be linked with diverse tumor activities like tumor origination, malignant advancement, movement of cancer cells, dissemination of metastasis, and resilience to treatment [18–21] (Fig. 1).

Cellular chromatin and transcriptional patterns are modified during various EMT transitional phases. Gene regulatory networks (GRNs), which control how genes are expressed in cells, facilitate these changes. The active enhancers of epithelial and mesenchymal tumor cells contain a number of transcription factors (TF) binding sites that are substantially enriched, indicating that similar TFs are necessary to cause chromatin remodeling in the two distinct EMT transition stages. Acting as both epithelial and mesenchymal transcription factors are AP1, Ets, Nfi, Tead, Runx, and NF-κB [20].

The expression of EMT-promoting factors is known to be influenced by inflammatory processes, physical restrictions, metabolic stress, abnormal activation of signaling pathways such as those controlled by Wnt, Notch, TGF-β, and hyperactivation of RAS–ERK1/2 and NF-κB signaling. Through these pathways, Twist, Snail, and ZEB families can be promoted. Completion of transdifferentiation towards a mesenchymal phenotype is influenced by permissive microenvironmental signals that encourage cell motility and invasion [22].

A variety of miRNA-targeted genes participate in the regulation of EMT/MET, including those of EMT-ATFs, affecting invasiveness and metastasis. MiR200a/b/c, miR141, and miR429 maintain epithelial growth and prevent EMT by interacting with ZEB1 and ZEB2 [23]. Overexpression of either miR-30 or miR-34, like miR-200, target Snail1 and prevents TGF-β-induced EMT. miRNAs interact again with Snail2 in a negative feedback loop: miR-1 and miR-200 inhibit Snail2 expression while both are repressed by Snail2 [24]. By directly binding to E-boxes in the promoters of miR-10b, miR-199a, and miR-214, Twist1 activates their expression. The miR-10b expression is found in breast cancer metastatic cells, causing cell motility and migration [23].

A class of molecules called long noncoding RNAs have recently been described to play a role in normal cellular function and tumorigenesis. The length of these RNAs is greater than 200 base pairs, but do not code for proteins [25]. Unlike messenger RNA, long non-coding RNAs (lncRNAs) are transcribed by RNA polymerase II, but their action is mediated by a variety of mechanisms, including competitive endogenous RNA (ceRNA), enhancers, scaffolds, signals, and guides. When competitive endogenous RNAs are involved, lncRNAs act as functional sponges or decoys, which prevent other molecules from executing their functions, such as in miRNA-lncRNA sponge interactions. LncRNAs can act as transcription factor-like molecules in cells which enhance gene expression by acting as an enhancer. As a scaffold, lncRNAs can bring proteins closer to each other, aiding the formation of ribonuclear proteins. An lncRNA acts as a signal for molecules such as transcription factors to activate or repress gene expression. LncRNA plays a role as a guide molecule for proteins to recruit them to the nucleus [26,27]. Elevated lncRNA expression turned into frequently related to worse survival. Many lncRNAs mediate their effect via competitive endogenous RNA or transcription factor regulation. The ZEB1, 2/ E-cadherin, Wnt/β-catenin signaling, and chromatin transforming pathways are mentioned specifically [28].

EMT and tumor invasion have been shown to be promoted by hypoxia. The role of SUMO-specific protease 1 (SENP1) in regulating hypoxia-induced migration and invasion is substantial, as it stimulates multiple EMT-related factors. The depletion of SENP1 led to a reduction in vimentin and N-cadherin levels while increasing E-cadherin levels. It has been shown that SENP1 is involved in hypoxia-induced Hypoxia-Inducible Factor-1 (HIF-1) signaling, suggesting a positive feedback loop between SENP1 and HIF-1 [29]. There is quite a lot of complex signaling involving HIF-1α, which has positive and negative feedback loops with several key pathways including STAT3, Notch, NF-κB, and PKM2 [29–31]. As a result of hypoxia, mitochondria produce reactive oxygen species (ROS) that are known to cause pleiotropic effects, including activation of HIF-1α and NF-κB signaling, and inhibition of glycogen synthase kinase-3b (GSK3b). In the end, the basic knowledge on

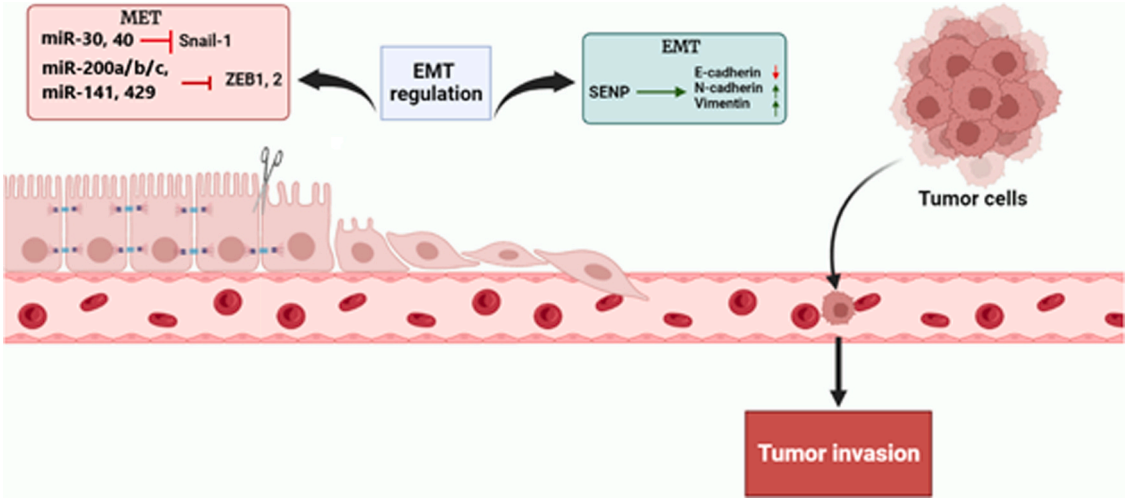

Fig. 1. The illustration indicates some factors which are involved in EMT/MET regulation. Some microRNAs (miRs) are involved in EMT/MET regulation such as miR-30, 34 that inhibit Snail-1 and miR-200a/b/c, miR-141, 429 inhibit ZEB1, 2. Both of those processes change the game in favor of MET. On the other hand, SENP plays in the EMT side by increasing N-cadherin and Vimentin and decreasing E-cadherin levels.

mechanisms controlling EMT should be applied toward developing new therapeutic strategies to prevent cancer progression, metastasis, and resistance to therapy in humans.

Moreover, this illustration simply indicates the EMT process in which epithelial cells of blood vessels shift into mesenchymal form. In this process, the variability of vessels is increased and tumor cells can migrate to another part of the body.

3. Association between epithelial-mesenchymal transition (EMT) and chemo-resistance in solid tumors

The cellular process of EMT often occurs under normal or pathological conditions. It plays a crucial role in embryonic development, wound healing, and tumor growth [32]. EMT can be triggered by a number of factors, including the tumor microenvironment (TME), and inflammatory cytokines [33]. EMT also strengthens tumor immunity, boosts resistance to anti-cancer therapies, and increases cancer stem cells. In addition, EMT plays a crucial role in the invasion-metastasis cascade and chemo-resistance of a variety of solid tumors, including glioblastoma, lung cancer, breast cancer, pancreatic cancer, gastric cancer, hepatocellular carcinoma, and ovarian cancer, among others [34–37] (Fig. 2).

3.1. Glioblastoma

Among the deadliest types of brain cancer, glioblastoma is the most lethal [38–41]. The typical lifespan for individuals with grade IV glioma (also known as glioblastoma or GBM) is a maximum of two years, despite undergoing comprehensive surgical removal, radiotherapy, and chemotherapy, which are the current standard treatment options for glioblastoma [42].

Glioblastoma has the most dismal prognosis of any malignant intracranial tumor [43]. Multipotent glioma stem cells (GSCs), which are aggressive and resistant to therapy, are among the cells that make up a glioblastoma [44].

EMT has been found to be a significant contributor to the development of resistance to glioblastoma treatments [45]. The autophagy-mediated EMT has been reported to act as a survival-promoting mechanism in gliomas [43]. EMT mediates invasion and metastasis in several tumors, including gliomas [46,47]. HERT3 plays a crucial role in autophagy-induced EMT, and it activates the TGF-β signaling pathway, which is dependent on SMAD2/3 degradation of SMAD7, characteristic of the endosomal-lysosomal pathway [48].

In glioblastoma, EMT induced by activators, such as members of the SNAI family (e.g., ZEB1 and ZEB2), can induce cell features comparable to mesenchymal cells, such as longer projections (pseudopodia) and greater invasive ability [49] (Fig. 2). Furthermore, EMT can also cause non-cancer stem cells to dedifferentiate, resulting in the cells being able to self-renew and initiate tumors, as well as be tolerant to chemotherapy. Therefore, these studies suggest that E3 ubiquitin ligases could play an essential role in regulating the EMT state in cancer cells [43].

3.2. Lung cancer

Lung cancer is the most common cancer with a survival rate of 16.6% and consists of non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) [50,51]. The diagnosis and prognosis of lung carcinoma are still poor, despite great progress in experimental research and clinical treatments. [52]. Globally, lung cancer is the leading cause of cancer mortality, primarily because of metastasis and treatment resistance. The most common type of lung cancer is NSCLC, and most patients are diagnosed in late stages with poor survival outcomes [53]. As a result of the downregulation of epithelial properties and remodeling of the cytoskeleton to enhance migration, the developmental EMT occurs [53]. EMT has been connected with metastasis and acquired resistance to chemotherapy [54,55] in many cancers, including NSCLC [56] (Fig. 2). The development of a wide range of small molecule agents to target EMT in lung carcinoma has been going on in preclinical phases [57]. As an example, bufalin, a Chinese medicine, hinders the migration of A549 human lung cancer cells and the TGF-β- induced EMT [58]. EMT appears to cause tumors to move from a hot to a cold state, decreasing their susceptibility to immunotherapy. In the case of non-small cell lung cancer (NSCLC), an EMT signature has been shown to be inversely related to T-cell infiltration [59]. Studies have also found that reversing EMT makes anticancer drugs more effective [60]. Additionally, EMT often generates cells with stem cell properties [61] and these cells are thus more resistant to apoptosis and other forms of programmed death, improving their ability to self-renew. As outlined above, therapeutic resistance is in many cases related to epithelial-mesenchymal phenotypes [62]. Forkhead box protein C2 (FOXC2) was shown to promote resistance to the same drug by induction of EMT in non-small cell lung cancer A549 cells. It activates the v-AKT murine thymoma viral oncogene homolog 1/ Glycogen synthase kinase 3 (AKT/ GSK3) signaling pathway and enhances Snail expression [63].

The type of cancer that is well comprehended in terms of the correlation between EMT and treatment resistance is lung cancer [64]. It is

