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Research on Tumor Drug Resistance Mediated by Epithelial-mesenchymal Transition

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Abstract:

Epithelial-mesenchymal transition (EMT) is a key biological process driving tumor invasion and metastasis, and its activation is widely regarded as one of the core mechanisms leading to tumor resistance to multiple therapeutic approaches. Current research indicates that EMT mediates drug resistance through multiple pathways, such as conferring stem cell-like properties to cancer cells, miRNA delivery via exosomes, and promoting drug efflux. The underlying mechanisms of related signaling pathways and key transcription factors are being intensively investigated. However, effectively translating the basic research findings targeting EMT to overcome drug resistance into clinical applications still faces significant challenges. This article systematically reviews the core molecular mechanisms by which EMT mediates tumor drug resistance, with a focus on how EMT confers drug-resistant phenotypes to cancer cells by regulating tumor stem cell characteristics and drug pharmacokinetics. It also reviews experimental strategies targeting key EMT molecules to reverse drug resistance and their preclinical/clinical research evidence. This review provides a theoretical framework for a deeper understanding of the role of EMT in tumor drug resistance and lays the foundation for developing novel combination treatment regimens based on EMT intervention. Future research urgently needs to explore more selective EMT-targeting strategies, identify reliable predictive biomarkers, and optimize their synergistic effects with traditional radiotherapy, chemotherapy, and immunotherapy to ultimately improve the prognosis of patients with refractory tumors.

Keywords:- Epithelial-mesenchymal transition; tumor drug resistance; treatment

I. Introduction *(Heading 1)*

The primary reason for the failure of cancer treatment is tumor drug resistance, which significantly restricts the clinical effectiveness of chemotherapy, targeted therapy, and immunotherapy. Although treatment approaches continue to innovate, tumor cells avoid drug-induced killing via mechanisms like genetic mutations, epigenetic regulation, and microenvironment adaptation. This leads to patient recurrence, metastasis, and a worsening of prognosis [1]. Drug resistance can be divided into primary drug resistance (such as inherent drug resistance of tumor stem cells) and acquired drug resistance (such as target mutation or signal pathway reprogramming), both of which are closely related to tumor heterogeneity and dynamic evolution [2]. It is notable that the plasticity of tumor cells - especially Epithelial-Mesenchymal Transition (EMT) - has been confirmed to be the core hub mediating multi-drug resistance (MDR) [3].

EMT represents a crucial process through which epithelial cells lose their polarity and gain an invasive mesenchymal phenotype. Regulated by signaling pathways including TGF-β and Wnt/β-catenin, this process is marked by the down-regulation of e-cadherin alongside the up-regulation of vimentin and N-cadherin [4]. Studies have shown that EMT not only promotes tumor metastasis but also drives drug resistance through multi-dimensional mechanisms: mediating drug resistance by delivering exosomes through miRNA; EMT works in synergy with the characteristics of tumor stem cells (CSCs) to upregulate drug effloression pumps (such as ABC transporters) and DNA repair capabilities.

Recent studies have further revealed that EMT is not a static binary transformation but presents a continuous dynamic spectrum. Single-cell sequencing confirmed that the “partial EMT” subpopulation simultaneously possesses the characteristics of epithelial/mesenchymal mixture, and its drug resistance and metastasis potential are significantly higher than those of complete EMT cells [5]. In addition, epigenetic modifications (such as regulation by the miR-200 family) and tumor microenvironment signals (such as the secretion of TGF-β by CAFs) can dynamically regulate the EMT process and thereby affect the drug resistance phenotype [6]. Although therapies targeting key nodes of EMT (such as TGF-β inhibitors) have entered clinical trials, the reversibility of EMT and tumor heterogeneity remain the main obstacles to intervention strategies. This paper is focused on the molecular mechanism of the EMT mediated tumor resistance, through the system analytical EMT multi-dimensional role in drug resistance, in order to provide a new perspective in order to optimize the accurate treatment.

