Review

Molecular Mechanisms for Targeting Metastatic Cancer Cells and to Overcome or Prevent Chemotherapy Resistance

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Abstract: Cancer is a devastating disease, causing tremendous morbidity and mortality each year. Cancer can be considered as a genetic disease in the sense that instabilities in protooncogenes and tumor suppressor genes are among the hallmarks of cancer progression and metastasis. However, a particular cancer can express different proteins in different patients, making cancer a heterogeneous disease. This heterogeneity in part influences treatment resistance and failure. Therefore, it is crucial to understand the mechanism by which cancer cells develop and enhance resistance to different agents. This review aims to present the general paradigm and recent updates on cancer cell resistance to different antitumor agents. It demonstrates that tumor resistance results from a myriad of factors, including tumor microenvironment, supporting immune cells, and cancer stem cells. This interaction contributes to cancer cells overcoming the therapeutic effects of different classes of antitumor agents, such as cytotoxic chemotherapeutics, targeted agents, and immunotherapies. With the development of advanced molecular analysis, specialized genomic assessment has assisted clinicians and researchers in choosing selected agents combating cancer cells. Together, this approach can potentially reduce treatment toxicity, health system burden, and financial costs while improving patient quality of life. Understanding the exact mechanism of drug resistance in cancer cells can open the way to new effective and less toxic therapeutics.

Keywords: chemotherapy resistance; molecular targeting; signalling pathway; metastasis; apoptosis; tumor microenvironment; cancer stemness

1. INTRODUCTION

Cancer is a heterogeneous and highly complex disease that annually claims the lives of millions of people, making it one of the leading causes of death worldwide [1]. The number of deaths caused by cancer is growing exponentially. Estimates show that in 2018, 9.6 million cancer-related deaths occurred. However, by 2030, it is projected that around 30 million people may die annually from cancer [2]. That is why cancer is a very serious challenge for public health worldwide. The mainstay of cancer treatment consists of surgery, radiation therapy, and systemic therapies, including chemotherapy, targeted therapy, and immunotherapy. Chemotherapy, however, faces many challenges, such as non-specific targeting of cancer cells, treatment resistance, and cancer recurrence even after successful treatment.

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The use of targeted small-molecule drugs can improve the treatment outcome over certain chemotherapies. Because of low molecular weight (<1000 Da) and small size, targeted therapy can bind to various targets outside and inside cancer cells [3]. Since the FDA approval of the first small molecule tyrosine kinase inhibitor (TKI), imatinib, in 2001, more than 80 small molecule drugs for cancer treatment have been approved by the FDA and the National Medical Products Administration (NMPA) of China [4]. However, the therapeutic results of targeted small molecules are limited. Improving the outcomes of small molecule-based therapies as adjunctive treatment to overcome chemotherapeutic challenges requires a critical understanding of the mechanisms of chemical resistance in cancer. This review comprehensively evaluates these factors and mechanisms from seven aspects: oncogenic signaling pathways, drug efflux pumps, apoptosis and other cell death pathways, tumor microenvironment, immunomodulation, DNA repair mechanisms, and the role of cancer stem cells. It is crucial and essential for drug designers and scientists in this field to extensively investigate these mechanisms for the proper and effective design of targeted small molecule drugs as adjunctive chemotherapy treatments.

2. ONCOGENIC SIGNALING PATHWAYS

The carcinogenesis process results from increased cell proliferation, resistance to apoptosis, genetic instability, induction of angiogenesis, metabolic modifications, and augmented migratory capability [5,6]. The trigger for most of these changes is the dysregulation of cellular signal transduction pathways [7]. Recent progress in DNA sequencing has made it possible to study these genetic changes systematically, providing us with a more profound knowledge of the various involved signaling pathways [8,9]. This information has contributed to the design of the molecular structure involved in thesignaling pathways.

It has been demonstrated that genetic or epigenetic alterations in tumor cells are the basis of cancer development [10]. Generally, biological functions are preserved by certain genes that cooperate in functional pathways. It has been recognized that several signaling pathways contribute to carcinogenesis [11]. Genetic changes in cancer cells regulate signaling pathways that lead to tumorigenesis-related disruption of the control processes. Oncogenic mutations can affect proteins implicated in several signaling pathways [11]. Studies show that numerous tumor suppressors and proto-oncogenes contribute to tumorigenesis when inactivated or activated by mutations, respectively [12].

There is uniform recognition of the importance of epigenetics (heritable non-structural changes in gene expression), as a major mechanism that can drive acquired resistance to chemotherapy [13]. For example, epigenetic mechanisms such as non-coding RNA (ncRNA) (e.g., microRNAs) and DNA methylation are important drivers that influence the chemo-responsiveness of tumors and acquired drug resistance [14]. Although drug resistance can be overcome using epigenetic therapies in experimental models, clinical studies of epigenetic therapies have highlighted challenges for different cancers, and there is a need to identify more targeted approaches [15].

As a result of genetic and epigenetic alterations, cancer cells obtain specific features that contribute to their progression, including augmented cell proliferation, resistance to apoptosis, metabolic changes, induction of angiogenesis, genetic instability as well as enhanced invasion and migratory capacity [6,9,16]. Most of these characteristics regulate various cellular and extracellular signaling pathways enhancing tumorigenesis through (1) extracellular matrix (ECM) modification, (2) angiogenesis, and (3) inflammation These processes are outlined below.[17,18].