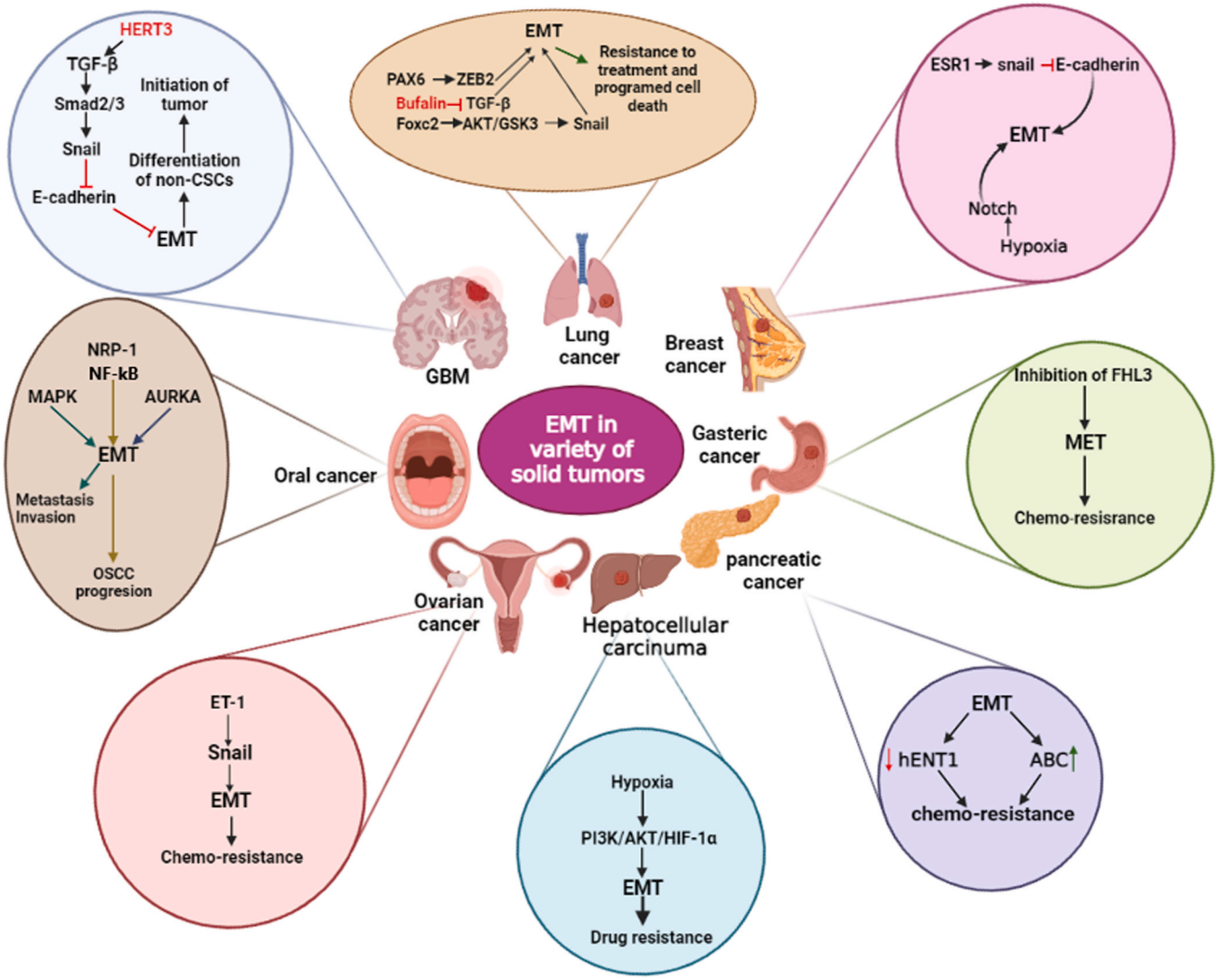

Fig. 2. As shown in the figure, EMT is involved in variety of cancers. In this illustration we have described different pathways in which EMT is activated. Glioblastoma: HERT3 inhibits E-cadherin via TGF-β/ Smad2, 3/ Snail pathway. E-cadherin is an inhibitory factor of EMT, which, if inhibited, causes EMT to be activated. Oral cancer: MAPK, AURKA, and NRP-1and NF-κB stimulate EMT that leads to metastasis and invasion. Ovarian cancer: ET-1/ Snail/ EMT axis promotes Chemotherapy resistance in this type of cancer. Hepatocellular carcinoma: Hypoxia leads to EMT by PI3K/AKT/ HIF-1α signaling pathway that results in Drug-resistance. Pancreatic cancer: EMT stimulates chemo-resistance by activation of ATP-binding cassette (ABC) and hENT 1inhibition. Gastric cancer: in this type of cancer, inhibition of FHL3 causes chemoresistance by MET activation. Breast cancer: in breast cancer two main pathway stimulate EMT. A) ESR-1/Snail that inhibits E-cadherin B) Hypoxia that activates notch factor. Lung cancer: EMT in lung cancer is affected by three different pathways. A) PAX6/ ZEB2 axis, B) Bufalin which inhibits TGF-β and C) Foxo2/ Akt/ GSK3/ Snail axis.

clear from many publications that EMT-TFs play a crucial role in drug resistance [65]. Overexpressed Snail and Slug in lung cancer cell lines with EGFR mutations have been reported to induce resistance to gefitinib [66]. PAX6 was also shown to promote EMT and cisplatin resistance via the regulation of ZEB2 expression [67]. Based to research acquired resistance to the EGFR-TKI osimertinib can be predicted by upregulation of the EMT-associated gene AXL [68]. The involvement of cell stem features, the suppression of Bcl-2-like protein 11, or chromatin remodeling brought on by EMT-TFs are three biological mechanisms that contribute to this therapeutic resistance [69,70]. Additionally, MET-driven EMT has also been shown to create chemo-resistance. The MET expression of cisplatin-resistant NSCLC cell lines is overexpressed compared to parental cells, and this is accompanied by an increase in N-cadherin, Vimentin, ZEB1, and Snail expression, as well as a reduction in E-cadherin expression [71]. Meanwhile, miR-206-mediated MET downregulation reversed EMT and also sensitized resistant NSCLC cells to cisplatin [71].

In conclusion, it has been shown that EMT can cause chemo-resistance in lung cancer by various researches.

3.3. Breast cancer

The most frequently diagnosed invasive cancer in women is breast cancer [72–76].

An estimated 5–10% of breast cancers are hereditary and are the result of genetic mutations. Even if breast cancer at an early, non-metastatic stage can be cured, the prognosis for locally advanced and inflammatory cancer is unpredictable, and strongly influenced by the tumors' biological properties [77].

In the case of breast tumors, the usual course of action involves surgery, radiation, and various systemic treatments, such as hormone therapy for hormone-sensitive cases, HER2-targeted drugs for HER2-enriched tumors, and chemotherapy and poly (ADP-ribose) polymerase inhibitors for triple-negative breast cancers [78,79]. Additionally,

immunotherapy has become an option in recent times [78]. Nonetheless, the intricate intercommunication between malignant and stromal cells in the breast TME, as well as the reconfiguration of multiple signaling pathways and the involvement of breast cancer stem cells (BCSCs), are all contributing factors to the overall drug resistance in breast cancer [78].

Currently, drug resistance poses a major challenge in the treatment of breast cancer. BCSCs cause BC-related drug resistance, relapse, and metastasis in patients with this cancer [80].

According to a study on breast cancer, TFs such as Twist, Snail, and FOXC2 overexpression increase promoter activity of ATP-binding cassette (ABC) transporters. This suggests that EMT may be a novel regulatory factor of ABC transport. As a result, EMT-TFs are proposed as new strategies for treating metastasis and drug resistance [81]. Induction of twist overexpression or inhibition of E-cadherin confers resistance to paclitaxel and doxorubicin, which is a second important example showing the role of EMT-TFs in drug resistance in normal and transformed human mammary epithelial cells. Likewise, Snail confers resistance to docetaxel and gemcitabine on basal-like MDA-MB-231 cells [82–84]. However, breast cancer cells with mesenchymal characteristics can be sensitive to paclitaxel. Indeed, it has been demonstrated that induction of EMT activates PERK-eIF2α and promotes sensitivity to agents that disrupt endoplasmic reticulum function, showing a new vulnerability of cancer cells involved in EMT that is characterized by a sensitivity to endoplasmic reticulum stress [82–84]. Indeed, estrogen receptor alpha gene fusion proteins (ESR1) in breast cancer cell lines stimulate estrogen-independent EMT through increased Snail expression and decreased E-cadherin expression [85].

NF-κB transcription factors are involved in the pathogenesis and resistance to treatment of breast cancer. Breast cancer in particular is said to have a high level of NF-κB activity [86].

Notch signaling activates genes necessary for EMT, a prerequisite for metastasizing from the primary site (breast) to distant organs [87]. Hypoxia promotes EMT in breast cancer cells through Notch activation [88]. HMECs which have undergone EMT acquire a cancerous, stem cell-like phenotype. Researchers have demonstrated that HMECs overexpressing either Snail or Twist undergo EMT successfully [89].

Wnt signaling is involved in the proliferation and metastasis of breast cancer cells [90]. In cell proliferation and oncogenesis, the Wnt pathway plays an important role [91].

Taken together, a number of studies have demonstrated that EMT can result in chemo-resistance in breast cancer.

3.4. Pancreatic cancer

Pancreatic cancer (PC) is the world's seventh most common cause of cancer mortality. The overwhelming majority of PC patients develop metastases, which leads to poor treatment outcomes. Despite significant advances in treatment techniques in recent decades, widespread drug resistance still exists, posing a significant barrier to successful anticancer therapy for pancreatic ductal adenocarcinoma (PDAC) [92,93]. During tumorigenesis, a number of factors and signaling pathways can control EMT (Fig. 2). Factors promoting growth, such as transforming growth factor (TGF), epidermal growth factor, and hepatocyte growth factor, along with the Wnt/beta-catenin and Notch pathways, have the potential to activate pathways that stimulate EMT. In pancreatic cancer cells that are resistant to gemcitabine (GR) and have undergone EMT, researchers found that Notch-2 activation was present [94]. Gemcitabine, a nucleoside analogue that affects DNA synthesis and transcription, is used in the majority of pancreatic cancer chemotherapies. Gemcitabine resistance is known to be promoted by in vivo EMT [95]. EMT causes cancer cells to take on the characteristics of cancer stem cells (CSCs) and increases their neoplastic replicative potential while also enhancing chemotherapy resistance [96,97]. Additionally, epigenetic changes can lead to EMT-induced chemo-resistance by reducing the expression of hENT1 nucleoside transporter needed for gemcitabine uptake. ABC transporters are often expressed in CSCs with an EMT phenotype. Overexpression of ABC family efflux transporters enhances therapeutic drug efflux from cells; for example, the MDR1 and MRP1 ABC efflux transporters become resistance to gemcitabine [95].

3.5. Gastric cancer

A common malignancy in East Asian countries is gastric cancer. In spite of great advances in diagnosis and multimodal treatments, this cancer remains the leading cause of mortality [98–100]. In advanced gastric cancer, cisplatin (CP) is the most important and effective chemotherapeutic agent [101]. CP is a key member of platinum compounds that have good anti-tumor action in a variety of malignancies, including breast cancer, lung cancer, prostate cancer, brain tumors, bladder cancer, and others [102–105]. The two main types of TAM (tumor-associated macrophages) are classically activated macrophages (CAMs) and alternatively activated macrophages [114]. Cancer migration and malignancy appear to be strongly influenced by CAMs. The migration ability of CAMs is increased by chemotherapy with CP. Molecular markers indicate that CP induces CAMs that trigger the EMT mechanism [114]. As a result of CP stimulation, CAMs produce chemokine ligand 20 (CCL20), without altering their phenotype. Cancer progression is facilitated by CCL20 which recruits T helper cells to maintain the immunosuppressive microenvironment. A secondary target of CCL20, the chemokine receptor 6 (CCR6) stimulates cancer metastasis and migration. Chemotherapy with CP stimulates CAMs to secrete CCL20, which then enhances tumor cell migration and induces the EMT mechanism, resulting in drug resistance caused by EMT. Additionally, CP induces EMT by activating oncogenic NF-κB signaling [114]. Furthermore, paclitaxel is a first-line chemotherapeutic treatment for gastric cancer, although it is limited in its efficacy due to resistance. According to studies, EMT expression in parental cells is evidence of increased resistance to paclitaxel [106]. Regarding a treatment strategy, we can say that Cao et al. discovered that inhibiting Half LIM Domains 3 (FHL3) enhanced the mesenchymal–epithelial transition (MET), which could improve chemotherapy resistance in HGC. Furthermore, they discovered that knocking down FHL3 reduced Multidrug Resistance Gene1 (MDR1) [107]. Finally, TGF/Smad-independent mechanisms were found to be the regulators of FHL3-mediated chemotherapeutic resistance, which can be the basis of further studies [107].

3.6. Hepatocellular carcinoma

Hepatocellular carcinoma is one of the most frequent and fatal cancers worldwide, and the prognosis for patients has remained unchanged in recent years. Hepatocellular carcinoma has been shown to be very resistant to both targeted and conventional cytotoxic treatments. Doxorubicin is the most extensively used cytotoxic agent for the treatment of hepatocellular carcinoma. However, resistance to it leads to reduced response rates or the need for higher medication dosages, both of which are associated with significant adverse effects. According to Dai et al. EMT transcriptional regulators, Snail and Slug may lead to doxorubicin resistance in hepatocellular cancer mesenchymal cells [108].

Jun li Ma et al. [109] created the oxaliplatin (OXA)-resistant cell line Bel-7402/OXA by exposing it to steadily increasing concentrations of OXA to better understand drug resistance. With the EMT phenotype, they noticed that Bel-7402/OXA developed greater migratory and invasion potential. Inhibition of the EMT transcription factor Snail could reverse EMT and sensitize Bel-7402/OXA cells to OXA. Because EMT is one mechanism of drug resistance, it might be a new target for drug resistance therapy [109].

In addition, hypoxia has been shown to promote cancer development and induce chemo-resistance. According to Jiao et al., hepatocellular carcinoma cells experienced EMT after being exposed to hypoxic conditions, which resulted in increased cell migration and invasion as well

as significant resistance to treatment [35]. Hypoxia-induced EMT and chemo-resistance were shown to be coupled by elevated HIF-1α expression and AKT activation. HIF-1α activation was inhibited by the PI3K inhibitor LY294002, showing that the PI3K/AKT pathway was involved. They also discovered that inhibiting PI3K/AKT and HIF-1α improved the therapeutic efficiency of hypoxic chemotherapy in an HCC xenograft model [35]. Their findings suggest that the PI3K/AKT/HIF-1α pathway is important in mediating hypoxia-induced EMT and drug resistance, which leads to poor treatment outcomes and can be the basis of further studies about malignant progression triggered by the hypoxic microenvironment in HCC cells [35].

3.7. Ovarian cancer

Ovarian cancer is the fifth most common type of cancer death among women [110,111]. Chemo-resistant illness, which can manifest as innate or acquired resistance to medicines, is one of the primary causes of mortality in high-grade serous ovarian cancer (HGSOC) [112]. Moreover, several investigations have demonstrated that ovarian cancer cells that are resistant to carboplatin and/or paclitaxel usually acquire mesenchymal traits [113]. EMT is considered significant in the development and advancement of ovarian cancer (Fig. 2). The work by Rosan et al. elucidates the role of the endothelin-1 (ET-1) axis in the acquisition of chemo-resistance and the EMT phenotype. They discovered that ET-1 induces substantial tumorigenic signals, including the activation of the EMT-driver Snail, in a combination in-vitro/in-vivo model of epithelial ovarian cancer (EOC) cells resistant to taxol and cisplatinum [114]. As a result, Endothelin A receptor (ET_AR) blockade may reduce drug resistance through the reversal of EMT [114]. Furthermore, other research has shown that EMT and CSCs work together, and platinum-based chemotherapy can promote EMT and CSCs in chemotherapy-treated remaining cancer cells [115]. In ovarian cancer, several signaling pathways can help CSCs get started. PI3K/AKT/PTEN, JAK2/STAT3, NF-κB, Wnt, Notch, and Hedgehog have all been linked to ovarian cancer tumor development and treatment resistance. In cell lines and animal models, inhibiting these pathways in-vitro cultures has been demonstrated to reduce tumorigenesis and chemosensitivity [115].

