

Mechanism and Potential Therapeutic Strategies Based on PRMT5 in Chemotherapy-Induced Drug Resistance in Non-Small Cell Lung Cancer

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ABSTRACT

As a malignant tumor with high morbidity and mortality in the world, the treatment of non-small cell lung cancer is still facing great challenges. Although new breakthroughs have been made in recent years and great progress has been made in chemotherapy and targeted therapy, the five-year survival rate of most NSCLC patients is still at a low level. The emergence of drug resistance is one of the important factors affecting the therapeutic effect and survival rate of patients. PRMT5 (protein arginine methyltransferase 5), as a type II arginine methyltransferase, plays an important role in cancer cell proliferation, differentiation, apoptosis and tumorigenesis. At present, people pay more and more attention to the research on the mechanism of PRMT5 in tumor drug resistance. In this review, we summarize the mechanism of PRMT5 in chemotherapy resistance of non-small cell lung cancer and discuss potential strategies to avoid or overcome chemotherapy resistance.

KEYWORDS

NSCLC; Drug Resistance; PRMT5

1. INTRODUCTION

Cancer is one of the highest mortality rates among non-communicable diseases worldwide. According to the International Agency for Research on Cancer, lung cancer has become the most common type of cancer in the world with nearly 2.5 million new cases by 2022. Lung cancer is mainly divided into two categories: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), of which non-small cell lung cancer accounts for about 80% of all lung cancer, which is the most common type of lung cancer. About 75% of patients with non-small cell lung cancer are found to be in the middle and advanced stage, with a low 5-year survival rate.

The treatment of non-small cell lung cancer includes surgery, radiotherapy and chemotherapy. Chemotherapy is of great significance for the treatment of non-small cell lung cancer. It is often used to prolong the survival time of patients, improve the quality of life, and in some cases, as an adjuvant treatment to create favorable conditions for other treatments, such as surgery or radiotherapy. At present, the commonly used drugs for non-small cell lung cancer include VP16, platinum drugs led by cisplatin, paclitaxel drugs and so on. These drugs can achieve the purpose of anti-tumor by interfering with the synthesis, replication or function of DNA. However, as one of the common means of lung cancer, chemotherapy often occurs in the process of treatment, the initial treatment effect is low and the effect is gradually lost due to acquired drug resistance. Molecular studies have shown that treatment-induced dormancy surface changes, such as senescence, cell cycle arrest and polyploid giant cancer cells, are the causes of acquired drug resistance [1]. Some studies have also found that in some patients with EGFR mutations, NSCLC patients treated with EGFR inhibitors are converted

to more difficult SCLC [2, 3]. This process is similar to the change in the treatment of prostate cancer. Prostate cancer is transformed into neuroendocrine prostate cancer under the action of androgen receptor targeting drugs. NED has been widely studied in prostate cancer for more than 30 years. Many preclinical and clinical studies have shown that in addition to AR targeted therapy, radiotherapy and chemotherapy can also induce prostate cancer cells to produce NE [4, 5]. Therefore, NED seems to be the key to acquired drug resistance in prostate cancer cells.

As an important methylation enzyme, PRMT5 regulates the growth and division of cancer cells by methylation modification of key proteins. This methylation modification can affect the process of cell cycle, promote cells from G1 phase to S phase, and then accelerate cell proliferation [6]. At the same time, PRMT5 also participates in the regulation of signal pathways related to cell growth and survival, which further promotes the growth and survival of cancer cells [7]. As an epigenetic regulator, PRMT5 can also affect gene transcription and expression by methylation of histone and transcription factors [8, 9]. In cancer cells, PRMT5 further promotes the malignant transformation and progression of cancer cells by up-regulating the expression of genes related to cell proliferation, survival and metastasis [10]. By exploring the behavior and mechanism of drug resistance of PRMT5 in NSCLC chemotherapy, we can explore targeting PRMT5 as a new chemosensitization method for the treatment of non-small cell lung cancer.

2. MECHANISM OF CHEMOTHERAPY RESISTANCE IN NON-SMALL CELL LUNG CANCER

2.1. DNA Repair

DNA is considered to be the action site of many anticancer drugs. When drugs cause DNA damage, cancer cells can also achieve drug resistance through DNA repair. Some studies have found that platinum forms adducts with DNA, at the same time, it also leads to the initiation of intracellular DNA repair program. NER (nucleotide excision repair) and MMR (mismatch repair) are well-known DNA repair pathways for chemotherapy resistance [11, 12]. ERCC1 overexpression has been shown to be associated with reduced efficacy of platinum-based therapy in non-small cell lung cancer, and response or survival rates vary depending on host genotype ERCC1 polymorphism. However, ERCC1 is mainly involved in the removal of interchain crosslinks, rather than in the treatment of important intrachain crosslinks [13]. NER pathway (nucleotide excision repair pathway) is also one of the important factors of cisplatin resistance. DNA damage induced by cisplatin can effectively block RNA polymerase II, thus affecting the process of DNA transcription, while NER pathway can effectively remove cisplatin adducts, resulting in cisplatin resistance.