II. EMT

A. Summary of EMT

EMT refers to the specific physiological conditions, the connection between epithelial cells and cells and basement membrane, epithelial cell migration and invasion ability and loss of polarity, ectomesenchymal cells features into a biological process. During the occurrence of EMT, epithelial cells undergo a series of appearance and structural changes such as recombination of the cell network skeleton and loss of polarity. Therefore, cells can move from a specific tissue to other nearby tissues [7]. In this target tissue, the reverse process of EMT—mesenchymal-to-epithelial transition (MET)—takes place, allowing cells to integrate into the new tissue. This entire process occurs during biological processes like growth and development, wound healing, and tissue regeneration [7].

B. EMT and the Occurrence of Cancer

When cancer cells hijack and overactivate the EMT transition, it can drive tumor spreading, invasion, and the development of drug resistance. Cells accomplish this by decreasing the production of proteins specific to epithelial cells while boosting those typical of mesenchymal cells [8]. Under normal conditions, a key sign of EMT in cells is the loss of E-cadherin, a protein that maintains cell adhesion [9]. Several major signaling networks—including TGF-β, Wnt, Notch, and Hedgehog—play roles in EMT. For example, TGF-β triggers EMT through two different pathways: one that involves SmMAD proteins and another that doesn’t. This process increases the activity of certain gene regulators while directly blocking E-cadherin production [10]. Moreover, TGF-β promotes enzymes that break down the extracellular matrix, helping cells move more freely [11]. Upon Wnt activation, β-catenin translocates to the nucleus, binds to TCF/LEF, and activates EMT-related genes Furthermore, Notch signaling directly upregulates Snail and Slug expression while repressing E-cadherin [12]. After the Hedgehog ligand binds to the Patched receptor, it releases Smoothened (Smo), activates the GLI transcription factor (gli1/2), GLI1 directly binds to the SNAI1 promoter and promotes the expression of TGFβ [13]. As shown in Figure 1, this figure summarizes the signaling pathways related to EMT and the transcriptional targets that play a key role in EMT.

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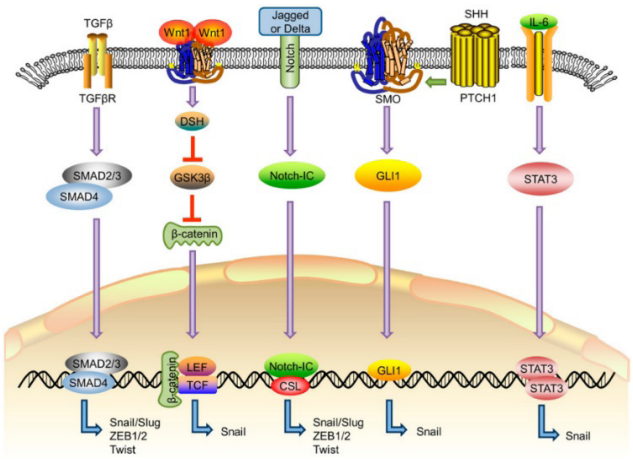

Figure 1.EMT-related signal pathways [3].

III. Tumor drug resistance related to EMT

A. EMT-related miRNAs Deliver Exosomes to Mediate Drug Resistance

Exosomes are small membrane-bound vesicles, typically measuring 40 to 160 nanometers in diameter, that encapsulate diverse RNA molecules and proteins. Research has shown that exosome membranes can directly fuse with target cell membranes, releasing their cargo—including proteins, mRNAs, and miRNAs—non-selectively to facilitate cell-to-cell communication. In the tumor microenvironment, exosomes can bind to and be internalized by adjacent cells.These cells change the phenotype of recipient cells by exchanging genetic information, thereby influencing the EMT process to mediate tumor drug resistance. Juliana and others found that overexpression of miR - 155 breast cancer cells to obtain the characteristics of EMT, promoted the higher mobility, and can form more breast ball, this suggests that miR - 155 May adjust some associated with drug resistance to treatment breast CSCs gene [14]. As shown in Figure 2, chemotherapy-resistant tumor cells secrete exosomes containing miR-155. The recipient cells receive the exosomes, increasing the expression of miR-155, downregulating the expression of miR-155 target genes, obtaining EMT characteristics in the cells, and transforming epithelial cells into mesenchymal characteristic cells, resulting in reduced chemotherapy sensitivity and the occurrence of tumor drug resistance. Although current studies have shown that miR-155 can promote the EMT phenotype, the specific mechanism by which miR-155 regulates the EMT process remains unclear.