3.8. Oral squamous cell carcinoma (OSCC)

Oral cancer is one of the most prevalent malignancies worldwide [116]. It is a serious health issue and the leading cause of oral disease-related deaths in many nations [117].

Alchohol and tobacco consumption, Human papillomavirus (HPV), chronic inflammation, ultraviolet (UV) radiation (for lip cancer), and diet are among the risk factors for oral cancer in addition to genetic susceptibility and chronic inflammation [118]. Oral squamous cell carcinoma (OSCC) is the most common type of oral cancer, accounting for 90% of occurrences [118].

Treatment options for OSCC involve solitary management with surgery (excision/resection), radiotherapy, systemic cytotoxic chemotherapy, and blocking of epithelial growth factor receptor (EGF-R) [119]. Based on the disease demonstration and pathological observations, different combinations of these methods may also be used [119,120]. Chemotherapy is commonly used in neoadjuvant, adjuvant, chemoradiotherapy, and palliative [121]. Even though OSCC patients have access to multimodal therapy options, tumor drug resistance is still a concern that must be resolved [122,123]. This leads to increased tumor invasiveness in OSCC patients, a worse prognosis over the long term, and a higher risk of metastasis [124].

EMT is an initial stage in the development of invasiveness in malignant tumors such as OSCC and is one of the causes of drug resistance in cancer patients [125,126].

A study demonstrated that by increasing MAPK signaling pathway components, P38, JNK, and ERK, TNF-α might encourage the establishment of EMT and increase the potential of OSCCs to invade and metastasize [127]. In addition, after the activity of specific pathway inhibitors, the potential to promote invasion and metastasis was considerably reduced. Therefore, we can conclude that the MAPK signaling pathway is crucial for the invasion and metastasis of oral squamous cell cancer [127]. A serine-threonine kinase called aurora kinase A (AURKA) has been linked to the development of diverse human cancers. A study showed that AURKA increases the development of OSCC by regulating the EMT [128].

It has been observed that OSCC tissue has unusually high levels of the C-C chemokine receptor 7 (CCR7) and its ligand chemokine ligand 21 (CCL21), also concluded that the CCL21/CCR7 attachment controlled the development of EMT and may be a useful target for the prevention and therapy of OSCC [129].

In addition to the above, a recent study proved that Naa10p's interaction with IKKα causes EMT in OSCC cells through TGF-β1/Smad, demonstrating a unique OSCC prevention route [130].

Through NF-κB activation, neuropilin-1 (NRP-1) controls the EMT process in OSCC tissues, and increased NRP-1 expression levels are linked to lymph node metastases and a poor prognosis in OSCC patients. Hence, NRP-1 and its related pathways can be a beneficial target for the treatment of oral cancer cases [131]. .

4. Applications of nanotechnology in inhibiting epithelial-mesenchymal transition (EMT) in solid tumors

The EMT, which happens when a cell with epithelial phenotype changes to a mesenchymal phenotype cell, is a fundamental step for embryonic growth that happens also in the life of an adult, notably throughout the growth of a tumor [136]. The link between EMT and cancer was discovered in the early 1980 s. Due to EMT, benign tumor cells gain invading and metastasizing abilities as the tumor progress. EMT occurs in the great majority of tumors as they advance, to the point that tumors generated from epithelia are those in which the EMT process is crucial [137].

Cytokines, growth factors, and hypoxia produced by the anticancer medication therapy, stroma interaction, innate and adaptive immunological responses, tumor microenvironment, and metabolic alterations, are all examples of EMT inducers in cancer [62].

Complex regulatory networks including transcriptional factors and control, E12/E47, ZEB1, ZEB2, SNAI1, SNAI2, and Twist, ncRNA or non-coding-RNAs (long non-coding RNAs (lncRNAs), and MicroRNAs (miRNAs)), epigenetic modifications, and chromatin remodeling, alternative splicing, protein stability, post-translational regulation, and subcellular localization are all involved in the gene expression switching from epithelial to mesenchymal phenotype [138].

EMT is a reversible physiological phenomenon wherein well-polarized epithelial cells lose their firm cell-cell associations and apical-basal polarity, transforming into an extra spindle-formed mesenchymal-like structure with improved movability and traveling capabilities [139]. Cancer cells through EMT have elevated motility and invasiveness, making them more likely to spread to distant locations and generate metastases. They also develop resistance to programmed cell death and antitumor medicines, participate in the suppression of the immune system, and operate as cancer stem cells (CSCs) [140,141]. Attenuation of proliferation is another feature of tumor cells undergoing EMT [142,143]. Tumor tissues that received a mesenchymal phenotype may encounter an operation called EMT, that permits them to reclaim an epithelial phenotype and associated capabilities, such as the ability to recover proliferation [136].

4.1. Inhibiting EMT by Nanotechnology

Nowadays, there is a widespread use of NPs to prevent EMT. NPs are effective at interacting with cells and enhancing their therapeutic effects because of their high surface area-to-volume ratio [144]. Because of their small size and biocompatibility, NPs can also effectively transport

Table 1
The association of EMT in progression and chemo-resistance of different solid tumors.

Cancer type	Description	Ref.
Glioblastoma	1) HERT3 plays a crucial role in autophagy-induced EMT, and it activates the TGF-β signaling pathway, which is dependent on SMAD2/3 degradation of SMAD7. 2) EMT induced by activators, such as members of the SNAI family (e.g., ZEB1 and ZEB2), can induce cell features comparable to mesenchymal cells including longer projections (pseudopodia) and greater invasive ability. 3) EMT causes non-cancer stem cells to dedifferentiate, resulting in the cells being able to self-renew and initiate tumors, as well as be tolerant to chemotherapy.	[43,49]
Lung cancer	1) EMT has been connected with metastasis and acquired resistance to chemotherapy. 2) EMT appears to cause tumors to move from a hot to a cold state, decreasing their susceptibility to immunotherapy. 3) The MET expression of cisplatin-resistant NSCLC cell lines is overexpressed compared to parental cells accompanied by an increase in N-cadherin, Vimentin, ZEB1, and Snail expression, as well as a reduction in E-cadherin expression. 4) In NSCLC, Shh signaling pathways induce the development of EMT phenotypes, resulting in cisplatin resistance.	[56,60, 132]
Breast cancer	1) TFs such as Twist, Snail, and FOXC2 overexpression increase promoter activity of ATP-binding cassette (ABC) transporters. So, EMT-TFs are proposed as new strategies for treating metastasis and drug resistance. 2) Induction of EMT activates PERK-eIF2α and promotes sensitivity to agents that disrupt endoplasmic reticulum function, showing a new vulnerability of cancer cells involved in EMT. 3) Notch and Wnt signaling pathways activates genes necessary for EMT and metastasis.	[81,82, 133]
Pancreatic cancer	1) Factors promoting growth, such as transforming growth factor (TGF), epidermal growth factor, and hepatocyte growth factor, along with the Wnt/beta-catenin and Notch pathways, have the potential to activate pathways that stimulate EMT. 2) Epigenetic changes can lead to EMT-induced chemo-resistance by reducing the expression of hENT1 nucleoside transporter needed for gemcitabine uptake	[94, 134]
Gastric cancer	1) EMT expression in parental cells is evidence of increased resistance to paclitaxel. 2) Inhibiting Half LIM Domains 3 (FHL3) enhanced the mesenchymal–epithelial transition (MET), which could improve chemotherapy resistance in HGC	[106, 135]
Hepatocellular carcinoma	1) EMT not only has the potential to self-renew and develop malignancy in advanced liver cancer, but it also allows for increased resistance to conventional chemo- and radiotherapies. 2) Inhibition of the EMT transcription factor Snail could reverse EMT and sensitize Bel-7402/OXA cells to OXA. 3) Hypoxia-induced EMT and chemoresistance were shown to be coupled by elevated HIF-1α expression and AKT activation.	[35, 108, 109]
Ovarian cancer	1) ET-1 induces substantial tumorigenic signals, including the activation of the EMT-driver Snail, in a combination in-vitro/in-vivo model of epithelial ovarian cancer (EOC) cells resistant to taxol and cisplatinum. 2) EMT and CSCs work together, and platinum-based chemotherapy can promote EMT and CSCs in chemotherapy-treated remaining cancer cells via PI3K/AKT/PTEN, JAK2/STAT3, NF-κB, Wnt, Notch, and Hedgehog signaling pathways.	[115]
Oral squamous cell carcinoma (OSCC)	1) By increasing MAPK signaling pathway components, P38, JNK, and ERK, TNF-α might encourage the establishment of EMT and increase the potential of OSCCs to invade and metastasize. 2) Aurora kinase A (AURKA) increases the development of OSCC by regulating the EMT. 3) The CCL21/CCR7 attachment controlled the development of EMT and may be a useful target for the prevention and therapy of OSCC. 4) Through NF-κB activation, neuropilin-1 (NRP-1) controls the EMT process in OSCC tissues, and increased NRP-1 expression levels are linked to lymph node metastases and a poor prognosis in OSCC patients.	[128, 129, 131]

therapeutic agents to target cells, particularly those undergoing EMT. This enhances the effectiveness of treatments aimed at preventing EMT [145]. In addition, NPs can be designed to target specific markers or cells associated with EMT, improving their precision in delivering therapeutic payloads to the right location [146]. Moreover, biomimetic NPs, such as those coated with platelet membranes, can extend circulation time and improve immune evasion, increasing their efficacy in preventing EMT [147]. But in addition to the many advantages of using NPs, there are also limitations to the spread of these particles in preventing EMT. For example NPs may raise safety concerns due to potential toxicity and unforeseen side effects, which require thorough testing and evaluation before clinical use [148]. Also, rapid clearance and elimination of NPs from the body may limit their therapeutic effectiveness. Strategies are needed to prolong their circulation time [149]. Moreover, achieving high specificity in targeting EMT-related processes can be challenging, and NPs must be carefully engineered to avoid off-target effects [150]. Finally, the use of NPs for medical applications may face regulatory challenges related to approval and safety assessments [151]. In summary, nanoparticles offer promising advantages in preventing EMT, primarily related to enhanced drug delivery and targeting capabilities. However, safety, specificity, and regulatory considerations are important restrictions that need to be addressed for their successful application in EMT prevention.

Carbon-derived NPs, polymeric NPs (PLGA, micelle, and chitosan,), hybrid nanocomposites, (Organics-In-Inorganics and Inorganics-In-Organics), and Inorganic NPs (metal oxide and metal NPs), have all shown to inhibit EMT. Natural nanomaterials (exosomes and liposomes) have unique properties as EMT inhibitors and drug delivery vehicles, in addition to synthetic NPs. Furthermore, various additional NPs in which arbitrate the suppression of metastasis and EMT are described in this review, also encapsulated with an individual inhibitory compound or another conjoint therapeutic module (for instance, encapsulated by a mixture of medicines or suppressions).

Generally, in this article, we have reviewed recent research on nanomaterials' capacity to suppress the process of EMT in cancerous cells, which may be used to control numerous essential aspects for instance invasive/migratory capacities, the phenotype of stem cells, and growth of tumor [152,153].

4.2. Gold nanoparticles (AuNPs)

Due to its exceptional features like the synthesis simplicity and characterization, biocompatibility, negligible cytotoxicity, and constancy, gold NPs have taken a broad range of biomedicine usages [154]. They also have excellent surface modification capabilities related to their great capacity to link molecules containing the amino (–NH2–) and thiol (–SH–) groups, that enhances protein binding through cysteine and lysine residues [154].

In 2017, Li et al. [155] generated AuNPs, which enhance blood flow, help normalize tumor vasculature, and reduce hypoxia in skin cancer, AuNPs have also been shown to inverse EMT in cancers, which was followed via a reduction in metastasis of lung. AuNPs suppressed B16F10 cells relocation and inversed EMT in B16F10 cells, demonstrating that these NPs may control EMT independently of hypoxia enhancements. Overall, the findings showed that AuNPs might normalize the vasculature of tumor and opposite EMT, leading to a reduction in metastasis of melanoma tumors [155].

Another research on Au-NPs was performed in 2016 by Balakrishnan et al. (Fig. 3), in this study, an anti-oxidative flavonoid of Quercetin (Qu) with powerful anti-cancer cell activity was loaded on the AuNPs and via aiming the EGFR/VEGFR-2 signaling pathway, AuNPs-Qu-5 could inhibit EMT, metastasis, and angiogenesis, in breast tumor cells [156].

Another study reported that AuNPs might be used to make pancreatic cancer (PC) cells more sensitive to gemcitabine [157]. According to Huai et al.'s findings, PC cell therapy with AuNPs suppressed migration and colony formation. Pre-treatment of PC cells with AuNPs reduced gemcitabine-induced EMT, stemness, and MAPK activation on a mechanistic level [157].

Agarwallart et al. designed a (glucocorticoid receptor) GR-targeted gold-withaferin nanoconjugate that might slow the development of solid tumors. Via GR-mediated inversion of EMT and promotion of medicine sensitivity in cancer cells, this gold NPs formulation may produce cancer cell-specific cytotoxicity and dramatically suppress the growth of aggressive melanoma tumors [158].

4.3. Metal Oxides and other metal Nanoparticles

As a therapeutic module, metal oxide NPs were used to carry a broad range of chemotherapy medicines and metabolite suppressions [159]. Different kinds of metal oxide NPs were assessed for potential EMT inhibition properties. For instance, the recent research which was performed by Wang et al. discovered that ZnO-NPs can suppress cell proliferation, trigger apoptosis, and EMT in SMMC-7721 liver cancer cells and they are able to be employed as a novel NP carrier for liver cancer therapy [159].