2.1. Extracellular Matrix

The extracellular matrix (ECM) is a scaffold that provides a bioactive molecules source supporting cell migration and adhesion [19]. It is constantly being renovated away from a static framework, and its conformation plays a pivotal role in controlling the behavior of the cell. ECM signaling results in the activation of canonical processes during tumorigenesis. Collagen, laminin, fibronectin, and other elements of the ECM act as ligands to activate integrin, which contributes to tumor cells proliferation, survival, invasion, and migration [11,20].

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2.2. Angiogenesis

Like all tissues, tumor cells require blood flow. Angiogenesis is a process by which oxygen and nutrients are recruited for the growing tumor. Cancer cells can activate angiogenesis through the growth and incorporation of endothelial cells, which physiologically occurs during wound healing. The main signaling molecules for angiogenesis include angiopoietin, interleukin (IL) 8, fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), and platelet-derived growth factor (PDGF). The PI3K-AKT signaling pathway regulates the induction and stabilization phases of angiogenesis [19]. This effect has been considered an opportunity in the treatment of different malignancies [21,22].

2.3. Inflammation

Inflammatory cells can secrete FGF and epidermal growth factor (EGF), which activate the PI3K-AKT and Ras-ERK signaling regulators in cancer cells. They also generate colony-stimulating factor 1 (CSF1), a key signaling molecule that induces macrophages to secrete more EGF. In addition, immune cells can release VEGF and matrix metalloproteinases (MMPs) that stimulate angiogenesis [22]. In both tumor-associated inflammatory cells and cancer cells, signaling via the transcription factor NF-κB is essential because it can support cell proliferation and growth, thus promoting cytokine production, like tumor necrosis factor (TNF) [23].

3. DRUG EFFLUX PUMP

Drug resistance is a major concern worldwide, ranging from microbes' resistance to antimicrobials to cancer cells' resistance to chemotherapeutics [24,25]. Due to adaptive evolution, worked by the indiscriminate usage of antimicrobials and chemotherapeutics, the drug targets in microbes and mammalian cells have evolved to new resistant forms [25]. The world health organization (WHO) declared antimicrobial resistance an increasingly serious threat to global public health and released a list of twelve priority pathogens that typically exhibit drug-resistant phenotypes [24]. To tackle these multi-drug resistant (MDR) pathogens, urgent concerted action from all government sectors and societies is required, in the absence of which, even common infections and minor injuries can assume life-threatening proportions [24,25]. Multiple causes for resistance exist in bacteria, namely, target site mutation, enzymatic inactivation, drug modification, preventing drug entry, and drug efflux [26]. Similarly, cancerous cells also exhibit the MDR phenotype, which is a major factor in the failure of many forms of chemotherapy in a variety of hematologic and solid cancers [27]. The various mechanisms by which cancerous cells acquire drug resistance include loss of cell surface receptor, drug metabolism, mutation of drug target, decreased uptake, increased efflux via MDR pumps, and variation in membrane lipids such as ceramide and through extracellular vesicles that carry MDR pumps [28,29]. Limiting intracellular accumulation of anti-cancer drugs would lead to a reduction in apoptosis, activation of DNA repair, altered cell cycle checkpoints, and drug detoxification that ultimately results in decreased cytotoxicity of these drugs [30]. Among these diverse mechanisms, active drug efflux is a common mechanism shared by both MDR bacteria and drug-resistant cancerous cells [31,32]. Efflux pumps are widely distributed in both prokaryotes and eukaryotes, whose primary purpose is to import or export nutritional factors, metabolites, toxins, or host-derived antimicrobial agents. Many of these molecules are predominantly amphipathic or hydrophobic, as many drugs also exhibit similar chemistry; they have become incidental substrates for these pumps, eventually evolving to accommodate structurally diverse substrates rendering microbes or cancerous cells resistant [31,33]. Therefore, a defense mechanism embraced by both MDR bacteria and cancer cells is the overexpression of efflux pumps [28].

4. CELL DEATH PATHWAYS

4.1. Apoptosis

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Apoptosis is a form of programmed cell death, an evolutionarily conserved process that plays an essential role in organism development and tissue homeostasis [9]. However, in pathological conditions, particularly cancer cells lose their ability to undergo apoptosis-induced death leading to uncontrolled proliferation [9,34]. Cancer cells are often found to overexpress the proteins involved in apoptosis resistance. In other words, one of the major hallmarks of human cancers is the intrinsic or acquired resistance to apoptosis [35]. Evasion of apoptosis may contribute to tumor development, progression, and resistance against different treatment modalities, including radiotherapy, chemotherapy, and immunotherapy [29,36,37]. Several mechanisms allow cells to escape programmed cell death, including the over-expression of the anti-apoptotic molecules [38], including BCL-2 and hsp90.

4.1.1. B-cell lymphoma-2

The B-cell lymphoma-2 (Bcl-2) is an anti-apoptotic protein [39]. It functions through hetero-dimerization with pro-apoptotic members of the BH3 family to prevent mitochondrial pore formation, cytochrome C release, and initiation of apoptosis [40]. However, there is evidence suggesting that Bcl-2 may play an oncogenic role through survival pathways other than its function at the mitochondrial membrane.