2.2. Decrease of Drug Concentration

In addition to DNA repair, when stimulated by drugs, cells can also reduce drug concentration by reducing drug uptake and increasing drug excretion, so as to reduce drug efficacy. Li ZH research group [14] found Copper transporter P-type adenosine triphosphatase (ATP7A) is also involved in platinum transport, and the expression of ATP7A in drug-resistant A549 cells is significantly higher than that in A549 cells at mRNA and protein levels, and clinical studies have also shown that cisplatin tolerance in ATP7A positive groups is significantly higher than that in normal groups. In addition, other studies have shown that undetectable tumor CTR1 expression is associated with reduced platinum concentration and tumor response [15]. The above studies show that in addition to passive fusion, many cation transporters are involved in the process of drug transport.

2.3. Cancer Cell Metabolism

Glycolysis, mitochondrial respiration, glutamate decomposition and fatty acid metabolism are important participants in cancer development. These processes provide adaptable metabolic characteristics for cancer cells and provide material and energy basis for cancer cell activity [16]. At the same time, abnormal metabolism of cancer cells is also thought to be associated with drug resistance. PPAR γ coactivator-1 α (PGC1 α) is considered to be an important participant in many metabolic pathways. In cancer cells, once induced by stress, PGC1 α interacts with specific transcription factors to promote mitochondrial respiration, fatty acid metabolism or ROS detoxification, thereby promoting cancer metabolic adaptation [17]. It was also found that cisplatin-resistant NSCLC cells were strongly dependent on glutamine, and glutamine-driven nucleoside biosynthesis had a strong rescue effect on hungry CDDP-resistant cells [18].

2.4. Destruction of Platinum-Mediated Cell Cycle Arrest

Cisplatin-induced DNA damage activates a variety of pathways, one of which eventually leads to the activation of cell cycle checkpoints, which temporarily induces temporary S-phase arrest, and then inhibits cyclin An or B kinase in Cdc2- cells, resulting in lasting G2/M arrest [19]. It was found that compared with cisplatin-resistant cells, parental A549 cells showed a significant decrease in G1/G0 phase, and a more significant difference was observed in G2/M phase. Parental cells showed obvious cell cycle arrest, while cells in S phase showed no significant difference between them, and the expression of pATM in drug-resistant cells was not obvious [20]. In cisplatin-resistant cells, the expression of circular RNAhsa_circ_0096157 was the highest. Its knockdown could inhibit the proliferation, migration, invasion and cell cycle process of A549/DDP cells, but promote apoptosis [21].

2.5. Tumor Microenvironment

Tumor microenvironment refers to the accumulation of cancer cells and their nearby infiltration and resident host cells, secretory factors and extracellular matrix [22]. There are great differences in physical and chemical properties and components between tumor microenvironment and normal physiological environment, and many cancer markers are also related to it, so they have gradually become active participants in the role of drugs. However, some studies have shown that tumor microenvironment also plays an important role in chemotherapy resistance. Through the comparison of drug-resistant and sensitive clusters by scRNA-seq, it is found that drug resistance is closely related to TME, and drug-resistant cells may achieve sustained proliferation by changing metabolism and changing TME. By changing TME and cutting off the pathways related to drug resistance, the specific treatment of chemotherapy resistance can be realized [23]. Tumor-associated fibroblasts (CAF) is one of the key cell components in tumor microenvironment. It is formed by normal fibroblasts (NAF) under the action of cancer cells, and can regulate the proliferation, metastasis and drug resistance of cancer cells [24]. Existing studies have shown that cancer-associated fibroblasts (CAF) interact with lung cancer cells to obtain malignant tumors and therapeutic drug resistance through paracrine rings through EMT signals in the tumor microenvironment. In addition, CAF regulates the cellular activity of immune cells through various cytokines and chemokines to create a microenvironment for immune tolerance [25].