In another study in 2021, Zhan et al. discovered that MEG3 performs a significant role in the progress of nickel oxide (NiO) NPs-induced lung fibrosis. By decreasing transforming growth factor-β1 (TGF-β1) expression and EMT, Maternally expressed gene 3 (MEG3) may act as a pulmonary fibrosis suppressor [160]. These findings revealed a novel molecular understanding of the mechanisms behind NiO NP-induced lung fibrosis and may lead to potential treatment options [160]. In 2018, Li and colleagues [161] demonstrated that waterborne titanium dioxide NPs (TiO_2-NPs) can inhibit EMT and tissue regeneration. TiO_2-NPs are absorbed by the cells and inhibit EMT-mediated cell reconstruction and transmigration sans causing cytotoxicity. TGFβ signaling was blocked by TiO_2-NPs, which inhibits the EMT process. TiO_2-NPs, in particular, make a connection with the TGFβ receptor TβRI/II complex, causing its degradation of lysosomal and, as a result, downregulating TGFβ target gene expression [161].

In the other investigation by Wang in 2018, VP16-loaded layered double hydroxide (LDH) was developed and made as a nanosensitizer for quite effective synergistic glioma treatment. In-vivo and in-vitro data revealed that nanocomposites have a long-lasting and suitable cargo loading potential, inhibiting glioma stem cell (GSC) proliferation and reducing tumor development in mouse models [162]. Additionally, following treatment with nanocomposite, the expression of GSC pluripotency genes was reduced, and the EMT procedure was inverted [162].

4.4. Hybrid nanocomposites

Hybrid nanocomposites are made up of two or further components (organic and inorganic) combined into a single structure with improved characteristics than their single versions.

The results of a study imply that chemically modified TWIST1 (Twist Family BHLH Transcription Factor 1) siRNA reverses EMT in-vivo and in-vitro [163]. TWIST1 could target genes and migratory capacity was reduced in-vitro after siRNA administration through polyethyleneimine-coated mesoporous silica NPs (MSN) [163]. In several solid tumor types, therapeutic use of TWIST1 siRNA given by MSNs has the ability to suppress cancer development and EMT [163].

To enhance traditional therapeutics, Fan et al. in 2017 (Fig. 4) created multi-functional epigallocatechin gallate/iron nano-complexes (EIN) as a useful material for coating. This method was shown to be effective in eliminating EMT-type cancer cells in-vitro [164]. EIN was also able to down-regulate the downstream expression of metastasis-associated proteins, reduce cancerous cell migratory capacity, and prevent cancer cells from developing resistance to drugs, according to mechanism studies [164]. EIN was shown to have a greater capacity to increase the healing impact of conventional nanomedicines while also inhibiting the EMT program in-vivo [164].

Huang et al. in 2019, developed ZnAs and SiO_2 NPs to recognize if

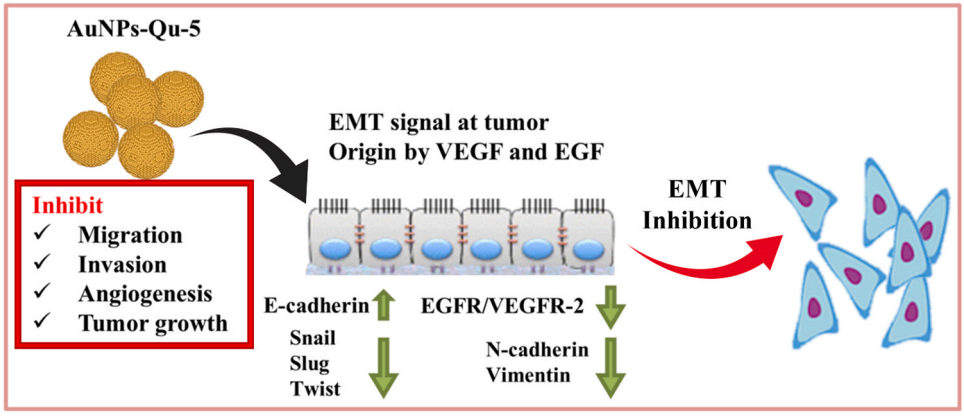

Fig. 3. The comprehensive schematic description of AuNPs-Qu-5 suppression on EMT, angiogenesis, invasion, tumor development, and migration, at the molecular level. The figure is modified from ref. [156].

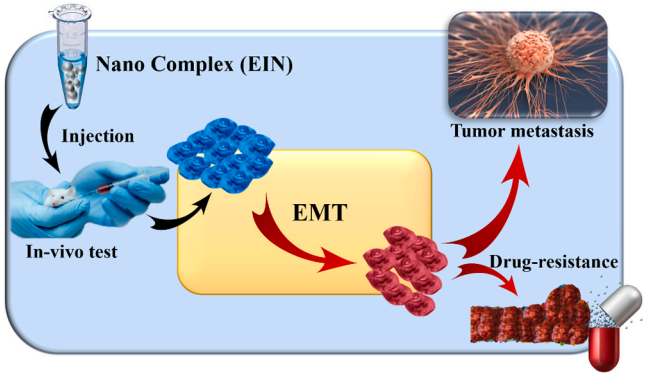

Fig. 4. EIN-coated nanomedicines are shown in a schematic figure to inhibit cancerous cells from developing drug resistance and to terminate EMT-type cancerous cells for tumor metastasis inhibition. Modified figure from ref. [164].

NP-based carriers can increase the effectiveness of arsenic trioxide (ATO). These NPs efficiently inhibit the growth, initiation, and metastasis of tumors, and suppress EMT and stemness in liver cancerous cells in-vitro and in-vivo by adjusting the SHP-1/JAK2/STAT3 signaling pathway [165].

In the other study, by Berber et al. in 2020, on the surface of MWCNT/PBI nanocomposites, Pt-NPs with the tiny size of particles were homogeneously distributed [166]. MWCNT/PBI/Pt showed a substantial preventing impact on the EMT and CSCs' cell cycle markers, as well as a drastic drop in the CSC proliferation rate [166].

4.5. *Organic-based Nanoparticles*

One of the biocompatible nanostructures with simply adjustable surfaces is nanodiamonds (NDs) and they are being promoted as potential biomedical candidates. In the recent study by Guo et al., the consequence of carboxylated NDs on the migration of tumor cells was examined. The epithelial cancer cells' migration was stopped by blocking EMT via the TGF-β signaling pathway [167]. Furthermore, the findings demonstrated that cNDs successfully inhibited metastasis in murine B16 melanoma cells [167].

Ma et al. in 2017, generated polyethylene glycol-polyethyleneimine-chlorin e6 (PEG-PEI-Ce6) NPs to effectively transport Wnt-1 small interfering RNA (siRNA) to the cytoplasm of KB cells (oral squamous cell carcinoma) that had undergone photodynamic therapy (PDT) [168]. The Wnt/β-catenin signaling pathway was efficiently blocked by Wnt-1 siRNA, which reduced the expression of Wnt-1, β-catenin, and vimentin, all of which are important in the EMT [168]. PEG-PEI-Ce6 NP-mediated PDT decreased cell proliferation and significantly improved cancerous cell death when combined with Wnt-1 siRNA [168]. The findings demonstrate that combining PEG-PEI-Ce6 NPs with PDT for Wnt-1 siRNA delivery and PDT in oral cancer treatment has potential [168].

The other research has explored the efficacy of the unique formulation of Carboxymethyl dextran (CMD)-chitosan NPs for selective delivery of encapsulated DOX/siRNA (knockdown HMGA2 expression) and antitumor effects on the lung cancer (A549) cell line which includes drug sensitivity, apoptosis, EMT inhibition, and cell migration [169].

Zhou and colleagues designed a co-delivery system using hydroxyethyl starch-polylactide (HES-PLA) NPs, wherein DOX and the TGF-β receptor inhibitor, LY2157299 (LY), have delivered concurrently. In-vitro and in-vivo investigations show that the mentioned co-delivery method is able to reduce both original cancer and remote metastases [170]. Additional research on immunofluorescence pictures of main tumors confirms that a modest dosage of DOX aggravates the EMT program, but the co-delivery NPs can significantly decrease EMT development [170].

To improve the α-mangostin's biological activity, Chandra Boinpelly et al. created α-mangostin-encapsulated PLGA NPs (Mang-NPs) and investigated the molecular pathways through which Mang-NPs prevent EMT, cell survival of CRC, formation of the colony, and cause apoptosis [171]. Mang-NPs also prevented EMT by upregulating E-cadherin and stopping N-cadherin in addition to the transcription factors Zeb1, Snail, and Slug [171].

In recent research Zoledronic acid (ZOL)-loaded lipidic NPs were developed by Sabzichi et al. to improve the efficacy of paclitaxel (Pac) in terms of apoptosis, cytotoxicity, and invasiveness in HepG2 cancer cells by inhibiting EMT [172].

In the other research, Cai evaluated the efficacy of various doses of paclitaxel-containing nano-apoliposomes on cisplatin (DDP)-resistant nasopharyngeal cancer cells, known as CNE1/DDP and CNE2/DDP, in-vitro [173]. Paclitaxel-containing nano-apoliposomes prevented the incursion, proliferation, relocation, and EMT of CNE1/DDP and CNE2/DDP cells, revealing their inhibitory activity on cisplatin-resistant nasopharyngeal cancerous cells [173].

To selectively target and downregulate anexelekto, Suresh et al. designed a siRNA-gelatin-antibody nanoconjugate [174]. They achieved moderate downregulation effectiveness of around 70–80% by delivering siRNA using covalently attached EGFR-targeted gelatin NPs. The outcomes from this investigation verify the anexelekto's role in inhibiting p53 protein via the adjustment of EMT and mTOR [174]. These consequences demonstrate the significance of anexelekto and the nanotechnology application to struggle resistance of drugs in tumors [174].

Li et al. used a targeted co-delivery nanocarrier to produce a combination treatment of microRNA-21 antisense oligonucleotides (ASO-miR-21) and gemcitabine (Gem) and evaluated the synergistic suppression efficacy on the PC cells metastasis and proliferation [175].

ASO-miR-21 and Gem are co-delivered via polyethylene glycol–polyethylene-imine–magnetic iron oxide NPs. By applying a tailored nanomedicine co-delivery method, the researchers discovered that miR-21 ASO and Gem have a synergetic inhibitory impact on human pancreatic cancer cells [175]. Downregulation of oncogenic miR-21 by ASO led to overexpression of cancer-inhibitor genes and EMT blocking, which reduced PC cell proliferation, migration, clonal formation, and invasion in-vitro and greatly decreased in-vivo liver metastasis [175].

In the other research to boost the anticancer impact of cargos against colorectal cancer cells, Hong and colleagues created NPs with a core of polymer that carries miR-139 or afatinib and were enclosed by modified lipids with a targeting ligand and a pH-responsive penetrating peptide [176]. This multifunctional NP was designed to improve the colon cancer cells' susceptibility to afatinib by modulating apoptosis, HER, EGFR, EMT, resistance, and progression pathways. [176].

In 2016, Shen et al., administered 188Re-Liposome intraperitoneally to destroy CSC-like cells in tumors and altered metabolism from glycolysis to oxidative phosphorylation [177]. In addition, intraperitoneal distribution of 188Re-Liposome therapy could prevent EMT and restore p53 operation. The molecular alterations combine to provide a potent tumor-killing impact [177].

Another study by Lu et al. revealed that folate (FA)-labeled human serum albumin (HSA) can inhibit colony formation, cell invasion, and EMT [178].

Applications of nanotechnology in inhibiting EMT in solid tumors are listed in Table 2.

5. Conclusion and future outlook

Resistance to chemotherapy remains a significant challenge in the treatment of cancer. Recent research has presented compelling evidence that the reactivation of EMT, a latent developmental process, plays a critical role in chemo-resistance in various solid tumors such as glioblastoma, lung cancer, breast cancer, pancreatic cancer, gastric cancer, hepatocellular carcinoma, and ovarian cancer. By targeting EMT in solid tumors, we may discover a new approach to overcome chemo-resistance. This can be achieved by using nanotechnology to either

Table 2
Applications of nanotechnology in inhibiting EMT in solid tumors.