4.1.2. Heat shock protein 90

Heat shock protein 90 (hsp90) is one of the most abundant proteins in eukaryotic cells. It is an enzymatic chaperone molecule with ATPase activity that is highly active in malignant cells compared to non-neoplastic cells [41]. In line with its activity pattern and expression profile, hsp90 can drive tumor progression by enhancing proliferation, migration, and metastasis [42,43]. In addition, it also confers resistance to programmed cell death by several mechanisms [41,43]. By its chaperoning activity, hsp90 stabilizes several mutated and non-mutated kinases and several anti-apoptotic factors within the cytosol that favor resistance to apoptosis and mostly drive proliferation and resistance of tumor cells to various treatment regimens [43].

4.1.3. Proteasome pathway and apoptosis resistance

The eukaryotic 26S proteasome is a 2.5 MDa large complex protein consisting of two 19S regulatory particles and one 20S catalytic core [44]. Each 19S regulatory particle is composed of the lid, which is responsible for the recognition and docking of polyubiquitinylated proteins into the 20S catalytic core, and the base, which oversees the unfolding and linearization of large proteins [45]. The 20S catalytic core harbors seven distinct β subunits, arranged in a stacked barrel, among which mainly three sets of subunits, β_1 (caspase-like or peptidyl glutamyl peptide-hydrolyzing [PGPH]-like), β_2 (trypsin-like), and β_5 (chymotrypsin-like) are proteolytically active [14].Unlike common proteolytic enzymes that contain a catalytic triad, the proteasome catalytic subunits belong to a special group termed N-terminal nucleophile hydrolases, which utilizes the side chain of the N-terminal residue as the catalytic nucleophile. All three catalytic -subunits react with peptide bonds of substrates through their OH group of the N-terminal threonine (Thr1), degrading protein into small fragments of less than ten amino acids [14,44]. It has been well documented that the proteasome is required for cell cycle progression by regulating the turnover of cyclins and cyclin-dependent kinase inhibitors, and therefore inhibition of proteasome function could result in cell cycle arrest and apoptosis [14,45].

4.1.4. The role of nuclear transport in apoptosis resistance

Compartmentalization of proteins inside the eukaryotic cell is an evolutionarily conserved mechanism [46]. Each protein (especially apoptosis inducers) requires proper sub-cellular localization to mediate its specified function [47]. This is especially true for tumor suppressor proteins (TSPs) that usually reside in the cell nucleus where they exert their function through sequence-

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specific binding to DNA, modulation of gene expression, and assessment of the integrity of the genome [48,49].

4.2. Autophagy

Autophagy serves to maintain intracellular homeostasis through a process that involves lysosomal degradation and recycling of unnecessary or damaged cellular components, and in turn promotes cell survival [50,51]. Autophagy can prevent cellular damage caused by chemotherapeutics as it attempts to maintain intracellular balance through the removal of dysfunctional organelles and the elimination of cellular stress [51]. It has been suggested that this temporal survival mechanism may facilitate chemoresistance as a byproduct of its function in keeping the cancer cells alive. Indeed, autophagy has been observed to guard cancer cells against apoptosis upon encountering certain anticancer drugs [51].

4.3. Necrotic Cell Death and Necroptosis

Necrosis is an unprogrammed cell death process morphologically characterized by a gain in cell volume, swelling of organelles, plasma membrane rupture, and subsequent loss of intracellular contents [42]. This contrasts with programmed apoptosis, although it was long thought that necrosis is an uncontrolled cell death that is characterized by progressive loss of cytoplasmic membrane integrity, rapid influx of Na^{+}, Ca^{2+}, and water, resulting in cytoplasmic swelling, and nuclear pyknosis. It has been realized that necrotic cell death can be represented as a programmed form of cell death, termed necroptosis [42,52].

4.4. Senescence Induced chemoresistance

Senescence is a major response to carcinogenesis but new data shows its role in chemotherapy resistance formation. Addresing to cancer therapy, cellular senescence is a state of irreversible growth arrest that can be induced by various stressors, including chemotherapy. It is considered a double-edged sword in cancer therapy. On one hand, senescence can contribute to tumor suppression by halting the growth of cancer cells. On the other hand, senescent cells can exhibit altered phenotypes and secretory profiles that promote tumor progression, inflammation, and resistance to chemotherapy [53]. Senescent cells secrete a variety of factors collectively known as senescence-associated secretory phenotype (SASP), which include pro-inflammatory cytokines, growth factors, and proteases. SASP components can create a tumor-promoting microenvironment and impact the response of neighboring cells to chemotherapy. They can enhance cancer cell survival, activate pro-survival signaling pathways, and contribute to therapy resistance [54]. Senescent cells can also communicate with neighboring cancer cells and influence their behavior through paracrine signaling. This intercellular communication can contribute to chemoresistance by promoting cell survival, DNA repair, and evasion of apoptosis [55]. Given the potential role of senescent cells in chemotherapy resistance, there is interest in developing therapeutic strategies to target and eliminate these cells. In this regard, senolytics as the drugs that selectively induce apoptosis in senescent cells, have shown promise in preclinical studies and may enhance the efficacy of chemotherapy by reducing the presence of therapy-resistant cells [56].