2.6. Activate Signal Transduction Related to Proliferation and Survival

It is reported that chemotherapeutic resistance is related to the activation of many proliferation and inventory-related signal transduction, including EGFR receptors and their downstream targets, such as PI3K-AKT signaling pathway, MAPK, NF- κ B and so on. Consistent with this conclusion, the

survival rate of NSCLC patients was significantly and continuously improved after treatment with enotinib.

It has been proved that p38 MAPK/P53/EGFR axis is the key signal pathway leading to PTX drug resistance. Cells exposed to continuous stress use p38 MAPK and p53 to repair cumulative cell damage. P38 MAPK activation and increased transcription increase the expression of EGFR in paclitaxel-resistant cells [26]. In addition, the data showed that calpain-2 was up-regulated in NSCLC, while knocking down calpain-2 inhibited cell proliferation and migration and promoted cell apoptosis in vitro. In vivo, calpain-2 knock-down cells form smaller subcutaneous tumors. Simultaneous knockdown of calpain-2 can down-regulate the expression of EGFR and pAKT, weaken the chemotherapy resistance of NSCLC cells to paclitaxel by inhibiting cell proliferation and inducing apoptosis, and even enhance the down-regulation of EGFR and pAKT mediated by paclitaxel [27].

2.7. MiRNA

MicroRNA (miRNA) is a kind of non-coding single-stranded RNA encoded by endogenous genes with a length of about 22 nucleotides, which plays a role in the post-transcriptional regulation of gene expression. At present, studies have confirmed that miRNA can promote chemotherapy resistance during cisplatin treatment, and may be used as a biomarker of cisplatin resistance [28]. Based on this, it was found that miR-4443 was enriched in cisplatin-resistant clinical samples and drug-resistant cell lines. In addition, functional studies have shown that exocrine miR-4443 can promote cisplatin resistance of NSCLC cells through FSP1m6A-mediated iron death. On the other hand, miRNA can target different genes by inhibiting transporters and down-regulating the expression of DNA repair-related proteins, thus inhibiting the repair of DNA damage and promoting drug resistance [29]. It has been reported that miRNA inhibits the growth of non-small cell lung cancer cells and increases the sensitivity to cisplatin by regulating the cell cycle. Overexpression of miR-381 significantly inhibited cell proliferation, colony formation and tumorigenesis in vivo. The ectopic expression of miR-381 was blocked in NSCLC cells at G0/G1 phase, accompanied by increased expression of p21 and p27, and decreased expression of cyclin D1 and CDK4. Compared with A549 parent cells, the miR-381 level of cisplatin resistant equivalent (A549/CDDP) decreased. MiR-381 re-sensitized A549/CDDP cells to cisplatin and enhanced cisplatin-induced apoptosis [30].

2.8. Pathological Phenotypic Transformation

Some tumor patients will undergo pathological phenotypic transformation, cell morphological changes and even tumor tissue types, such as transformation from non-small cell lung cancer to small cell lung cancer. In the study of Coll ín-ValZ group, after being stimulated by PM2.5, A549 cells formed multicellular tumor spheres and increased cell proliferation, migration and chemotherapy resistance [31]; In the treatment of patients with EGFR mutations, patients treated with EGFR inhibitors experienced a transition from NSCLC to SCLC [2, 3].

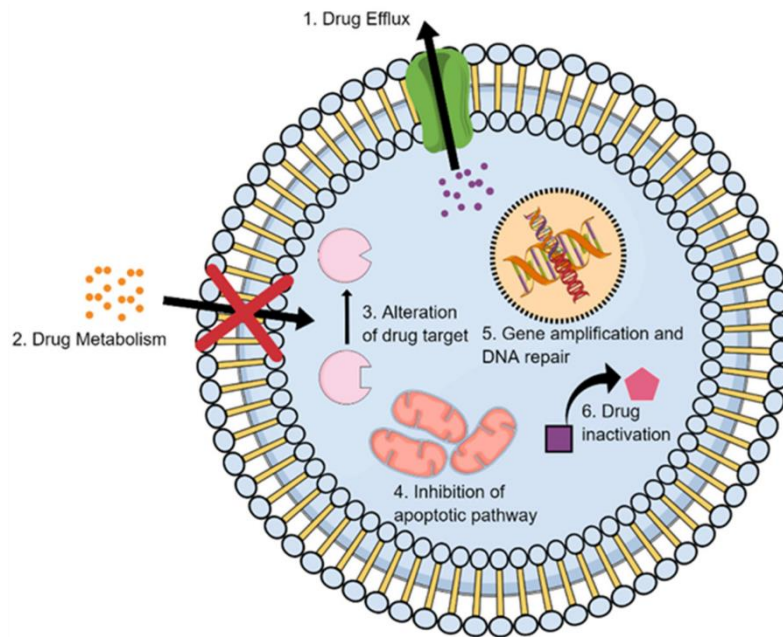


Figure 1. mechanism of drug resistance in non-small cell lung cancer [32]