Type of Nanoparticle	Utilized cancer type	Description	Ref.
Gold nanoparticles (AuNPs)	Skin cancer and Lung cancer (B16F10 cells)	Enhanced blood flow, help normalize tumor vasculature, and reduce hypoxia.	[179]
	Pancreatic cancer	Suppressed migration and colony formation and reduced gemcitabine-induced EMT, stemness, and MAPK activation on a mechanistic level.	[156]
	Melanoma cancer	GR-targeted gold-withaferin nanoconjugate slowed the development of solid tumors.	[157]
	Breast cancer	AuNPs-Qu-5 inhibited EMT, metastasis, and angiogenesis, in breast cancer cells.	[158]
Metal Oxides and other metal Nanoparticles	Liver cancer (SMMC-7721 cell line)	ZnO-NPs can suppress cell proliferation, and trigger apoptosis, and EMT.	[159]
	Lung cancer	MEG3 performs a significant role in the progress of nickel oxide (NiO) NPs-induced lung fibrosis. By decreasing transforming growth factor-β1 (TGF-β1) expression and EMT, maternally expressed gene 3 (MEG3) may act as a pulmonary fibrosis suppressor.	[160]
	Lung cancer (A549 cell line)	TGFβ signaling was blocked by TiO_2-NPs, which inhibits the EMT process. TiO_2-NPs, in particular, make a connection with the TGFβ receptor TβRI/II complex, causing its degradation of lysosomal and, as a result, downregulating TGFβ target gene expression.	[161]
	Glioblastoma	VP16-loaded layered double hydroxide (LDH) reduced the expression of GSC pluripotency genes and inverted the EMT procedure.	[162]
Hybrid nanocomposites	Several solid tumor types	TWIST1 targeted genes and migratory capacity were reduced in-vitro after siRNA administration through polyethyleneimine-coated mesoporous silica NPs (MSN0).	[163]
	EMT-type cancer cells	epigallocatechin gallate/iron nano-complexes (EIN) was shown to be effective in eliminating EMT-type cancer cells in-vitro and down-regulated the downstream expression of metastasis-associated proteins, reduced cancerous cell migratory capacity, and prevented cancer cells from developing resistance to drugs.	[164]
	Liver cancer	ZnAs and SiO_2 efficiently inhibited the growth, initiation, and metastasis of tumors, and suppressed EMT and stemness in liver cancerous cells in-vitro and in-vivo by adjusting the SHP-1/JAK2/STAT3 signaling pathway.	[165]
	Breast cancer	MWCNT/PBI/Pt showed a substantial preventing impact on the EMT and CSCs' cell cycle markers, as well as a drastic drop in the CSC proliferation rate.	[166]
Organic-based Nanoparticles	Murine B16 melanoma cells	Carboxylated NDs stopped the migration and metastasis by blocking EMT via the TGF-β signaling pathway.	[167]
	KB cells (oral squamous cell carcinoma)	PEG-PEI-Ce6 NPs were used to effectively transport Wnt-1 small interfering RNA (siRNA) to the cytoplasm of KB cells. The Wnt/β-catenin signaling pathway was efficiently blocked by Wnt-1 siRNA, which reduced the expression of Wnt-1, β-catenin, and vimentin, all of which are important in the EMT.	[168]
	lung cancer (A549 cell line)	Carboxymethyl dextran (CMD)-chitosan NPs lead to drug sensitivity, apoptosis, and EMT inhibition.	[169]
	Breast cancer (4T1 cell line)	Hydroxyethyl starch-polylactide (HES-PLA) NPs able to reduce both original cancer and remote metastases	[170]
	Colorectal cancer	α-mangostin-encapsulated PLGA NPs (Mang-NPs) prevented EMT, cell survival of CRC, formation of the colony, and caused apoptosis. Mang-NPs also prevented EMT by upregulating E-cadherin and stopping N-cadherin in addition to the transcription factors Zeb1, Snail, and Slug.	[171]
	Liver cancer (HepG2 cancer cells)	Zoledronic acid (ZOL)-loaded lipidic NPs improved the efficacy of paclitaxel (Pac) in terms of apoptosis, cytotoxicity, and invasiveness in HepG2 cancer cells by inhibiting EMT.	[180]
	Nasopharyngeal cancer cells	Paclitaxel-containing nano-apoliposomes prevented the incursion, proliferation, relocation, and EMT of CNE1/DDP and CNE2/DDP cells.	[173]
	Pancreatic cancer	Downregulation of oncogenic miR-21 by ASO led to overexpression of cancer-inhibitor genes and EMT blocking.	[175]

(*continued on next page*)

Table 2 (*continued*)

Type of Nanoparticle	Utilized cancer type	Description	Ref.
	Colorectal cancer	Created NPs with a core of polymer that carries miR-139 or afatinib improved the colon cancer cells' susceptibility to afatinib by modulating apoptosis, HER, EGFR, EMT, resistance, and progression pathways.	[176]
	CSC-like cells	88Re-Liposome therapy prevented EMT and restored p53 operation.	[177]
	Nasopharyngeal cancer cells	Folate (FA)-labeled human serum albumin (HSA) inhibited colony formation, cell invasion, and EMT.	[178, 181]

inhibit EMT or deliver therapeutic agents against EMT pathways. The use of these functional nanomaterials enhances chemosensitivity and the effectiveness of therapy. In conclusion, the evidence presented in this review indicates that nanomedicine-based therapeutic strategies that target EMT may lower tumor cell resistance to both traditional and unconventional chemotherapy treatments in solid tumors.

In the future, more investigations are necessary to explore the potential of combining nanotechnology with other emerging techniques in cancer treatment, such as immunotherapy and gene therapy.

Recent research has shown that combining nanotechnology with immunotherapy can enhance the effectiveness of immune checkpoint inhibitors, which are a type of cancer treatment that helps the body's immune system to attack cancer cells. Further studies are required to examine if combining nanotechnology with other emerging techniques in cancer treatment or nanotechnology-based gene therapy could promise to inhibit EMT and reduce chemo-resistance in solid tumors.

CRediT authorship contribution statement

Razlansari Mahtab: Writing – original draft. **Liaghat Mahsa:** Writing – original draft. **Akbari Abdullatif:** Writing – original draft. **Ebrahimi Narges:** Writing – original draft. **Noorbakhsh Varnosfaderani Seyed Mostafa:** Writing – original draft. **Norouzi Ali:** Writing – original draft. **Maleki-Sheikhabadi Fahimeh:** Writing – review & editing, Writing – original draft, Resources. **Zalpoor Hamidreza:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Investigation, Conceptualization. **Bakhtiyari Maryam:** Writing – original draft, Software. **Rahdar Abbas:** Visualization, Supervision. **Heidari Ali H.:** Writing – original draft. **Nabi-Afjadi Mohsen:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Conceptualization. **Tangsiri Mona:** Writing – original draft.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Author contributions

H.Z and MN-A conceived and designed the study and headings. M.T, AHH, M.R, N.E, M.L, A.A, SM.NV, F.M, H.Z and M.N-A wrote the manuscript. H.Z and M.N-A edited the final manuscript. H.Z, M.N-A and A.R supervised the study. M.T, M.L, F.M, A.HH, H.Z, and M.N-A revised the manuscript. All authors read and approved the final manuscript.

References

[1] L.A. Torre, F. Bray, R.L. Siegel, J. Ferlay, J. Lortet-Tieulent, A. Jemal, Global cancer statistics, 2012, CA: a Cancer J. Clin. 65 (2) (2015) 87–108.
[2] S.T. Pan, Z.L. Li, Z.X. He, J.X. Qiu, S.F. Zhou, Molecular mechanisms for tumour resistance to chemotherapy, Clin. Exp. Pharmacol. Physiol. 43 (8) (2016) 723–737.
[3] R.A. Gatenby, A change of strategy in the war on cancer, Nature 459 (7246) (2009) 508–509.
[4] B.A. Chabner, T.G. Roberts, Chemotherapy and the war on cancer, Nat. Rev. Cancer 5 (1) (2005) 65–72.
[5] W. Chen, R. Zheng, P.D. Baade, S. Zhang, H. Zeng, F. Bray, et al., Cancer statistics in China, 2015, CA: a Cancer J. Clin. 66 (2) (2016) 115–132.
[6] M.T. Piccolo, C. Menale, S. Crispi, Combined anticancer therapies: an overview of the latest applications, Anti-Cancer Agents Med. Chem. 15 (4) (2015) 408–422.
[7] P. Ramos, M. Bentires-Alj, Mechanism-based cancer therapy: resistance to therapy, therapy for resistance, Oncogene 34 (28) (2015) 3617–3626.
[8] L.S. Goodman, M.M. Wintrobe, W. Dameshek, M.J. Goodman, A. Gilman, M. T. McLENNAN, Nitrogen mustard therapy: Use of methyl-bis (beta-chloroethyl) amine hydrochloride and tris (beta-chloroethyl) amine hydrochloride for hodgkin's disease, lymphosarcoma, leukemia and certain allied and miscellaneous disorders, J. Am. Med. Assoc. 132 (3) (1946) 126–132.
[9] S. Seton-Rogers, Preventing competitive release, Nat. Rev. Cancer 16 (4) (2016) 199.
[10] S.D. Undevia, G. Gomez-Abuin, M.J. Ratain, Pharmacokinetic variability of anticancer agents, Nat. Rev. Cancer 5 (6) (2005) 447–458.
[11] H.-C. Zheng, The molecular mechanisms of chemoresistance in cancers, Oncotarget 8 (35) (2017) 59950.
[12] M.C. Cavaco, C. Pereira, B. Kreutzer, L.F. Gouveia, B. Silva-Lima, A.M. Brito, et al., Evading P-glycoprotein mediated-efflux chemoresistance using solid lipid nanoparticles, Eur. J. Pharm. Biopharm. 110 (2017) 76–84.
[13] M. Kumari, P.T. Krishnamurthy, P. Sola, Targeted drug therapy to overcome chemoresistance in triple-negative breast cancer, Curr. Cancer Drug Targets 20 (8) (2020) 559–572.
[14] Q.-Y. Wei, Y.-M. Xu, A.T. Lau, Recent progress of nanocarrier-based therapy for solid malignancies, Cancers 12 (10) (2020) 2783.
[15] N.K. Garg, N. Tandel, R.S. Jadon, R.K. Tyagi, O.P. Katare, Lipid–polymer hybrid nanocarrier-mediated cancer therapeutics: current status and future directions, Drug Discov. Today 23 (9) (2018) 1610–1621.
[16] E. Pérez-Herrero, A. Fernández-Medarde, Advanced targeted therapies in cancer: drug nanocarriers, the future of chemotherapy, Eur. J. Pharm. Biopharm. 93 (2015) 52–79.
[17] P. Jain, H. Kathuria, M. Momin, Clinical therapies and nano drug delivery systems for urinary bladder cancer, Pharmacol. Ther. 226 (2021), 107871.
[18] M.A. Nieto, R.Y.-J. Huang, R.A. Jackson, J.P. Thiery, EMT: 2016, Cell 166 (1) (2016) 21–45.
[19] T. Brabletz, To differentiate or not—routes towards metastasis, Nat. Rev. Cancer 12 (6) (2012) 425–436.
[20] I. Pastushenko, C. Blanpain, EMT transition states during tumor progression and metastasis, Trends Cell Biol. 29 (3) (2019) 212–226.
[21] S. Razi, A. Haghparast, S. Chodari Khameneh, A. Ebrahimi Sadrabadi, F. Aziziyan, M. Bakhtiyari, et al., The role of tumor microenvironment on cancer stem cell fate in solid tumors, Cell Commun. Signal. 21 (1) (2023) 1–23.
[22] A. Puisieux, T. Brabletz, J. Caramel, Oncogenic roles of EMT-inducing transcription factors, Nat. Cell Biol. 16 (6) (2014) 488–494.
[23] E. Sánchez-Tilló, Y. Liu, O. de Barrios, L. Siles, L. Fanlo, M. Cuatrecasas, et al., EMT-activating transcription factors in cancer: beyond EMT and tumor invasiveness, Cell. Mol. Life Sci. 69 (20) (2012) 3429–3456.
[24] Y.N. Liu, J.J. Yin, W. Abou-Kheir, P.G. Hynes, O.M. Casey, L. Fang, et al., MiR-1 and miR-200 inhibit EMT via Slug-dependent and tumorigenesis via Slug-independent mechanisms, Oncogene 32 (3) (2013) 296–306.
[25] Y. Sun, A. Daemen, G. Hatzivassiliou, D. Arnott, C. Wilson, G. Zhuang, et al., Metabolic and transcriptional profiling reveals pyruvate dehydrogenase kinase 4 as a mediator of epithelial-mesenchymal transition and drug resistance in tumor cells, Cancer Metab. 2 (1) (2014) 1–14.
[26] K.C. Wang, H.Y. Chang, Molecular mechanisms of long noncoding RNAs, Mol. Cell 43 (6) (2011) 904–914.
[27] Y.G. Chen, A.T. Satpathy, H.Y. Chang, Gene regulation in the immune system by long noncoding RNAs, Nat. Immunol. 18 (9) (2017) 962–972.
[28] S.J. O'Brien, C. Bishop, J. Hallion, C. Fiechter, K. Scheurlen, M. Paas, et al., Long non-coding RNA (lncRNA) and epithelial-mesenchymal transition (EMT) in colorectal cancer: a systematic review, Cancer Biol. Ther. 21 (9) (2020) 769–781.
[29] X. Wang, X. Liang, H. Liang, B. Wang, SENP1/HIF-1α feedback loop modulates hypoxia-induced cell proliferation, invasion, and EMT in human osteosarcoma cells, J. Cell. Biochem. 119 (2) (2018) 1819–1826.
[30] K.H.I.F. Balamurugan, -1 at the crossroads of hypoxia, inflammation, and cancer, Int. J. Cancer 138 (5) (2016) 1058–1066.
[31] W. Liu, S.-M. Shen, X.-Y. Zhao, G.-Q. Chen, Targeted genes and interacting proteins of hypoxia inducible factor-1, Int. J. Biochem. Mol. Biol. 3 (2) (2012) 165.