4.5. ER Stress and tumor evasion of chemotherapy

Studies have suggested that endoplasmic reticulum (ER) stress induces destabilization of p53 and therefore prevents cells from p53-dependent apoptosis, which could form an important mechanism of resistance to chemotherapy [57]. In certain circumstances, reducing ER stress and increasing autophagy can either speed up or slow down the evolution of cancer. One such example is Sestrin2, which inhibits ER stress and causes cancer cells to undergo autophagy and death. Additionally, Sestrin2 expression is correlated with survival and metastasis in a number of human cancers, including colorectal, lung, and hepatocellular carcinomas. By using cutting-edge methods like non-coding RNA delivery and vector systems, targeted therapy for Sestrin2 or modulation of its

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expression may enhance cancer chemotherapy and defeat chemoresistance, metastasis, and immune evasion [58].

5. TUMOR MICROENVIRONMENT

The tumor microenvironment (TME) provides a secure environment for cancer cells to evade the desired outcomes of various treatments [59]. The TME is a complex and dynamic ecosystem composed of diverse factors that play crucial roles in inhibiting apoptosis and supporting proliferation, migration, immune evasion, treatment resistance, metastasis, metabolic reprogramming, and all stages of tumorigenesis [59]. The microenvironmental factors are generally divided into two main components: (a) cellular components (such as tumor-associated macrophages [TAMs], tumor-infiltrating lymphocytes [TILs], and various types of stromal cells, such as cancer-associated fibroblasts [CAFs] and endothelial cells [ECs] and (b) extracellular matrix including non-cellular components (such as growth factors, various chemokines and cytokines, interstitial fluids, metabolites, and exosomes) [60–63]. Targeting the TME is a potentially effective strategy for achieving fruitful outcomes of cancer therapy, and small molecules can easily penetrate the TME and ultimately reach tumor cells and affect them [4].

TME is a hypoxic environment with an acidic pH [64]. The rapid growth of tumor cells causes hypoxia, which subsequently causes the release of stimulating factors such as MMPs and hypoxia-inducible factor 1α (HIF-1α) [62,65]. Also, the hypoxic condition of TME is a means by which angiogenic factors (e.g., VEGF) are secreted from the tumor, affecting endothelial cells and subsequently promoting angiogenesis [64]. In addition, the acidic status of TME hinders the infiltration of immune cells [66]. TME remodeling creates the conditions for tumor cells to interact with surrounding fibroblasts, immune cells, and endothelial cells, leading to the induction of a variety of biological events, including angiogenesis, migration, proliferation, immune system suppression and drug resistance, which ultimately causes tumor promotion [59,67]. CAFs are the most common stromal cells of TME. They facilitate the tumor cells migration by modification of ECM. An important event in the TME is cell interaction and cell communication with the ECM. This interaction causes the release of factors mediating ECM regeneration and immune escape, ultimately enhancing treatment resistance [68,69]. Other important events are the generation of exosomes by malignant cells, TME-specific metabolic patterns, and deregulated circulating microRNAs that ultimately increase the treatment resistance [61,70]. There are many different types of immune cells in the TME that block the antitumor immune response [71]. In addition, around the tumor cells, there are a set of inflammatory moleculescause the failure to identify and eliminate cancer cells, making the TME a complex and heterogeneous space [72,73]. Also, they often cause an uncontrollable process in the growth and development of tumors [74]. In general, a wide range of events and factors, from biochemical agents and hypoxic environment to abnormal mechanical forces, cause treatment resistance [65,75]. In the following, the importance of extracellular vesicles and mesenchymal stem cells in TME are specifically outlined.

5.1. Extracellular Vesicles

Extracellular vesicles (EVs) act as intermediaries in intercellular communication and are secreted by various cell types[76]. EVs are composed of a lipid bilayer that protects their contents from enzymatic degradation [77,78]. They carry diverse biological active molecules such as lipids, proteins, and nucleic acids (miRNA or lncRNA). They can regulate cellular processes and functions, leading to changes in gene expression and activation of multiple signaling pathways [79]. Tumor-derived EVs can modulate the TME [80]. By transferring surface markers and signaling molecules, nucleic acids, and oncogenic proteins to stromal cells, EVs can prepare the TME for tumor growth, invasion, and metastasis [78,81]. They also facilitate immune evasion and angiogenesis [81,82]. Studies stating conflicting effects of EVs on angiogenesis are noteworthy, nonetheless. For instance, in nasopharyngeal cancer, EVs harboring miR-23a directly targeted the testis-specific gene antigen (TSGA10) to induce angiogenesis [83]. TSGA10 in turn prevents nuclear localization of the hypoxia-inducible factor (HIF)-1alpha, and therefore has an anti-angiogenic effect [84]. The important role of

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TSGA10 in dividing cells and its overexpression in different cancers including brain tumors have been demonstrated for more than a decade [85,86]. Nowaday it may be considered as a candidate target and important protein playing a role via EV in chemoresistance [87]. Stromal- and cancer cell-derived EVs improve the heterogeneity and complexity of TME [88]. EVs create favorable conditions for tumor growth and resistance to anti-cancer drugs by transferring bioactive materials [89]. They enhance drug resistance through various mechanisms, including drug export and sequestration, reduction of drug concentration in target sites, pump-mediated drug efflux, the interaction of cancer and stromal cells, transfer of survival factors, apoptosis inhibitors, and non-coding RNAs [79,89]. By providing growth factors (such as transforming growth factor β [TGF-β]) and various miRNAs, EVs can convert MSCs and other bone marrow-derived cells into tumor-supporting cells [78,79,90].