3. PRMTs

3.1. The Function of PRMTs

Protein arginine methyltransferase (PRMTs) is an important enzyme that catalyzes the methylation of protein arginine in vivo. Protein arginine methyltransferase (PRMTs) is a kind of enzyme that uses S-AdenosylMethionine (SAM) as a methyl donor to catalyze N ω -methylation of protein arginine [33]. According to the different ways of catalytic methylation of arginine, PRMTs can be divided into three categories: type I includes PRMT1-4, which can catalyze monomethylation and asymmetric dimethylation; type II, including PRMT5 and 9, can catalyze monomethylation and symmetrical dimethylation; type III PRMT7 can only catalyze monomethylation [34-38] (Figure 2-3). PRMTs plays an important role in cell biology, including DNA transcription, signal transduction, protein stability and so on. PRMTs plays an important role in tumorigenesis, including cancer cell proliferation, differentiation, apoptosis and so on. Different from the specific expression of other family members in different organs, PRMT5 is expressed in many human tissues (Figure 4)

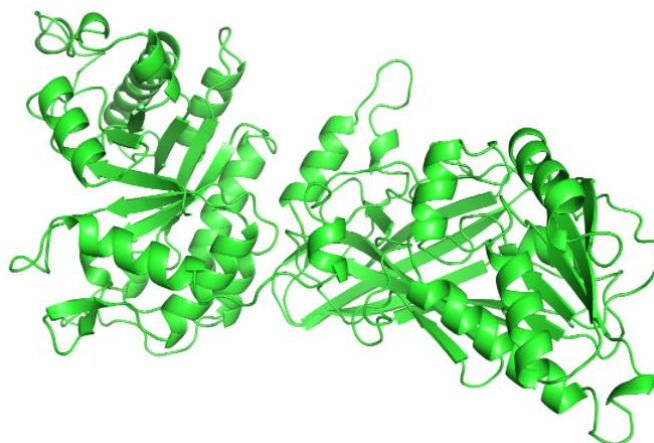


Figure 2. the structure of human PRMT5

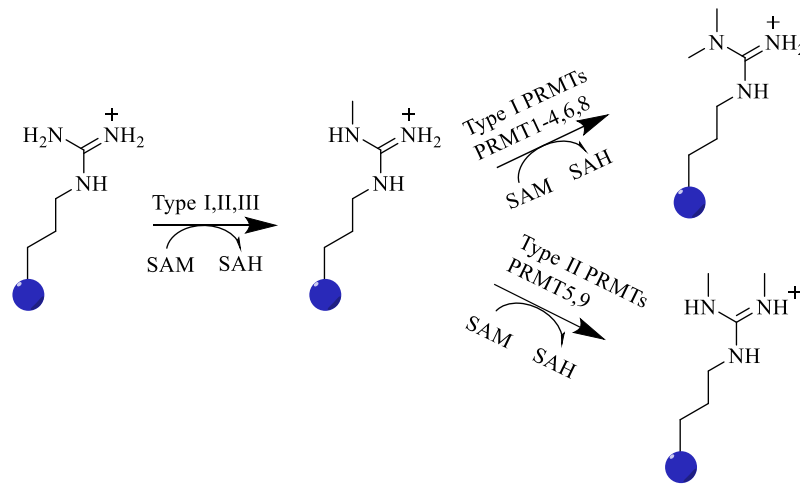


Figure 3. three ways of protein arginine methylation

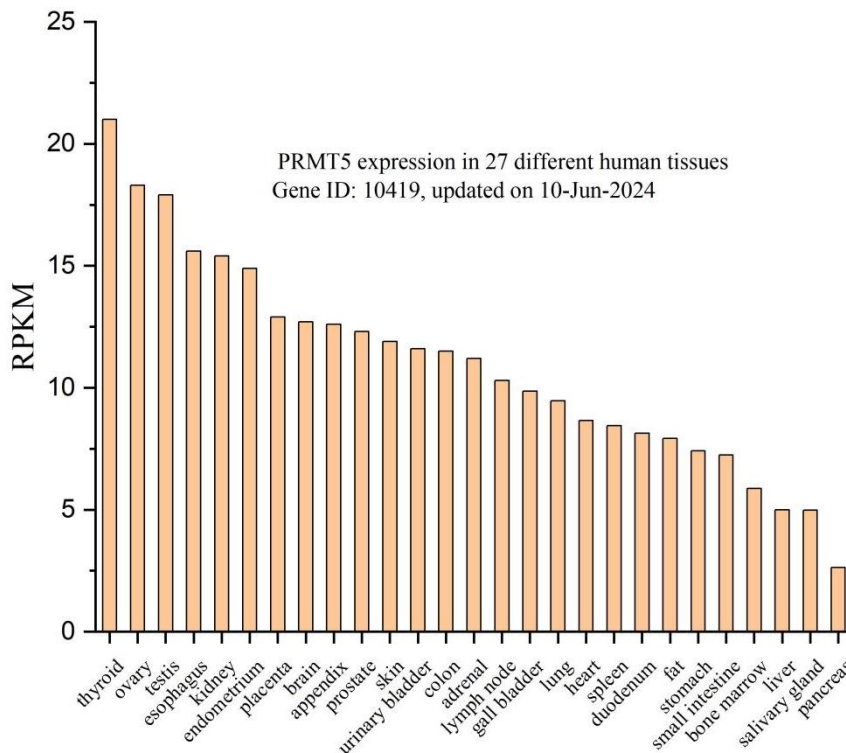


Figure 4. PRMT5 gene expression profile of human tissue

(Data come from <https://www.ncbi.nlm.nih.gov/>)

3.2. The Role of PRMTs in Cancer