[32] A. Dongre, R.A. Weinberg, New insights into the mechanisms of epithelial–mesenchymal transition and implications for cancer, Nat. Rev. Mol. Cell Biol. 20 (2) (2019) 69–84.
[33] R. Yang, M. Yi, B. Xiang, Novel Insights on Lipid Metabolism Alterations in Drug Resistance in Cancer, Front. Cell Dev. Biol. 10 (2022), 875318.
[34] H. Zalpoor, M. Bakhtiyari, H. Shapourian, P. Rostampour, C. Tavakol, M. Nabi-Afjadi, Hesperetin as an anti-SARS-CoV-2 agent can inhibit COVID-19-associated cancer progression by suppressing intracellular signaling pathways, Inflammopharmacology (2022) 1–7.
[35] M. Jiao, K.-J. Nan, Activation of PI3 kinase/Akt/HIF-1α pathway contributes to hypoxia-induced epithelial-mesenchymal transition and chemoresistance in hepatocellular carcinoma, Int. J. Oncol. 40 (2) (2012) 461–468.
[36] Z. Xu, Y. Zhang, H. Dai, B. Han, Epithelial–Mesenchymal Transition-Mediated Tumor Therapeutic Resistance, Molecules 27 (15) (2022) 4750.
[37] H. Zalpoor, A. Akbari, M. Nabi-Afjadi, Ephrin (Eph) receptor and downstream signaling pathways: a promising potential targeted therapy for COVID-19 and associated cancers and diseases, Hum. Cell 35 (3) (2022) 952–954.
[38] H. Zalpoor, A. Akbari, A. Samei, R. Forghaniesfidvajani, M. Kamali, A. Afzalnia, et al., The roles of Eph receptors, neuropilin-1, P2X7, and CD147 in COVID-19-associated neurodegenerative diseases: inflammasome and JaK inhibitors as potential promising therapies, Cell. Mol. Biol. Lett. 27 (1) (2022) 1–21.
[39] H. Zalpoor, H. Shapourian, A. Akbari, S. Shahveh, L. Haghshenas, Increased neuropilin-1 expression by COVID-19: a possible cause of long-term neurological complications and progression of primary brain tumors, Hum. Cell (2022) 1–3.
[40] M. Karami Fath, N. Karimfar, A. Fazlollahpour Naghibi, S. Shafa, M. Ghasemi Shiran, M. Ataei, et al., Revisiting characteristics of oncogenic extrachromosomal DNA as mobile enhancers on neuroblastoma and glioma cancers, Cancer Cell Int. 22 (1) (2022) 1–14.
[41] H. Fahmideh, H. Shapourian, R. Moltafeti, C. Tavakol, R. Forghaniesfidvajani, H. Zalpoor, et al., The role of natural products as inhibitors of JAK/STAT signaling pathways in glioblastoma treatment, Oxid. Med. Cell. Longev. (2022) 2022.
[42] W. Ning, Z. Qiu, X. Ji, X. Wang, Y. An, S. Wang, et al., The prognostic value of EMT in glioma and its role in the glioma immune microenvironment, J. Mol. Neurosci. 70 (10) (2020) 1501–1511.
[43] H. Li, J. Li, L. Chen, S. Qi, S. Yu, Z. Weng, et al., HERC3-mediated SMAD7 ubiquitination degradation promotes autophagy-induced EMT and chemoresistance in glioblastoma, Clin. Cancer Res. 25 (12) (2019) 3602–3616.
[44] S. Guelfi, B. Orsetti, V. Deleuze, V. Rigau, L. Bauchet, H. Duffau, et al., SLUG and truncated TAL1 reduce glioblastoma stem cell growth downstream of notch1 and define distinct vascular subpopulations in glioblastoma multiforme, Cancers 13 (21) (2021) 5393.
[45] G. Finocchiaro, G. Berzero, Glioblastomas, MDPI (2021) 104.
[46] T. Brabletz, A. Jung, S. Reu, M. Porzner, F. Hlubek, L.A. Kunz-Schughart, et al., Variable β-catenin expression in colorectal cancers indicates tumor progression driven by the tumor environment, Proc. Natl. Acad. Sci. 98 (18) (2001) 10356–10361.
[47] T. Brabletz, A. Jung, S. Spaderna, F. Hlubek, T. Kirchner, Migrating cancer stem cells—an integrated concept of malignant tumour progression, Nat. Rev. Cancer 5 (9) (2005) 744–749.
[48] J.A. Nathan, H. Tae Kim, L. Ting, S.P. Gygi, A.L. Goldberg, Why do cellular proteins linked to K63–polyubiquitin chains not associate with proteasomes? EMBO J. 32 (4) (2013) 552–565.
[49] U.D. Kahlert, D. Maciaczyk, S. Doostkam, B.A. Orr, B. Simons, T. Bogiel, et al., Activation of canonical WNT/β-catenin signaling enhances in vitro motility of glioblastoma cells by activation of ZEB1 and other activators of epithelial-to-mesenchymal transition, Cancer Lett. 325 (1) (2012) 42–53.
[50] X. Di, X. Jin, R. Li, M. Zhao, K. Wang, CircRNAs and lung cancer: biomarkers and master regulators, Life Sci. 220 (2019) 177–185.
[51] J. Zhou, S. Zhang, Z. Chen, Z. He, Y. Xu, Z. Li, CircRNA-ENO1 promoted glycolysis and tumor progression in lung adenocarcinoma through upregulating its host gene ENO1, Cell Death Dis. 10 (12) (2019) 1–14.
[52] C. Wang, S. Tan, W.-R. Liu, Q. Lei, W. Qiao, Y. Wu, et al., RNA-Seq profiling of circular RNA in human lung adenocarcinoma and squamous cell carcinoma, Mol. Cancer 18 (1) (2019) 1–6.
[53] R.J. Lobb, R. van Amerongen, A. Wiegmans, S. Ham, J.E. Larsen, A. Möller, Exosomes derived from mesenchymal non-small cell lung cancer cells promote chemoresistance, Int. J. Cancer 141 (3) (2017) 614–620.
[54] K.R. Fischer, A. Durrans, S. Lee, J. Sheng, F. Li, S.T. Wong, et al., Epithelial-to-mesenchymal transition is not required for lung metastasis but contributes to chemoresistance, Nature 527 (7579) (2015) 472–476.
[55] X. Zheng, J.L. Carstens, J. Kim, M. Scheible, J. Kaye, H. Sugimoto, et al., Epithelial-to-mesenchymal transition is dispensable for metastasis but induces chemoresistance in pancreatic cancer, Nature 527 (7579) (2015) 525–530.
[56] J.E. Larsen, V. Nathan, J.K. Osborne, R.K. Farrow, D. Deb, J.P. Sullivan, et al., ZEB1 drives epithelial-to-mesenchymal transition in lung cancer, J. Clin. Investig. 126 (9) (2016) 3219–3235.
[57] Y. Otsuki, H. Saya, Y. Arima, Prospects for new lung cancer treatments that target EMT signaling, Dev. Dyn. 247 (3) (2018) 462–472.
[58] L. Zhao, S. Liu, X. Che, K. Hou, Y. Ma, C. Li, et al., Bufalin inhibits TGF-β-induced epithelial-to-mesenchymal transition and migration in human lung cancer A549 cells by downregulating TGF-β receptors, Int. J. Mol. Med. 36 (3) (2015) 645–652.
[59] Y.K. Chae, S. Chang, T. Ko, J. Anker, S. Agte, W. Iams, et al., Epithelial-mesenchymal transition (EMT) signature is inversely associated with T-cell infiltration in non-small cell lung cancer (NSCLC), Sci. Rep. 8 (1) (2018) 1–8.
[60] R.Y.-J. Huang, T.Y.-Y. Huang, A new dimension in drug discovery: reversing epithelial–mesenchymal transition (EMT), Cell Death Dis. 7 (10) (2016), e2417.
[61] S.A. Mani, W. Guo, M.-J. Liao, E.N. Eaton, A. Ayyanan, A.Y. Zhou, et al., The epithelial-mesenchymal transition generates cells with properties of stem cells, Cell 133 (4) (2008) 704–715.
[62] E.D. Williams, D. Gao, A. Redfern, E.W. Thompson, Controversies around epithelial–mesenchymal plasticity in cancer metastasis, Nat. Rev. Cancer 19 (12) (2019) 716–732.
[63] Y. He, H. Xie, P. Yu, S. Jiang, L. Wei, FOXC2 promotes epithelial–mesenchymal transition and cisplatin resistance of non-small cell lung cancer cells, Cancer Chemother. Pharmacol. 82 (6) (2018) 1049–1059.
[64] S. Raoof, I.J. Mulford, H. Frisco-Cabanos, V. Nangia, D. Timonina, E. Labrot, et al., Targeting FGFR overcomes EMT-mediated resistance in EGFR mutant non-small cell lung cancer, Oncogene 38 (37) (2019) 6399–6413.
[65] J. De Las Rivas, A. Brozovic, S. Izraely, A. Casas-Pais, I.P. Witz, A. Figueroa, Cancer drug resistance induced by EMT: novel therapeutic strategies, Arch. Toxicol. 95 (7) (2021) 2279–2297.
[66] A.-F. Lee, M.-C. Chen, C.-J. Chen, C.-J. Yang, M.-S. Huang, Y.-P. Liu, Reverse epithelial-mesenchymal transition contributes to the regain of drug sensitivity in tyrosine kinase inhibitor-resistant non-small cell lung cancer cells, PLoS One 12 (7) (2017), e0180383.
[67] D.-m Wu, T. Zhang, Y.-B. Liu, S.-h Deng, R. Han, T. Liu, et al., The PAX6-ZEB2 axis promotes metastasis and cisplatin resistance in non-small cell lung cancer through PI3K/AKT signaling, Cell Death Dis. 10 (5) (2019) 1–15.
[68] K. Namba, K. Shien, Y. Takahashi, H. Torigoe, H. Sato, T. Yoshioka, et al., Activation of AXL as a preclinical acquired resistance mechanism against osimertinib treatment in EGFR-Mutant non–small cell lung cancer cells, Mol. Cancer Res. 17 (2) (2019) 499–507.
[69] A.E. Sayan, T.R. Griffiths, R. Pal, G.J. Browne, A. Ruddick, T. Yagci, et al., SIP1 protein protects cells from DNA damage-induced apoptosis and has independent prognostic value in bladder cancer, Proc. Natl. Acad. Sci. 106 (35) (2009) 14884–14889.
[70] K.-A. Song, M.J. Niederst, T.L. Lochmann, A.N. Hata, H. Kitai, J. Ham, et al., Epithelial-to-mesenchymal transition antagonizes response to targeted therapies in lung cancer by suppressing BIM, Clin. Cancer Res. 24 (1) (2018) 197–208.
[71] Q.-y Chen, D.-m Jiao, J. Wang, H. Hu, X. Tang, J. Chen, et al., miR-206 regulates cisplatin resistance and EMT in human lung adenocarcinoma cells partly by targeting MET, Oncotarget 7 (17) (2016) 24510.
[72] M. Karami Fath, K. Babakhaniyan, M. Zokaei, A. Yaghoubian, S. Akbari, M. Khorsandi, et al., Anti-cancer peptide-based therapeutic strategies in solid tumors, Cell. Mol. Biol. Lett. 27 (1) (2022) 1–26.
[73] M. Moslemi, Y. Moradi, H. Dehghanbanadaki, H. Afkhami, M. Khaledi, N. Sedighimehr, et al., The association between ATM variants and risk of breast cancer: a systematic review and meta-analysis, BMC Cancer 21 (1) (2021) 1–12.
[74] E. Sohrabi, M. Moslemi, E. Rezaie, N. Nafissi, M. Khaledi, H. Afkhami, et al., The tissue expression of MCT3, MCT8, and MCT9 genes in women with breast cancer, Genes Genom. 43 (9) (2021) 1065–1077.
[75] M. Karami Fath, A. Azargoonjahromi, A. Kiani, F. Jalalifar, P. Osati, M. Akbari Oryani, et al., The role of epigenetic modifications in drug resistance and treatment of breast cancer, Cell. Mol. Biol. Lett. 27 (1) (2022) 1–25.
[76] A. Gorgzadeh, A. Hheidari, P. Ghanbarikondori, M. Arastonejad, T.G. Goki, M. Aria, et al., Investigating the Properties and Cytotoxicity of Cisplatin-Loaded Nano-Polybutylcyanoacrylate on Breast Cancer Cells, Asian Pac. J. Cancer Biol. 8 (4) (2023) 345–350.
[77] Y. Lu, Y. Ding, J. Wei, S. He, X. Liu, H. Pan, et al., Anticancer effects of Traditional Chinese Medicine on epithelial-mesenchymal transition (EMT) in breast cancer: cellular and molecular targets, Eur. J. Pharmacol. 907 (2021), 174275.
[78] T. Saha, K.E. Lukong, Breast cancer stem-like cells in drug resistance: a review of mechanisms and novel therapeutic strategies to overcome drug resistance, Front. Oncol. 12 (2022), 856974.
[79] F. Seif, Z. Torki, H. Zalpoor, M. Habibi, M. Pornour, Breast cancer tumor microenvironment affects Treg/IL-17-producing Treg/Th17 cell axis: Molecular and therapeutic perspectives, Mol. Ther. Oncolytics 28 (2023) 132.
[80] Q. Zheng, M. Zhang, F. Zhou, L. Zhang, X. Meng, The breast Cancer stem cells traits and drug resistance, Front. Pharmacol. 2120 (2021).
[81] M. Saxena, M.A. Stephens, H. Pathak, A. Rangarajan, Transcription factors that mediate epithelial–mesenchymal transition lead to multidrug resistance by upregulating ABC transporters, Cell death Dis. 2 (7) (2011) e179-e179.
[82] Y.-x Feng, E.S. Sokol, C.A. Del Vecchio, S. Sanduja, J.H. Claessen, T.A. Proia, et al., Epithelial-to-mesenchymal transition activates PERK–eIF2α and sensitizes cells to endoplasmic reticulum stress, Cancer Discov. 4 (6) (2014) 702–715.
[83] P.B. Gupta, T.T. Onder, G. Jiang, K. Tao, C. Kuperwasser, R.A. Weinberg, et al., Identification of selective inhibitors of cancer stem cells by high-throughput screening, Cell 138 (4) (2009) 645–659.
[84] D. Olmeda, G. Moreno-Bueno, J.M. Flores, A. Fabra, F. Portillo, A. Cano, SNAI1 is required for tumor growth and lymph node metastasis of human breast carcinoma MDA-MB-231 cells, Cancer Res. 67 (24) (2007) 11721–11731.
[85] J.T. Lei, J. Shao, J. Zhang, M. Iglesia, D.W. Chan, J. Cao, et al., Functional annotation of ESR1 gene fusions in estrogen receptor-positive breast cancer, Cell Rep. 24 (6) (2018) 1434–1444, e7.
[86] S.M. Abdin, M.F. Tolba, D.M. Zaher, H.A. Omar, Nuclear factor-κB signaling inhibitors revert multidrug-resistance in breast cancer cells, Chem. -Biol. Interact. 340 (2021), 109450.
[87] M.K. Wendt, T.M. Allington, W.P. Schiemann, Mechanisms of the epithelial–mesenchymal transition by TGF-β, Future Oncol. 5 (8) (2009) 1145–1168.