Exosomes are a class of EVs that mediate apoptosis escape, immune suppression, cell proliferation, inflammatory responses, angiogenesis, invasion, metastasis, and chemotherapeutic sensitivity [88,91]. Exosomes are also involved in acquired drug resistance through various cellular and molecular processes in the TME, including DNA repair, epithelial-mesenchymal transition (EMT), immune surveillance, and cell cycle [82,91]. They also contribute to drug resistance through various pathways, including drug efflux pumps, direct drug export, and miRNA signaling [79,82]. By transferring ABC transporters (drug efflux pumps) through exosomes, drug resistance is promoted in sensitive cells [81].

MicroRNAs (miRNAs) are short non-coding RNAs that regulate various biological functions in cancer cells, such as apoptosis, migration, proliferation, differentiation, drug resistance, and invasion[92–94]. Cancer cells have modified expression of miRNAs through genetic or epigenetic changes, which subsequently leads to abnormal expression of their target genes [93]. miRNAs act as elements that promote the formation and biological changes of TME [93]. Cancer-derived exosomal miRNAs can lead to heterogeneity and phenotypic changes in TME and subsequently promote uncontrolled tumor growth [95]. Exosomal miRNAs derived from tumors can improve resistance to chemotherapy, tumor growth, immune escape, and metastasis by reprogramming matrix pathways in TME [96,97]. Exosomal miRNAs secreted by cancer stem cells (CSCs) can target anti-apoptotic FOXO3a that activates the mTOR signaling pathway, inhibits apoptosis, and subsequently promotes tumor progression [98]. Therefore, This effect can inhibit drug-induced apoptosis[98]. Horizontal transfer of exosomal miRNAs released from cancer cells can induce a resistant phenotype in sensitive cancer cells and improves resistance to a wide range of anticancer drugs [99]. Exosomal miRNAs derived from cancer stem cells and non-cancerous cells assist drug resistance by creating different effects on target cells in TME [92,100]. In addition, exosomal miRNAs play a role in inducing resistance to specific molecular target drugs and cytotoxic drugs [92]. Due to the key role of miRNAs in cancer and their regulation of drug resistance in a specific tumor manner by some miRNAs, exosomal miRNAs can be considered potential cancer biomarkers for prediction and diagnosis using a broad or specific tumor approach [100].

Cancer-derived exosomal miRNAs can be transferred to fibroblasts in the TME and promote their differentiation into CAFs [101]. It has been demonstrated that primary tumor cells release exosomal miRNAs, such as miR-21, miR-155, miR-210, miR-1247-30, and miR-124, that are transferred to normal fibroblasts (NFs) and induce their conversion into CAFs by targeting proteins such as SPHK1, PTEN, and SOCS1, as well as activating molecules such as FGF-2, FAP, TGF-, and bFGF [93,101]. Ultimately, ECM undergoes remodeling [97]. ECM modifications facilitate uncontrolled tumor growth, angiogenesis, metabolic reprogramming, and inflammatory response [93,98,102]. Subsequently, exosomal miRNAs secreted by CAFs induce drug resistance in cancer cells through induction of proliferation, metastasis, and inhibition of anti-tumor effects of cytotoxic drugs such as cell cycle arrest and apoptosis [101]. It has been shown that the transfer of miR-21 from CAFs to ovarian cancer cells can inhibit apoptosis by reducing the expression of apoptotic protease activating factor 1 (APAF1) that improves the resistance to paclitaxel [102]. In the following, exosomes and their function in cancer promotion are outlined:

5.1.1. Exosomal miRNAs and tumor-associated macrophages

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The most abundant immune cell population in the TME is TAMs [100]. TAMs are highly plastic cells involved in various actions, including suppressing the immune system, promoting tumor angiogenesis, and increasing resistance of tumor cells to chemotherapy [100]. Poor prognosis in many types of cancer is directly related to the number of TAMs in the TME [59,103]. Studies have shown that in certain types of cancer, including lung, skin, head and neck, bladder, and ovarian cancer, miRNAs secreted by cancer cells can increase the recruitment of macrophages to the TME [102,104–108].

5.1.2. Exosomal miRNAs and epithelial-mesenchymal transition

Epithelial-mesenchymal transition (EMT) is a process by which cancer cells acquire increased motility and plasticity, resulting in loss of cell-cell adhesion and apical-basal polarity and acquisition of mesenchymal characteristics[109,110]. EMT enhances the invasive phenotype of cancer cells and is directly associated with metastasis, cancer progression, and drug resistance [108]. There is ample evidence that exosomes released from cancer cells can modulate the EMT process in the TME [107]. Xiao et al. showed that exosomal miRNAs regulating EMT, such as miR-191 and let-7a derived from melanoma, induce EMT in primary melanocytes [111]. In addition, studies have shown that exosomal miRNAs are involved in stabilizing EMT in primary tumor cells [112].