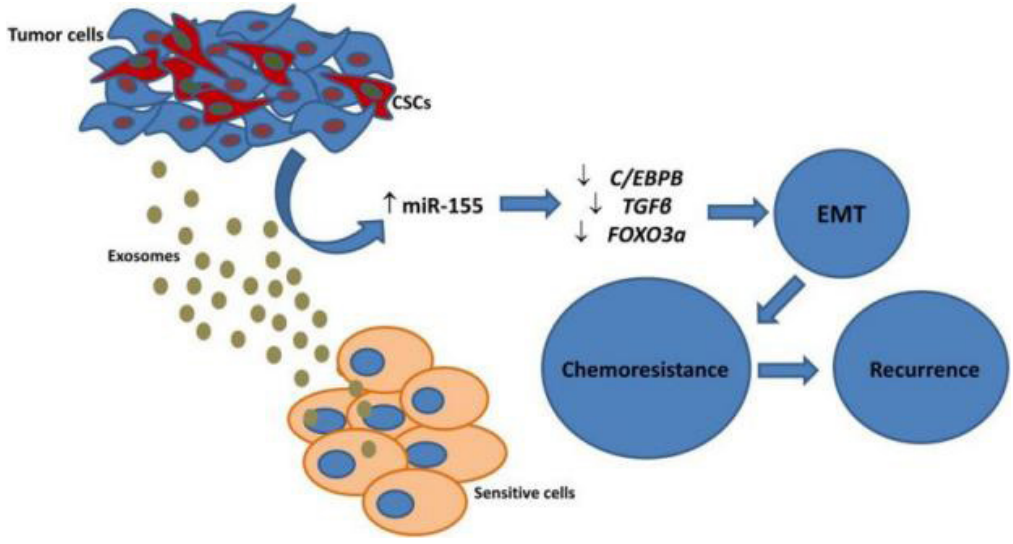

Figure 2. Illustration of the mechanism of miR-155 mediating EMT-related chemotherapy resistance [14].

Moreover, Xu et al. reported that in liver cancer, drug-resistant cells secrete exosomal miR-222-3p, which is taken up by drug-sensitive cells. By attaching to the 3'UTR region of PTEN mRNA and blocking its translation, this miRNA causes increased phosphorylation of Akt. This activation then triggers the anti-apoptotic protein Bcl-2 while suppressing the pro-apoptotic protein Bax, eventually leading to sorafenib resistance [15].

B. EMT-related Cancer Stem Cell-Mediated Drug Resistance

Cancer stem cells (CSCs) are defined as cancer cells exhibiting stem cell-like characteristics, endowed with the capacities for self-renewal and multi-lineage differenti-

ation. Typically, these cells are regarded as having the potential to initiate tumor formation and progress into cancer, displaying high tumorigenic potential.

Studies have found that cells EMT driven signal pathway and CSC carcinogenic activation of signaling pathways have similarity, occurred in the process of EMT cell stem cell sample characteristics, therefore occurred EMT cells Shared with CSC most signal pathway and drug resistance phenotype: EMT cells and CSC share the core nodes of the TGF-β/Smad, Wnt/β-catenin and Notch signaling pathways, and co-highly express ABC transport pumps (such as P-gp/ABCG2), DNA repair factors (such as CHK1), and anti-apoptotic proteins (such as Bcl-2/Survivin). It leads to enhanced excretion of chemotherapy drugs, maintenance of genomic stability and apoptosis resistance, and ultimately endows a cross-therapy drug resistance phenotype [16].

Among them, excessive drug excretion of the ABC(ATP-binding cassette) protein family is one of the main mechanisms of drug resistance in CSCs. The ABC transporter has extensive substrate specificity. Cells with EMT overexpress the ABC transporter and exhibit a drug resistance phenotype very similar to that of CSC. During the EMT process, the transcription factor ZEB1 drives the up-regulation of transcription by directly binding to the E-box element (CACCTG) in the promoter region of the ABCB1 (P-gp) gene [17]. Meanwhile, the TGF-β/Smad pathway activates NF-κB, which cooperates with the RelA/p50 heterodimer to bind to the ABCG2 promoter κB site, enhancing its expression [18]. At the epigenetic level, EMT-induced histone methyltransferase EZH2 catalyzed a reduction in H3K27me3 modification in the promoter region of the ABC transporter gene, opened chromatin conformation (for example, H3K27me3 in the promoter region of ABCG2 decreased by 5.8 times), and promoted the recruitment of transcription factors [19].