[88] C.J. Gröger, M. Grubinger, T. Waldhör, K. Vierlinger, W. Mikulits, Meta-analysis of gene expression signatures defining the epithelial to mesenchymal transition during cancer progression, PloS One 7 (12) (2012), e51136.
[89] Saremi M.A., Poorhasan N. Epithelial-Mesenchymal Transition Pathways in Breast Cancer. 2021.
[90] M.-Y. Ho, S.-J. Tang, M.-J. Chuang, T.-L. Cha, J.-Y. Li, G.-H. Sun, et al., TNF-α induces epithelial–mesenchymal transition of renal cell carcinoma cells via a GSK3β-dependent mechanism, Mol. Cancer Res. 10 (8) (2012) 1109–1119.
[91] M.V. Iorio, M. Ferracin, C.-G. Liu, A. Veronese, R. Spizzo, S. Sabbioni, et al., MicroRNA gene expression deregulation in human breast cancer, Cancer Res. 65 (16) (2005) 7065–7070.
[92] X. Hu, W. Chen, Role of epithelial-mesenchymal transition in chemoresistance in pancreatic ductal adenocarcinoma, World J. Clin. Cases 9 (19) (2021) 4998.
[93] Y. Lian, D. Jiang, J. Sun, Tumor suppressive role of miR-33a-5p in pancreatic ductal adenocarcinoma cells by directly targeting RAP2A, Cell. Mol. Biol. Lett. 26 (1) (2021) 1–13.
[94] O. Elaskalani, N.B.A. Razak, M. Falasca, P. Metharom, Epithelial-mesenchymal transition as a therapeutic target for overcoming chemoresistance in pancreatic cancer, World J. Gastrointest. Oncol. 9 (1) (2017) 37.
[95] A. Rice, E. Cortes, D. Lachowski, B. Cheung, S. Karim, J. Morton, et al., Matrix stiffness induces epithelial–mesenchymal transition and promotes chemoresistance in pancreatic cancer cells, Oncogenesis 6 (7) (2017) e352-e352.
[96] A. Cannon, C. Thompson, B.R. Hall, M. Jain, S. Kumar, S.K. Batra, Desmoplasia in pancreatic ductal adenocarcinoma: insight into pathological function and therapeutic potential, Genes Cancer 9 (3–4) (2018) 78.
[97] T. Celià-Terrassa, M.K. Jolly, Cancer stem cells and epithelial-to-mesenchymal transition in cancer metastasis, Cold Spring Harb. Perspect. Med. 10 (7) (2020) a036905.
[98] Z. Abedi Cham Heidari, P. Ghanbarikondori, E. Mortazavi Mamaghani, A. Hheidari, E. Saberian, E. Mozaffari, et al., Characteristics and cytotoxic effects of nano-liposomal paclitaxel on gastric cancer cells, Asian Pac. J. Cancer Prev. 24 (9) (2023) 3291–3296.
[99] A. Akbari, S.M. Noorbakhsh Varnosfaderani, M.S. Haeri, Z. Fathi, F. Aziziyan, A. Yousefi Rad, et al., Autophagy induced by Helicobacter Pylori infection can lead to gastric cancer dormancy, metastasis, and recurrence: new insights, Hum. Cell (2023) 1–15.
[100] H. Zalpoor, M. Nabi-Afjadi, R. Forghaniesfidvajani, C. Tavakol, F. Farahighasreaboonasr, F. Pakizeh, et al., Quercetin as a JAK–STAT inhibitor: a potential role in solid tumors and neurodegenerative diseases, Cell. Mol. Biol. Lett. 27 (1) (2022) 60.
[101] S. Tanida, T. Mizoshita, K. Ozeki, H. Tsukamoto, T. Kamiya, H. Kataoka, et al., Mechanisms of cisplatin-induced apoptosis and of cisplatin sensitivity: potential of BIN1 to act as a potent predictor of cisplatin sensitivity in gastric cancer treatment, Int. J. Surg. Oncol. 2012 (2012).
[102] M. Ashrafizadeh, A. Zarrabi, K. Hushmandi, M. Kalantari, R. Mohammadinejad, T. Javaheri, et al., Association of the epithelial–mesenchymal transition (EMT) with cisplatin resistance, Int. J. Mol. Sci. 21 (11) (2020) 4002.
[103] D. Fu, C. Wang, L. Yu, R. Yu, Induction of ferroptosis by ATF3 elevation alleviates cisplatin resistance in gastric cancer by restraining Nrf2/Keap1/xCT signaling, Cell. Mol. Biol. Lett. 26 (1) (2021) 1–14.
[104] J. Li, J. Yuan, Y. Li, J. Wang, D. Gong, Q. Xie, et al., d-Borneol enhances cisplatin sensitivity via p21/p27-mediated S-phase arrest and cell apoptosis in non-small cell lung cancer cells and a murine xenograft model, Cell. Mol. Biol. Lett. 27 (1) (2022) 1–20.
[105] M. Kanmalar, S.F. Abdul Sani, Raman spectroscopy biochemical characterisation of bladder cancer cisplatin resistance regulated by FDFT1: a review, Cell. Mol. Biol. Lett. 27 (1) (2022) 1–20.
[106] M. Wang, R. Qiu, S. Yu, X. Xu, G. Li, R. Gu, et al., Paclitaxel-resistant gastric cancer MGC-803 cells promote epithelial-to-mesenchymal transition and chemoresistance in paclitaxel-sensitive cells via exosomal delivery of miR-155–5p, Int. J. Oncol. 54 (1) (2019) 326–338.
[107] G. Cao, P. Li, X. He, M. Jin, M. Li, S. Chen, et al., FHL3 contributes to EMT and chemotherapy resistance through Up-regulation of slug and activation of TGFβ/smad-independent pathways in gastric cancer, Front. Oncol. 11 (2021).
[108] X. Dai, K.S. Ahn, L.Z. Wang, C. Kim, A. Deivasigamni, F. Arfuso, et al., Ascochlorin enhances the sensitivity of doxorubicin leading to the reversal of epithelial-to-mesenchymal transition in hepatocellular carcinoma, Mol. Cancer Ther. 15 (12) (2016) 2966–2976.
[109] J.L. Ma, S. Zeng, Y. Zhang, G.L. Deng, H. Shen, Epithelial–mesenchymal transition plays a critical role in drug resistance of hepatocellular carcinoma cells to oxaliplatin, Tumor Biol. 37 (2016) 6177–6184.
[110] M. Tian, Y. Tang, T. Huang, Y. Liu, Y. Pan, Amelioration of human peritoneal mesothelial cell co-culture-evoked malignant potential of ovarian cancer cells by acacetin involves LPA release-activated RAGE-PI3K/AKT signaling, Cell. Mol. Biol. Lett. 26 (1) (2021) 1–12.
[111] Z. Foruzandeh, F. Zeinali-Sehrig, K. Nejati, D. Rahmanpour, F. Pashazadeh, F. Seif, et al., CircRNAs as potent biomarkers in ovarian cancer: a systematic scoping review, Cell. Mol. Biol. Lett. 26 (1) (2021) 1–29.
[112] R. Cornelison, D.C. Llaneza, C.N. Landen, Emerging therapeutics to overcome chemoresistance in epithelial ovarian cancer: a mini-review, Int. J. Mol. Sci. 18 (10) (2017) 2171.
[113] M.A.A. Padilla, M. Binju, G. Wan, Y.S. Rahmanto, P. Kaur, Y. Yu, Relationship between ovarian cancer stem cells, epithelial mesenchymal transition and tumour recurrence, Cancer Drug Resist. 2 (4) (2019) 1127–1135.
[114] L. Rosanò, R. Cianfrocca, F. Spinella, V. Di Castro, M.R. Nicotra, A. Lucidi, et al., Acquisition of chemoresistance and EMT phenotype is linked with activation of the endothelin A receptor pathway in ovarian carcinoma cells, Clin. Cancer Res. 17 (8) (2011) 2350–2360.
[115] T. Wesley, S. Berzins, G. Kannourakis, N. Ahmed, The attributes of plakins in cancer and disease: perspectives on ovarian cancer progression, chemoresistance and recurrence, Cell Commun. Signal. 19 (1) (2021) 1–21.
[116] K. Dhanuthai, S. Rojanawatsirivej, W. Thosaporn, S. Kintarak, A. Subarnbhesaj, M. Darling, et al., Oral cancer: A multicenter study, Med. Oral., Patol. Oral. Y. cirugia Bucal 23 (1) (2018), e23.
[117] A. Almangush, A.A. Mäkitie, A. Triantafyllou, R. de Bree, P. Strojan, A. Rinaldo, et al., Staging and grading of oral squamous cell carcinoma: an update, Oral. Oncol. 107 (2020), 104799.
[118] S. Irani, New insights into oral cancer—risk factors and prevention: a review of literature, Int. J. Prev. Med. 11 (2020).
[119] S.H. Huang, Oral cancer: current role of radiotherapy and chemotherapy, Med. Oral., Patol. Oral. Y. cirugia Bucal 18 (2) (2013), e233.
[120] Feller L., Lemmer J. Oral squamous cell carcinoma: epidemiology, clinical presentation and treatment. 2012.
[121] L. Olasz, E. Orsi, T. Markó, J. Szalma, Induction chemotherapy response and recurrence rates in correlation with N0 or N+ stage in oral squamous cell cancer (OSCC), Cancer Metastas-.-. Rev. 29 (4) (2010) 607–611.
[122] A. Norouzi, F. Davodabadi, S.M. Noorbakhsh Varnosfaderani, H. Zalpoor, The potential role of acid ceramidase in oral squamous cell carcinoma chemo-resistance by inducing autophagy, Hum. Cell 36 (6) (2023) 2273–2275.
[123] A. Norouzi, M. Liaghat, M. Bakhtiyari, S.M.N. Varnosfaderani, H. Zalpoor, M. Nabi-Afjadi, et al., The potential role of COVID-19 in progression, chemo-resistance, and tumor recurrence of oral squamous cell carcinoma (OSCC), Oral. Oncol. (2023), 106483.
[124] Z.-J. Law, X.H. Khoo, P.T. Lim, B.H. Goh, L.C. Ming, W.-L. Lee, et al., Extracellular vesicle-mediated chemoresistance in oral squamous cell carcinoma, Front. Mol. Biosci. 8 (2021), 629888.
[125] T. Ishida, H. Hijioka, K. Kume, A. Miyawaki, N. Nakamura, Notch signaling induces EMT in OSCC cell lines in a hypoxic environment, Oncol. Lett. 6 (5) (2013) 1201–1206.
[126] B. Du, J.S. Shim, Targeting epithelial–mesenchymal transition (EMT) to overcome drug resistance in cancer, Molecules 21 (7) (2016) 965.
[127] X.-W. Zhao, J.-P. Zhou, Y.-L. Bi, J.-Y. Wang, R. Yu, C. Deng, et al., The role of MAPK signaling pathway in formation of EMT in oral squamous carcinoma cells induced by TNF-α, Mol. Biol. Rep. 46 (3) (2019) 3149–3156.
[128] H. Dawei, D. Honggang, W. Qian, AURKA contributes to the progression of oral squamous cell carcinoma (OSCC) through modulating epithelial-to-mesenchymal transition (EMT) and apoptosis via the regulation of ROS, Biochem. Biophys. Res. Commun. 507 (1–4) (2018) 83–90.
[129] Y. Chen, Z. Shao, E. Jiang, X. Zhou, L. Wang, H. Wang, et al., CCL21/CCR7 interaction promotes EMT and enhances the stemness of OSCC via a JAK2/STAT3 signaling pathway, J. Cell. Physiol. 235 (9) (2020) 5995–6009.
[130] S. Lv, T. Luo, Y. Yang, Y. Li, J. Yang, J. Xu, et al., Naa10p and IKKα interaction regulates EMT in oral squamous cell carcinoma via TGF-β1/Smad pathway, J. Cell. Mol. Med. 25 (14) (2021) 6760–6772.
[131] W. Chu, X. Song, X. Yang, L. Ma, J. Zhu, M. He, et al., Neuropilin-1 promotes epithelial-to-mesenchymal transition by stimulating nuclear factor-kappa B and is associated with poor prognosis in human oral squamous cell carcinoma, PloS One 9 (7) (2014), e101931.
[132] Y. He, H. Xie, P. Yu, S. Jiang, L. Wei, FOXC2 promotes epithelial–mesenchymal transition and cisplatin resistance of non-small cell lung cancer cells, Cancer Chemother. Pharmacol. 82 (2018) 1049–1059.
[133] Y. Wang, B.P. Zhou, Epithelial-mesenchymal transition—a hallmark of breast cancer metastasis, Cancer Hallm. 1 (1) (2013) 38–49.
[134] D. Kong, Y. Li, Z. Wang, F.H. Sarkar, Cancer stem cells and epithelial-to-mesenchymal transition (EMT)-phenotypic cells: are they cousins or twins? Cancers 3 (1) (2011) 716–729.
[135] G. Cao, P. Li, X. He, M. Jin, M. Li, S. Chen, et al., FHL3 contributes to EMT and chemotherapy resistance through up-regulation of slug and activation of tgf β/smad-independent pathways in gastric cancer, Front. Oncol. 11 (2021), 649029.
[136] F. Marcucci, G. Stassi, R. De Maria, Epithelial–mesenchymal transition: a new target in anticancer drug discovery, Nat. Rev. Drug Discov. 15 (5) (2016) 311–325.
[137] D. Ribatti, R. Tamma, T. Annese, Epithelial-mesenchymal transition in cancer: a historical overview, Transl. Oncol. 13 (6) (2020), 100773.
[138] B.D. Craene, G. Berx, Regulatory networks defining EMT during cancer initiation and progression, Nat. Rev. Cancer 13 (2) (2013) 97–110.
[139] S. Jonckheere, J. Adams, D. De Groote, K. Campbell, G. Berx, S. Goossens, Epithelial-mesenchymal transition (EMT) as a therapeutic target, Cells Tissues Organs (2021) 1–26.
[140] J.P. Thiery, H. Acloque, R.Y. Huang, M.A. Nieto, Epithelial-mesenchymal transitions in development and disease, cell 139 (5) (2009) 871–890.
[141] K. Polyak, R.A. Weinberg, Transitions between epithelial and mesenchymal states: acquisition of malignant and stem cell traits, Nat. Rev. Cancer 9 (4) (2009) 265–273.
[142] S. Vega, A.V. Morales, O.H. Ocaña, F. Valdés, I. Fabregat, M.A. Nieto, Snail blocks the cell cycle and confers resistance to cell death, Genes Dev. 18 (10) (2004) 1131–1143.
[143] J. Mejlvang, M. Kriajevska, C. Vandewalle, T. Chernova, A.E. Sayan, G. Berx, et al., Direct repression of cyclin D1 by SIP1 attenuates cell cycle progression in cells undergoing an epithelial mesenchymal transition, Mol. Biol. Cell 18 (11) (2007) 4615–4624.