The expression of PRMTs is abnormally high in a variety of tumors and is often associated with poor prognosis. It is reported that PRMT5 is highly expressed in urothelial carcinoma of bladder and is related to low overall survival rate. Low PRMT5 knockout leads to cell cycle G1/S arrest, Akt inactivation and mTOR phosphorylation in BUC cells [39]; The expression of PRMT6 is up-regulated in the development of endometrial carcinoma, and shows carcinogenic activity by activating AKT/mTOR pathway. In clinical studies, the increased expression of PRMT6 is significantly associated with higher histological tumor grade and poor prognosis. In lung cancer cells, PRMT1 has been found to be very important for drug resistance. Flap endonuclease 1 (FEN1), as the main component of base excision repair pathway, plays an important role in DNA replication and DNA

damage repair. Studies have shown that PRMT1 is a key factor to maintain the high expression level of FEN1, which is very important for DNA repair ability and chemotherapy resistance of lung cancer cells [40].

In addition, all PRMTs can promote the production and maintenance of drug-resistant cells through a variety of mechanisms, including changes in drug efflux transporters, DNA damage repair, autophagy, EMT and TME disorders, etc [41].

3.3. The Role of PRMT5 in Non-Small Cell Lung Cancer

PRMT5 (protein arginine methyltransferase 5), as a type II arginine methyltransferase, has attracted wide attention in the field of cancer research in recent years. It regulates a variety of physiological functions in mammalian cells by symmetrically dimethylating arginine residues on histone and non-histone, especially in the growth, migration and development of cancer cells. This methylation modification plays an important role in regulating key cellular processes such as cell growth, differentiation, DNA repair, cell cycle progression, transcriptional regulation and RNA splicing.