IV. Therapeutic strategies for tumor drug resistance mediated by EMT

The plasticity acquired by tumor cells through EMT is a key driving force for the formation of drug resistance. EMT not only directly regulates the survival and invasion ability of tumor cells, but also constructs a multi-dimensional drug resistance network through the delivery of exosome miRNA, the characteristics of CSCs and the dynamic interaction with the microenvironment. In response to these mechanisms, current therapeutic strategies mainly focus on blocking exosome-mediated drug resistance signal transmission, targeting the synergistic effect of EMT-CSCs, and developing combined treatment regimens, with the aim of dismantling the drug resistance barrier from multiple dimensions.

A. Block the Delivery of EMT-related Exosomal miRNAs

Tumor cells activated by EMT deliver pro-drug resistance molecules by secreting exosomes and construct a cross-cellular drug resistance network. Molecules such as miR-21 and miR-155 carried by exosomes can inhibit PTEN, activate the STAT3 pathway, and induce therapeutic resistance in adjacent cells [20].

Preclinical studies have revealed two potential strategies for overcoming tumor drug resistance. Studies have shown that treatment with the exosome generation inhibitor GW4869 (a compound targeting neutral sphingolipase 2, which blocks the biogenesis and secretion of exosomes by inhibiting sphingolipin hydrolysis) can significantly enhance the sensitivity of colorectal cancer cells to 5-fluorouracil, reducing their IC50 value by 50% [21]. A 50% reduction in IC50 (half-inhibitory concentration) means that the dose of 5-fluorouracil required to achieve the same cytotoxic effect is halved. This physiologically indicates a significant increase in the sensitivity of cancer cells to chemotherapy drugs, which may significantly reduce the effective therapeutic dose or improve the efficacy at the existing dose. It has significant potential value especially for patients who have or may develop drug resistance. Alternatively, in lung cancer studies, a compound called anti-Mir-155 LNA (which targets the miR-155 molecule) has been shown to reverse tumor resistance to EGFR-TKI drugs. The mechanism works by blocking the production of a protein called ZEB1, which is associated with a drop in tumor spreading [22].

ZEB1 acts as a key regulator of cell shape changes (a process known as EMT). The link between reduced ZEB1 levels and less tumor spread suggests that anti-Mir-155 LNA may weaken cancer cells' ability to invade and metastasize by inhibiting EMT, thereby overcoming resistance to EGFR-TKI therapies. However, the heterogeneity of exosome miRNAs (such as the coexistence of pro-drug resistance and tumor suppressor molecules) and off-target effects remain challenges. It is necessary to combine single-cell sequencing to screen exosome markers for specific EMT subsets to improve the targeting accuracy [23].

B. Targeted EMT-CSCs Synergistic Drug Resistance Network

The characteristics of EMT and CSCs form drug resistance synergy through transcription factors (such as ZEB1, Twist) and epigenetic regulation (such as CD44, ALDH1 activation) [24]. CSCs excrete chemotherapy drugs through high expression of ABCG2 and enhance DNA repair ability through the CHK1/BRCA1 pathway

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[25, 26].

Targeting strategies against cancer stem cells (CSCs) and drug efflux pumps have exhibited promising potential in overcoming drug resistance. The anti-CD44 monoclonal antibody RG7356 was developed based on the mechanism that CD44 serves as a key surface marker and functional protein of CSCs in triple-negative breast cancer (TNBC). CD44 regulates the maintenance of stemness, self-renewal capacity, and tumor-initiating ability of CSCs, while also participating in multiple pro-survival signaling pathways. Preclinical studies have demonstrated that RG7356 can specifically recognize and eliminate the CSC population in TNBC. When combined with paclitaxel, this antibody significantly suppresses tumor growth, leading to a 70% reduction in tumor volume [27].