[144] Y. Zhang, M. Li, X. Gao, Y. Chen, T. Liu, Nanotechnology in cancer diagnosis: progress, challenges and opportunities, J. Hematol. Oncol. 12 (1) (2019) 1–13.
[145] P. Sen, M. Saha, S.S. Ghosh, Nanoparticle mediated alteration of EMT dynamics: an approach to modulate cancer therapeutics, Mater. Adv. 1 (8) (2020) 2614–2630.
[146] B. Lu, X. Huang, J. Mo, W. Zhao, Drug delivery using nanoparticles for cancer stem-like cell targeting, Front. Pharmacol. 7 (2016) 84.
[147] H. Han, R. Bartolo, J. Li, M.-A. Shahbazi, H.A. Santos, Biomimetic platelet membrane-coated nanoparticles for targeted therapy, Eur. J. Pharm. Biopharm. 172 (2022) 1–15.
[148] J. Wolfram, M. Zhu, Y. Yang, J. Shen, E. Gentile, D. Paolino, et al., Safety of nanoparticles in medicine, Curr. Drug Targets 16 (14) (2015) 1671–1681.
[149] M. Zhang, S. Gao, D. Yang, Y. Fang, X. Lin, X. Jin, et al., Influencing factors and strategies of enhancing nanoparticles into tumors in vivo, Acta Pharm. Sin. B 11 (8) (2021) 2265–2285.
[150] S. Barua, S. Mitragotri, Challenges associated with penetration of nanoparticles across cell and tissue barriers: a review of current status and future prospects, Nano Today 9 (2) (2014) 223–243.
[151] V. Sainz, J. Conniot, A.I. Matos, C. Peres, E. Zupančič, L. Moura, et al., Regulatory aspects on nanomedicines, Biochem. Biophys. Res. Commun. 468 (3) (2015) 504–510.
[152] M. Cordani, R. Strippoli, Á. Somoza, Nanomaterials as inhibitors of epithelial mesenchymal transition in cancer treatment, Cancers 12 (1) (2019) 25.
[153] N. Mohammadi, N. Fayazi Hosseini, H. Nemati, H. Moradi-Sardareh, M. Nabi-Afjadi, G.A. Kardar, Revisiting of properties and modified polyethylenimine-based cancer gene delivery systems, Biochem. Genet. (2023) 1–22.
[154] R.R. Arvizo, S. Saha, E. Wang, J.D. Robertson, R. Bhattacharya, P. Mukherjee, Inhibition of tumor growth and metastasis by a self-therapeutic nanoparticle, Proc. Natl. Acad. Sci. 110 (17) (2013) 6700–6705.
[155] W. Li, X. Li, S. Liu, W. Yang, F. Pan, X.-Y. Yang, et al., Gold nanoparticles attenuate metastasis by tumor vasculature normalization and epithelial–mesenchymal transition inhibition. Int. J. Nanomed. 12 (2017) 3509.
[156] S. Balakrishnan, F. Bhat, P. Raja Singh, S. Mukherjee, P. Elumalai, S. Das, et al., Gold nanoparticle–conjugated quercetin inhibits epithelial–mesenchymal transition, angiogenesis and invasiveness via EGFR/VEGFR-2–mediated pathway in breast cancer, Cell Prolif. 49 (6) (2016) 678–697.
[157] Y. Huai, Y. Zhang, X. Xiong, S. Das, R. Bhattacharya, P. Mukherjee, Gold Nanoparticles sensitize pancreatic cancer cells to gemcitabine, Cell Stress 3 (8) (2019) 267.
[158] P. Agarwalla, S. Mukherjee, B. Sreedhar, R. Banerjee, Glucocorticoid receptor-mediated delivery of nano gold–withaferin conjugates for reversal of epithelial-to-mesenchymal transition and tumor regression, Nanomedicine 11 (19) (2016) 2529–2546.
[159] L. Wang, Y. Ruan, X. Wu, X. Zhou, Study of zinc oxide nanoparticles on epithelial-mesenchymal transition and toxicity of spontaneous monocyte-mediated cytotoxity-7721 cells, Mater. Express 11 (6) (2021) 832–838.
[160] H. Zhan, X. Chang, X. Wang, M. Yang, Q. Gao, H. Liu, et al., LncRNA MEG3 mediates nickel oxide nanoparticles-induced pulmonary fibrosis via suppressing TGF-β1 expression and epithelial-mesenchymal transition process, Environ. Toxicol. 36 (6) (2021) 1099–1110.
[161] X. Li, L. Song, X. Hu, C. Liu, J. Shi, H. Wang, et al., Inhibition of epithelial–Mesenchymal transition and tissue regeneration by waterborne titanium dioxide nanoparticles, ACS Appl. Mater. Interfaces 10 (4) (2018) 3449–3458.
[162] Z. Wang, P. Liang, X. He, B. Wu, Q. Liu, Z. Xu, et al., Etoposide loaded layered double hydroxide nanoparticles reversing chemoresistance and eradicating human glioma stem cells in vitro and in vivo, Nanoscale 10 (27) (2018) 13106–13121.
[163] J. Finlay, C.M. Roberts, J. Dong, J.I. Zink, F. Tamanoi, C.A. Glackin, Mesoporous silica nanoparticle delivery of chemically modified siRNA against TWIST1 leads to reduced tumor burden, Nanomed.: Nanotechnol., Biol. Med. 11 (7) (2015) 1657–1666.
[164] J.-X. Fan, D.-W. Zheng, L. Rong, J.-Y. Zhu, S. Hong, C. Li, et al., Targeting epithelial-mesenchymal transition: metal organic network nano-complexes for preventing tumor metastasis, Biomaterials 139 (2017) 116–126.
[165] Y. Huang, B. Zhou, H. Luo, J. Mao, Y. Huang, K. Zhang, et al., ZnAs@ SiO2 nanoparticles as a potential anti-tumor drug for targeting stemness and epithelial-mesenchymal transition in hepatocellular carcinoma via SHP-1/JAK2/STAT3 signaling, Theranostics 9 (15) (2019) 4391.
[166] M.R. Berber, H. Elkhenany, I.H. Hafez, A. El-Badawy, M. Essawy, N. El-Badri, Efficient tailoring of platinum nanoparticles supported on multiwalled carbon nanotubes for cancer therapy, Nanomedicine 15 (08) (2020) 793–808.
[167] Q. Guo, L. Li, G. Gao, R. Liu, Y. Einaga, J. Zhi, Nanodiamonds inhibit cancer cell migration by strengthening cell adhesion: implications for cancer treatment, ACS Appl. Mater. Interfaces 13 (8) (2021) 9620–9629.
[168] C. Ma, L. Shi, Y. Huang, L. Shen, H. Peng, X. Zhu, et al., Nanoparticle delivery of Wnt-1 siRNA enhances photodynamic therapy by inhibiting epithelial–mesenchymal transition for oral cancer, Biomater. Sci. 5 (3) (2017) 494–501.
[169] M. Seifi-Najmi, M. Hajivalili, R. Safaralizadeh, S. Sadreddini, S. Esmaeili, R. Razavi, et al., SiRNA/DOX lodeded chitosan based nanoparticles: development, Characterization and in vitro evaluation on A549 lung cancer cell line, Cell. Mol. Biol. 62 (11) (2016) 87–94.
[170] Q. Zhou, Y. Li, Y. Zhu, C. Yu, H. Jia, B. Bao, et al., Co-delivery nanoparticle to overcome metastasis promoted by insufficient chemotherapy, J. Control. Release 275 (2018) 67–77.
[171] V. Chandra Boinpelly, R.K. Verma, S. Srivastav, R.K. Srivastava, S. Shankar, α-Mangostin-encapsulated PLGA nanoparticles inhibit colorectal cancer growth by inhibiting Notch pathway, J. Cell. Mol. Med. 24 (19) (2020) 11343–11354.
[172] M. Sabzichi, O. Oladpour, J. Mohammadian, M. Rashidi, M. Hosseinzadeh, A. Mardomi, et al., Zoledronic acid-loaded lipidic nanoparticles enhance apoptosis and attenuate invasiveness by inhibiting epithelial to mesenchymal transition (EMT) in HepG2 cancer cells, Naunyn-Schmiede 'S. Arch. Pharmacol. 394 (12) (2021) 2429–2439.
[173] Z. Cai, Paclitaxel-containing nano-apoliposomes attenuate the growth and epithelial-mesenchymal transition of cisplatin-resistant nasopharyngeal carcinoma cells, Sci. Adv. Mater. 13 (9) (2021) 1637–1643.
[174] D. Suresh, A. Zambre, S. Mukherjee, S. Ghoshdastidar, Y. Jiang, T. Joshi, et al., Silencing AXL by covalent siRNA-gelatin-antibody nanoconjugate inactivates mTOR/EMT pathway and stimulates p53 for TKI sensitization in NSCLC, Nanomed.: Nanotechnol., Biol. Med. 20 (2019), 102007.
[175] Y. Li, Y. Chen, J. Li, Z. Zhang, C. Huang, G. Lian, et al., Co-delivery of micro RNA-21 antisense oligonucleotides and gemcitabine using nanomedicine for pancreatic cancer therapy, Cancer Sci. 108 (7) (2017) 1493–1503.
[176] S.-T. Hong, H. Lin, C.-S. Wang, C.-H. Chang, A.M.-Y. Lin, J.C.-H. Yang, et al., Improving the anticancer effect of afatinib and microRNA by using lipid polymeric nanoparticles conjugated with dual pH-responsive and targeting peptides. Journal of Nanobiotechnology 17 (1) (2019) 1–20.
[177] Y.A. Shen, K.L. Lan, C.H. Chang, L.T. Lin, C.L. He, P.H. Chen, et al., Intraperitoneal 188Re-Liposome delivery switches ovarian cancer metabolism from glycolysis to oxidative phosphorylation and effectively controls ovarian tumour growth in mice, Radiother. Oncol. 119 (2) (2016) 282–290.
[178] Y. Lu, Y. Liang, X. Zheng, X. Deng, W. Huang, G. Zhang, EVI1 promotes epithelial-to-mesenchymal transition, cancer stem cell features and chemo−/radioresistance in nasopharyngeal carcinoma, J. Exp. Clin. Cancer Res. 38 (1) (2019) 1–17.
[179] W. Li, X. Li, S. Liu, W. Yang, F. Pan, X.-Y. Yang, et al., Gold nanoparticles attenuate metastasis by tumor vasculature normalization and epithelial–mesenchymal transition inhibition, Int. J. Nanomed. (2017) 3509–3520.
[180] M. Sabzichi, O. Oladpour, J. Mohammadian, M. Rashidi, M. Hosseinzadeh, A. Mardomi, et al., Zoledronic acid-loaded lipidic nanoparticles enhance apoptosis and attenuate invasiveness by inhibiting epithelial to mesenchymal transition (EMT) in HepG 2 cancer cells, Naunyn-Schmiede 'S. Arch. Pharmacol. 394 (2021) 2429–2439.
[181] V. Karpisheh, J.F. Afjadi, M.N. Afjadi, M.S. Haeri, T.S.A. Sough, S.H. Asl, et al., Inhibition of HIF-1α/EP4 axis by hyaluronate-trimethyl chitosan-SPION nanoparticles markedly suppresses the growth and development of cancer cells, Int. J. Biol. Macromol. 167 (2021) 1006–1019.