Overexpression of PRMT5 has been shown to be associated with tumor cell proliferation and invasiveness in a variety of cancers, including non-small cell lung cancer [42]. Overexpression of PRMT5 in non-small cell lung cancer may promote the proliferation and invasion of tumor cells. Because the methylation of PRMT5 affects a variety of key cellular processes, its abnormal expression may affect the progression of non-small cell lung cancer by regulating these processes. Early studies have found that the expression level of PRMT5 in lung cancer tissues is higher than that in normal tissues. Inhibition of PRMT5 can inhibit the proliferation and metastasis of lung cancer cells [43]. In addition, PRMT5 may affect the development of non-small cell lung cancer by interacting with other proteins and signal pathways [44]. Huang J [45] found that PRMT5 is ectopically expressed in human lung cancer tissues and cell lines. It regulates EMT labeling through EGFR/Akt signal cascade. Knocking down PRMT5 or using specific inhibitors can reduce the level of EMT-related markers mRNA and protein. Zhang S research group [46] proved Down-regulation of PRMT5 by shRNA or inhibition of PRMT5 by GSK591 significantly inhibited the expression of cyclin E1 and cyclin D1 and cell proliferation. In addition, we found that PRMT5 promotes the proliferation of lung cancer cells by regulating Akt activation. PRMT5 co-locates and interacts with Akt directly, but does not interact with PTEN and mTOR. Down-regulation or inhibition of PRMT5 significantly reduces Akt phosphorylation at Thr308 and Ser473, while the expression of PTEN and mTOR phosphorylation remains unchanged, indicating that PRMT5 is an important upstream regulator of Akt and induces lung cancer cell proliferation. Zhou H [47] found The interaction between PRMT5 and KLF5, down-regulation of PRMT5 or drug inhibition can reduce the expression of KLF5 and its downstream targets in vitro and in vivo. In terms of mechanism, the dimethylation of KLF5 by PRMT5 stabilizes KLF5 at least partly by regulating the Akt/GSK3 β signal axis, thus promoting the maintenance and proliferation of lung cancer cells. There is also evidence that PRMT5, in cooperation with pICln, participates in the up-regulation of DNA damage expression by HR, NHEJ and G2 block (including RAD51, BRCA1 and BRCA2) as the main epigenetic activator of DNA damage response (DDR) gene [48]. Jing P [44] found that PRMT5 suppresses the transcription of miR-99 family through symmetrical dimethylation of histone H4R3, increases the expression of FGFR3 and activates Erk1/2 and Akt, which leads to tumor growth and metastasis, and is closely related to lung cancer metastasis to lymphatic system and poor prognosis of patients. In addition, in order to resist treatment, cancer cells often show a variety of phenotypes, including neuroendocrine differentiation (NED). Shen Q [49] found that cisplatin and etoposide can induce neuroendocrine differentiation of NSCLC cells, and PRMT5 is the key intermediary in this process. Targeting PRMT5 can kill NSCLC cells in cooperation with etoposide.

4. DRUG RESISTANCE TREATMENT STRATEGY FOR NON-SMALL CELL LUNG CANCER

At present, the drug resistance of non-small cell lung cancer induced by chemotherapy is still a problem to be overcome in the process of treatment. However, with the development of reasonable treatment strategies and new drugs, the problem has been alleviated to a certain extent. At present, the treatment methods to overcome the drug resistance of non-small cell lung cancer mainly include the application of targeted drugs, immunotherapy, combination of chemotherapeutic drugs and so on [50]. In addition, because of its unique advantages, drug delivery system is also often used in the treatment of drug resistance of cancer. Considering the role of PRMT5 in the process of NSCLC resistance, it is believed that many PRMT5 inhibitors being developed will also be used in the treatment of NSCLC drug resistance in the future.

4.1. Treatment Strategy Based on Drug Delivery System

Drug delivery system (Drug Delivery System, DDS) is a technical means to improve the effect of drugs in time, space and dose. Among them, nanotechnology plays an important role in overcoming drug resistance.

Nanoparticles can be used to improve the stability, safety, efficacy and pharmacokinetics of drugs [51]. Compared with traditional therapy, nanoparticles can be modified and customized, so they can effectively enhance the physical and chemical properties of drugs, enhance drug permeability and retention time in the human body [52]. On the other hand, nanoparticles can load drugs efficiently, which makes it possible to reduce the adverse reactions caused by chemotherapy, because normal cells can be protected from the effects of anticancer drugs. The mode of interaction between nanoparticles and drugs can be divided into internal empty nuclear loading, uniform distribution with drugs in the matrix, covalent connection with drugs and mutual attraction between charges (Figure 5).

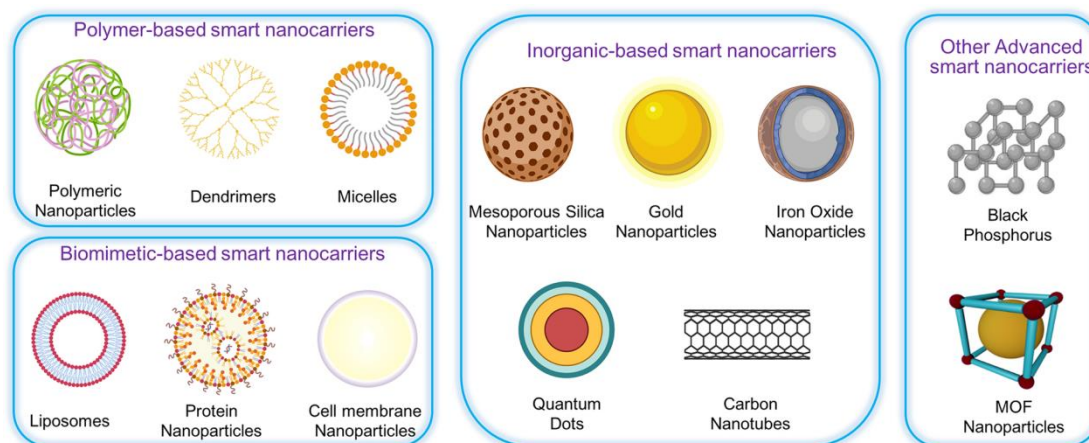


Figure 5. nanoparticles of different materials [53]