On the other hand, the development of the ABCG2 inhibitor Tariquidar is aimed at ABCG2 (ATP-binding cassette sub-family G member 2), an important drug excretion transporter. ABCG2 is highly expressed on the cell membranes of various tumors (including ovarian cancer), and can actively pump chemotherapy drugs (such as cisplatin) out of the cells, resulting in a decrease in intracellular drug concentration and the development of multidrug resistance (MDR). Inhibiting ABCG2 aims to block this effectional effect, thereby restoring the sensitivity of tumor cells to chemotherapy drugs. Studies have shown that in ovarian cancer models, Tariquidar significantly enhanced the efficacy of cisplatin by effectively inhibiting ABCG2 function, doubling the progression-free survival (PFS) [28].

Additionally, epigenetic regulators exhibit unique potential in reversing tumor drug resistance. The histone deacetylase (HDAC) inhibitor Panobinostat was developed based on its epigenetic mechanism: inhibiting HDAC activity to increase histone acetylation, thereby remodeling chromatin structure and regulating gene transcription. In ovarian cancer, this drug has been shown to restore expression of the epithelial marker E-cadherin, thereby suppressing epithelial-mesenchymal transition (EMT) and reducing the tumor stem cell (CSC) population. A Phase II clinical trial evaluated Panobinostat combined with carboplatin in recurrent ovarian cancer, demonstrating that the combination therapy achieved an objective response rate (ORR) of 35% [29]. However, the dynamic plasticity of EMT-CSCs contributes to resistance relapse. For instance, Notch inhibitors may trigger compensatory activation of the Wnt pathway [30], necessitating sequential treatment strategies (e.g., initial HDACi administration to eliminate CSCs).

V. Conclusion

This article provides a systematic exposition of the multi-level mechanisms by which epithelial-mesenchymal transition (EMT) mediates tumor drug resistance, with a particular emphasis on analyzing the molecular basis through which EMT confers broad-spectrum drug resistance to cancer cells. This involves core biological processes such as exosomal delivery of related miRNAs and induction of tumor stem cell characteristics. Studies have uncovered that dysregulated activation of key signaling pathways and cascade regulation by transcription factors serve as central hubs driving the EMT-resistance axis. Concurrently, the article reviews preclinical and early clinical evidence for targeting key EMT nodes—such as restoring E-cadherin expression or blocking pro-EMT signal transduction—to overcome resistance to chemotherapy, targeted therapy, and radiotherapy. The potential value of intervention strategies such as epigenetic regulators (HDAC inhibitors), microRNA regulators and EMT-specific small molecule inhibitors was emphasized.

The significance of this study is to build the EMT mediated resistance system theory framework, clarified the across cancer drug resistance of common mechanism, targeted for the development of EMT - stem cells -- microenvironment network joint treatment provides the key theoretical basis. Its core reference value is reflected in: revealing the complexity of cross-regulation of EMT by multiple signaling pathways, and suggesting that multi-target collaborative intervention strategies
need to be designed in the future; The direct association between the characteristics of tumor stem cells and drug resistance has been clarified, providing new ideas for eradicating drug-resistant clones. It emphasized the pivotal role of the microenvironment in drug resistance and promoted the exploration of microenvironment remodeling therapy.

It should be pointed out that this paper has certain limitations: The high dynamics and reversibility of EMT lead to the fact that the difficulty of its in vivo targeting has not been fully explored; The difference analysis of the contribution of different stages of EMT (partial EMT vs complete EMT) to drug resistance is insufficient.

Future studies should focus on three directions: first, develop spatio-temporal specificity EMT inhibitors (such as conditions activation type nano drugs), precision intervention EMT key transitional node; Secondly, integrate single-cell sequencing and spatial transcriptome technology to establish a drug resistance prediction model and classification system driven by EMT dynamic maps; Thirdly, deeply explore the synergistic mechanism between EMT-targeted therapy and novel therapies such as immune checkpoint blockade and CAR-T, with particular attention to the interaction between tumor antigen exposure and immune microenvironment reprogramming

after EMT reversal. These breakthroughs will promote the transformation of EMT targeting strategies from basic research to clinical practice, and ultimately enhance the long-term control rate of refractory tumors.

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