5.1.3. Exosomal miRNAs and autophagy

Autophagy is a catabolic process that removes damaged or redundant macromolecules and organelles to maintain homeostasis and metabolic adequacy [113]. This process is involved in increasing tumor resistance and tumor growth. During cancer development, autophagy promotes high cell survival and energy supply [114]. During a phenomenon called cell protective autophagy (a process caused by high levels of autophagy and the creation of hypoxic TME, oxidative stress), autophagy ultimately delays apoptosis and subsequently contributes to treatment resistance [113]. Exosomes can induce protective autophagy under cellular stress conditions in cancer cells [115]. Reactive oxygen species (ROS) can be increased by exosomes released from cancer cells, and by affecting the regulation of autophagy in target cells, they can increase the secretion of tumor growth factors [116]. Exosomal miRNAs can control autophagy and act as mediators in therapeutic resistance [116,117]. It has been demonstrated that tumor-derived exosomes lead to a resistant phenotype in target cells by inducing protective autophagy during chemotherapy [114]. For example, cisplatin-resistant non-small cell lung cancer (NSCLC) cells secrete exosomal miR-425-3p, which targets the AKT1/mTOR signaling pathway and subsequently leads to the upregulation of autophagy activity and subsequently, they reduce the results of cisplatin treatment [118–120].

5.1.4. Exosomal long non-coding RNAs

The transfer of exosomal long non-coding RNAs (lncRNAs) between the TME and tumor cells is involved in several processes, such as reprogramming the TME, growth, migration, and survival of cancer cells, as well as the development of mechanisms that cause resistance to chemotherapy [121,122]. . For example, lncRNA SBF2 induces temozolomide resistance in glioblastoma cells during chemotherapy [123].

In order to survive in the harsh condition of TME, cancer cells reprogram their metabolism. They do this by switching from oxidative phosphorylation to anaerobic glycolysis, which helps them maintain the adenosine triphosphate (ATP)/adenosine diphosphate (ADP) ratio in hypoxic conditions. This metabolic switch is known as the Warburg effect and persists even in normoxia, where it is called aerobic glycolysis [29]. In the metabolic reprogramming of cancer cells, several signaling pathways play a role, including phosphatidylinositol 3-kinase (PI3K)/Akt, c-Jun N-terminal kinase (JNK), extracellular signal-regulated kinase (ERK), and Ras, It has been demonstrated that exosome-derived lncRNAs can regulate these signaling pathways [124–126].As noted earlier, autophagy is crucial in cancer cell survival and progression. It gives a chance to cancer cells to protect themselves from environmental stress and replenish their energy source [113]. Studies show that

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lncRNAs are key regulators of autophagy [127]. In addition, CAF-secreted lncRNAs can lead to autophagy and plays a key role in the proliferation and survival of tumor cells in the TME [128].

The TME conditions can facilitate the lncRNA expression and function. It has been shown that hypoxia conditions promote cell survival through the transcription of several lncRNAs [128]. Due to the crucial role of exosomal lncRNAs in cancer development and treatment resistance, they can be applied potential targets for future targeted therapies [128].

5.2. Mesenchymal Stem Cells

Mesenchymal stem cells (MSCs) have the potential for self-renewal and differentiation into multiple cell lineages. They can easily recruit the tumor by detecting the inflammatory markers released in the TME and further support the cancer progression[129]. MSCs interact with tumor cells at multiple stages of cancer progression, such as EMT, angiogenesis, apoptosis resistance, metastasis, immune suppression, survival, and especially treatment resistance [130,131]. It has been demonstrated that MSCs can inherently improve chemotherapy resistance in distinct malignancies [131]. MSCs can increase drug resistance by secreting CXCL12, IL6, and IL8 and restoring CSC stemness through the NF-κB pathway. MSCs can enhance drug resistance through the following five methods:

(1) Direct cell-to-cell contact: This interaction triggers a series of signaling cascades in tumors [132,133]; (2) genetic mutations in MSCs: Genetic modifications occur not only in tumor cells but also in non-malignant cells, leading to treatment resistance [131,134]; (3) secretion of soluble factors: MSCs can release a variety of fatty acids, cytokines, and growth factors that lead to drug resistance [135,136]; (4) differentiation of MSCs into CSCs or CAFs: CSCs can lead to metastasis and promote tumor progression and can inherently be resistant to chemotherapy. Additionally, CAF-MSC cells can contribute to tumor growth, decrease apoptosis, increase proliferation, and resistance to chemotherapy. Therefore, by differentiating MSCs into CSCs or CAFs, they can cause treatment resistance [137,138]; (5) Release of exosomes: exosomes released from MSCs promote chemotherapy resistance among cancer cells through drug sequestration and delivery of specific mRNA molecules and proteins [139].

6. IMMUNOMODULATION

The immune system plays a crucial role in monitoring cancer and responding to chemotherapy. MDSCs, TAMs, dendritic cells (DCs), regulatory and effector T cells (T_{reg} and T_{eff}), B cells, and natural killer (NK) cells are the main immune cells in the TME [140]. These cells can have either opposing or stimulating effects on the tumor and play a key role in tumorigenesis (discussed below) [140].

Immune cells also contribute to the development of chemoresistance [141]. According to several studies, the relationship between MDSCs and malignant cells has a significant impact on chemotherapy resistance and immune system suppression [142]. An increase in T_{reg} infiltration in the microenvironment is associated with chemoresistance in several types of cancer, including colorectal, lung, kidney, head and neck, melanoma, ovarian, and glioblastoma [143]. Evidence suggests that tumor cells may manipulate local DCs to form suppressive T cells, ultimately leading to drug resistance [71]. Drug-resistant tumor cells can use tumor-associated neutrophils (TANs) to improve MDR-like activity [71]. TANs can enhance tumor cell proliferation due to their angiogenic properties. They can also suppress the antitumor immune response and improve drug resistance [144]. By activating various signaling pathways, TANs can reduce the efficacy of many cancer treatments, such as cytotoxic drugs and immune checkpoint inhibitors[141]. It has been demonstrated that NK cells may exhibit similar MDR-like activity, and this behavior can be inhibited by solutol HS-15 or verapamil [145].