In the treatment of drug resistance to cancer, nanoparticles have the following advantages: nanoparticles can be designed to target proteins, peptides, nucleic acids, etc., which can prolong the half-life of drugs and enhance their biological activity [54-56]. Based on the use of different nanoparticles, many biological, physical and pharmacological obstacles can be overcome [57]; Nanoparticles can simultaneously deliver one or more high-dose drugs to overcome single drug resistance [17, 58]. At present, the emergence of chemotherapy resistance mainly includes inactivation of tumor suppressor genes, activation of oncogenes and changes in the expression of related proteins caused by direct induction of drugs. Therefore, combination therapy is often used to overcome drug resistance [59]. However, due to the different mechanisms of different components in

combined therapy, the application of drugs is limited due to the damage and toxicity of drugs to normal tissues. Therefore, the functionalization of nano-drugs is often designed to target specific components in tumor cells to achieve specific effects on tumor cells [60].

Gu X team [61] designed a kind of CuS nanoparticles, which is a photodynamic nano-switch to specifically eliminate the overactive bypass signal transduction in drug-resistant tumor cells without interfering with the same signal pathway in normal cells. In gefitinib-resistant tumors induced by typical insulin growth factor-1 receptor (IGF1R) bypass activation, CuS NPs irradiated by near-infrared laser locally increased the level of reactive oxygen species (ROS) in tumor cells, resulting in cascade blockage of IGF1R and downstream AKT/ERK/NF- κ B signals. Therefore, CuS NPs irradiated by laser makes the tumor sensitive to gefitinib and prolongs the survival time of mice without obvious toxicity. Considering the role of GSH and DNA repair in chemotherapy resistance, a novel vanadium-based nano-platform was designed by coating platelet-derived growth factor receptor- β (PDGFR- β)-recognized cyclopeptide (PDGFB)-labeled liposomes on platinum-loaded hollow vanadium-doped mesoporous silica nanoparticles (HVMSN). The nano-platform actively targets tumor tissue, and then effectively responds to the weak acidity and high GSH of tumor microenvironment, so that Pt (IV) prodrugs and vanadium ions are accurately delivered and intelligently released. In addition vanadium ions significantly down-regulated the expression of glutamyl cysteine ligase (GCL) and excision repair cross complementarity 1 (ERCC1) thereby inhibiting intracellular GSH synthesis and repair of damaged DNA. These synergistic effects greatly increased the sensitivity of tumor cells to platinum-based drugs, and then reversed the drug resistance of CDDP [62]. Zhang X K [63] by encapsulating cisplatin and oleanolic acid in mesoporous silica nanoparticles, the nanosystem showed better anti-tumor effect than single cisplatin or single oleanolic acid under the EPR effect, and oleanolic acid increased the sensitivity of cisplatin, reduced drug resistance and effectively killed cancer cells.

In addition, nucleic acid therapy based on cDNA, mRNA, small interference RNA (siRNA) or microRNA (miRNA) has played a role in regulating the expression of DNA or RNA. The combination of gene therapy and nano-system has a great application prospect in chemotherapy drug resistance. Because nucleic acid has negative charge, high molecular weight and hydrophilicity, the permeability of nucleic acid in cell membrane is poor, and the role of intracellular nuclease, how to achieve effective uptake of nucleic acid and enhance endosome escape is still a great challenge. Through surface functionalization, nanoparticles can effectively absorb nucleic acid and deliver it to the site of action and realize endosome escape [64]. Kotmakci M [65] prepared a cationic surface lipid nanoparticles for delivery of RNAi-mediated plasmid DNA, which down-regulated STAT3 in cisplatin-resistant lung cancer cells. The particle effectively loaded the plasmid and protected it from DNase and serum-mediated degradation, effectively reduced the expression of STAT3 and enhanced the sensitivity of cells to cisplatin. Su W C [66] successfully synthesized polylactic acid-glycolic acid copolymer (PLGA) nanoparticles loaded with paclitaxel and Stat3siRNA, which successfully knocked down STAT3, and the results showed that the absorption in paclitaxel-resistant cells was greater than that of free paclitaxel, and finally induced more cell apoptosis. Ana Vanessa Nascimento [67] overcomes cisplatin resistance in non-small cell lung cancer (NSCLC) by using Mad2 silencing siRNA delivered by chitosan nanoparticles targeting EGFR. The nanoparticles can effectively deliver siRNA and exert the killing effect on tumor cells and reduce the damage to normal tissue at lower dosage. at the same time, targeted delivery can effectively improve the inhibition of tumor growth.