TAMs are derived from circulating monocytes and are one of the most abundant cells in solid tumors that have a significant impact on suppressing the immune system in the TME [146]. They also play a key role in chemoresistance and tumor development [147,148]. Among the immune cells present in the TME, macrophages have a prominent and critical role in chemoresistance due to their high numbers and capabilities [149]. Generally, TAMs are divided into two subgroups, M1 and M2

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[149]. In the TME, macrophages are usually polarized from M1 to M2. This change would suppress the antitumor immune response, facilitates tumor progression, and enhance drug resistance [150,151], . Drug-resistant tumor cells can secrete IL-34, which subsequently activates the signaling pathway (CSF1R)/AKT, leading to increased M2 polarization [152]. TAMs, like CAFs, release a wide range of soluble factors, including chemokines, enzymes, interleukins, and exosomes, to combat drug attack [153]. For example, TAMs can prevent paclitaxel-induced tumor cell death by expressing cathepsins S and B [153]. By secreting exosomal miR-365, TAMs can increase the metabolism of gemcitabine, which ultimately leads to apoptosis inhibition and increased tumor resistance [147]. TAMs upregulate Gfi-1 in tumor cells (by inducing TGF-β secretion), which ultimately leads to reduced sensitivity of tumor cells to gemcitabine by inhibiting HMGB1 (high mobility group box 1) and CTGF (connective tissue growth factor) myeloid-derived suppressor genes [154]. By expressing IGF, TAMs can cause resistance to chemotherapy with paclitaxel [155]. Additionally, TAMs can cause chemotherapy resistance in pancreatic cancer by inducing EMT [148]. According to evidence from prostate cancer treatment with androgen deprivation therapy (ADT), CSCs can remodel macrophages into TAMs, which increase stem-like CSC features and drug resistance through the IL6/STAT3 signaling pathway [148,156]. Overall, TAMs use various mechanisms to induce drug resistance, including regulating CSC properties, transforming into M2 suppressive phenotype, promoting EMT, releasing various cytokines, and suppressing immune cells [148,151–153].

7. DNA REPAIR MECHANISMS

Preserving the genome and transmitting a healthy genome to the next generation is essential for living organisms [157]. However, DNA is constantly exposed to both endogenous factors (such as alkylation, hydrolysis, and oxidation) and exogenous genotoxic agents (such as ionizing radiation (IR), ultraviolet (UV) radiation, and chemotherapeutic agents) [157]. Although DNA is a crucial target for radiotherapy and chemotherapy, it can also lead to the development of cancer [158]. Therefore, living organisms rely on a complex system and multiple mechanisms to counteract DNA-damaging factors and maintain genome integrity, collectively known as the DNA damage response (DDR) [159]. In this regard, epigenetic alterations play a key role in gene expression and tumor heterogeneity [160]. For instance, histone deacetylases (HDACs) can contribute to the preparation of chromatin for DSB repair through NHEJ and HR [161]. As a result, the regulation of epigenetic chromatin structures and the mechanisms involved in DNA repair pathways can impact the DDR [160,161]. In addition, miRNAs can regulate the expression levels of DNA repair genes and subsequently modulate the sensitivity of cancer cells to DNA-damaging agents [162].

Generally, the repair pathways in response to DNA damage are as follows: (1) base excision repair (BER), (2) nucleotide excision repair (NER), (3) homologous recombination (HR), (4) non-homologous end joining (NHEJ), (5) mismatch repair (MMR), (6) microhomology-mediated end joining (MMEJ), (7) DNA damage tolerance (DDT) (including translesion synthesis [TLS], template switching [TS]), (8) O^6-methylguanine-DNA methyltransferase (MGMT) pathway, and (9) Fanconi anemia (FA) pathway [158,159,163,164]. Among these pathways, BER, MMR, NER, HR, and NHEJ are the major and essential pathways in DNA repair in cancer cells [164].

There are several types of DNA damage, including (1) clustered damaged sites, (2) base damage, (3) single-strand breaks (SSBs), (4) double-strand breaks (DSBs), (5) sugar damage, (6) DNA cross-linking [165,166]. Among these, SSBs and DSBs are more prominent [166], and DSBs are the most destructive type [165]. The BER pathway can directly or indirectly repair SSBs, while the NHEJ and HR pathways repair DSB damage [164]. Additionally, DNA adducts and replication errors are repaired by the NER and MMR pathways, respectively [167]. Several chemotherapeutics can directly damage DNA structure, such as topoisomerase I or II inhibitors and alkylating agents (such as cisplatin) [165]. During chemotherapy using camptothecin (a topoisomerase I inhibitor), if SSB occurs, the BER pathway is activated and subsequently, PARP1 (poly [ADP-ribose] polymerase 1) and APE1 (apurinic/apyrimidinic endonuclease 1) enzymes are activated [165,168]. However, if DSB damage occurs, the HR and NHEJ pathways are activated, followed by the HR pathway activating AMT and CHK1 enzymes, and NHEJ activating DNA-PK enzyme [168]. When etoposide (a

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topoisomerase II inhibitor) is prescribed, DSB damage occurs, which activates the HR and NHEJ pathways [169]. The HR pathway activates ATM and CHK1 proteins, and NHEJ activates DNA-PK [169]. When cisplatin (an alkylating agent) is prescribed, DNA interstrand cross-link (ICL) damage (activating HR and NER pathways) and intrastrand cross-link damage (activating NER pathway) occur [170]. Then the HR pathway activates ATM and CHK1 proteins, and the NER pathway activates XPA, XPB, and XPG proteins [165,170].

8. CANCER STEM CELLS

One of the reasons for cancer progression and treatment failure is cancer heterogeneity [171]. Different types of cancer cells in the tumor contribute to tumor heterogeneity, and among these cells, CSCs are highly involved in the initiation and progression of cancer and have self-renewal and differentiation abilities [171,172]. CSCs can be divided into two categories based on their function: (1) resident stem cells that can initiate the tumor, (2) migratory stem cells that metastasize and form tumors in another location [173].

CSCs have a key role in tumor initiation, drug resistance, metastasis, and cancer recurrence [174,175]. During a successful chemotherapy treatment, although a significant proportion of tumor cells undergo apoptosis, a subset of CSCs may survive and cause cancer recurrence [176]. There is a wide range of mechanisms, factors, and features that contribute to the chemoresistance of CSCs, including (1) tumor microenvironment support (by inducing autophagy, inflammation, and hypoxia)), (2) EMT (in response to EMT-transcription factors), (3) enhanced self-renewal ability (due to increased telomerase activity), (4) high expression of CSCs markers (e.g., CD133, ALDH1, CD44, CD24+), (5) quiescence (6) activation of stemness genes (e.g., Bmi1 and Musashi [MSI]), (7) epigenetic modifications (DNA methylation, histone modifications), (8) specific signaling pathways (e.g., Hedgehog, Notch, and Wnt pathways), (9) resistance to DNA damage-induced apoptosis (by promoting the DNA repair capability, enhanced ROS scavenging, and activating the anti-apoptotic signaling pathways), (10) metabolic alteration, (11) and higher expression of multi-drug resistance (MDR) or detoxification proteins (aldehyde dehydrogenase (ALDH), drug-transporter proteins [ABCG1, ABCB1])[177–185]

Emerging evidence indicates that ncRNAs, including lncRNAs and miRNAs, play a key role in regulating CSC properties such as asymmetric cell division, cancer recurrence, tumor initiation, self-renewal, and drug resistance [185–189]. Additionally, ncRNAs control the progression, growth, and division of CSCs by regulating downstream signaling pathways and transcription factors [187]. As previously mentioned, exosomes present in the TME play a prominent role in cellular communications and interactions between different TME components and cancer cells. Moreover, ncRNAs play a crucial role in intracellular signaling pathways and intercellular communications between CSCs [189]. Therefore, it can be argued that ncRNAs are likely to be highly influential factors in the chemoresistance of CSCs [190]. Furthermore, CSCs can use their high survival capacity and chemoresistance to survive and utilize exosomes and ncRNAs to spread chemoresistance to other cancer cells by creating extensive intercellular communications with other factors in the TME, ultimately leading to increased chemoresistance and cancer recurrence [182,186,190]. Overall, ncRNA can be considered as one of the most prominent factor of CSCs chemoresistance[191].

9. CONCLUSIONS

Cancer cells employ a wide range of factors and mechanisms to resist chemotherapy. Among these factors, the triad of CSCs, exosomes, and ncRNAs are particularly prominent. CSCs not only utilize diverse molecular mechanisms to develop chemical resistance but also have a significant role in chemoresistance through their interactions with various components of TME and other cancer cells. It has also been established that CSCs play a crucial role in recurrence after successful chemotherapy. Exosomes present in the cancerous microenvironment have a prominent role in cellular communications and interactions between different components of TME and cancer cells. Additionally, ncRNAs have an important role in intracellular signaling pathways and intercellular communications between CSCs. Therefore, one may argue that ncRNAs are likely to have a

significant impact on the factors involved in chemotherapy resistance resulting from CSCs. Additionally, CSCs can utilize their high capacity for survival and chemical resistance to stay alive, using the combination of exosomes and ncRNAs to spread chemical resistance among other cancerous cells by establishing wide intercellular communication with neighboring cells and other agents in the TME. These effects ultimately lead to the exacerbation of resistance and cancer relapse.

Overall, we can consider ncRNA as the most prominent factor among other factors in the chemoresistance of CSCs. Therefore, understanding the triple relationship between CSCs, exosomes, and ncRNAs is crucial and vital in the outcomes of various cancer treatments, specifically chemotherapy, and research in these three areas is essential to identify their precise mechanisms in therapeutic resistance. In addition, we recommend that the use of smart nanocarriers as a drug delivery method for small molecules could be an effective approach for delivering a greater and more fruitful amount of small molecules to cancer cells, considering the distinct conditions within the TME (such as hypoxia, acidity, etc.).

One of the challenges in drug delivery is the limited understanding of drug targets. Large-scale screening studies using CRISPR-Cas technology can help to improve our understanding of high-priority drug targets. Overall, we can hope that extensive studies focusing on the identification of new drug targets through the CRISPR-Cas technology, and improving the efficiency of smart nanocarriers for drug delivery will lead to significant advancements in effectively delivering small molecules to cancer cells and overcoming the challenges in chemotherapy treatment.

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