To sum up, nanoparticles and their co-delivery with nucleic acids and drugs is a cancer treatment strategy with broad application prospects. Through precise targeted delivery and cooperative therapy, the problem of chemotherapy resistance can be overcome and the efficacy and safety of cancer treatment can be improved.

4.2. PRMT5 Inhibitor

Based on the abnormal expression of PRMT5 in most tumors, how to inhibit its activity has become a serious problem in targeted therapy. Up to now, based on the PRMT5 crystal structure model and computer-aided drug simulation design, a lot of research progress has been made on PRMT5 inhibitors, and many research groups have reported PRMT5 inhibitors. At present, PRMT5 inhibitors can be divided into the following categories according to their action mechanism: substrate competition inhibitors, SAM competition inhibitors, double SAM/ substrate competition inhibitors and MTA synergistic PRMT5 inhibitors.

4.2.1. Substrate competition inhibitor

As the fastest-growing PRMT5 inhibitor, GSK3326595 has achieved good results in clinical research. It can affect the activity of SAM through the cation- π interaction between tetrahydroisoquinoline group and PRMT5. At present, the drug has shown good efficacy in breast cancer, non-Hodgkin's lymphoma and recurrent / refractory mantle cell lymphoma.

4.2.2. SAM competitive inhibitor

As a competitive inhibitor of SAM, PF-06939999 shows anti-tumor activity in NSCLC, and can effectively reduce drug resistance, and shows controllable side effects in clinical studies.

As a powerful and oral brain permeability inhibitor, PRT811 can penetrate the blood-brain barrier and act directly on brain tumor cells. In clinic, it has good effect and safety for central nervous system lymphoma, recurrent high-grade glioma and advanced solid tumor.

4.2.3. Double SAM/ substrate competition inhibitors

JNJ-64619178 is a selective, time-dependent and effective cellular PRMT5 inhibitor double SAM/substrate competition inhibitor. Long-term resident JNJ-64619178 is achieved by interacting with SAM and substrate binding pocket of PRMT5. JNJ-64619178 shows prolonged inhibition of PRMT5 and effective anti-proliferation activity in cancer cell lines derived from various histological subsets, including lung, breast cancer, pancreas and hematological malignant tumors [68].

4.2.4. MTA cooperates with PRMT5 inhibitors

The results show that PRMT5 ·MTA complex has recently become a new synthetic lethal drug target for the treatment of MTAP deletion cancer, and MRTX1719 is an effective selective binder of PRMT5 ·MTA complex, which can selectively inhibit PRMT5 activity in MTAP deletion cells compared with MTAP wild type cells. Daily oral administration of MRTX1719 to tumor xenografts in mice showed a dose-dependent inhibition of PRMT5-dependent symmetrical dimethylarginine protein modification in MTAP-deficient tumors related to antitumor activity [69].

TNG908 is a MTAP synergistic PRMT5 inhibitor, which can cross the blood-brain barrier and has oral activity. Its selectivity to MTAP-negative cell lines is 15 times higher than that of MTAPWT cell lines, which makes it particularly suitable for cancer research. In the xenotransplantation model, the *in vivo* active TNG908 (1-120mg/kg, oral or intravenous) showed dose-dependent and antitumor activity. This compound has good therapeutic effect on malignant peripheral neurilemmoma (MPNST) and malignant glioma [70].

5. CONCLUSION

After an in-depth study of the relationship between PRMT5 and chemotherapy resistance in non-small cell lung cancer (NSCLC), it is not difficult to find that the research in this field is increasingly becoming the frontier and hot spot of oncology. As a key enzyme of methylation modification, PRMT5 plays a complex and important role in drug resistance of NSCLC, which not only provides a

new perspective for understanding the mechanism of drug resistance of NSCLC, but also provides a potential target for the development of new therapeutic strategies.

This review preliminarily reveals the regulatory network of PRMT5 in NSCLC chemotherapy resistance, and finds its interaction with multiple signal pathways and molecular markers, and summarizes the drug delivery systems and PRMT5 inhibitors with good application prospects. However, there are still many challenges in this field, such as the specific mechanism of PRMT5 in NSCLC, the difference of its expression in different subtypes and stages, and the development of specific inhibitors of PRMT5.

Looking forward to the future, we hope that through further research, we can more fully understand the mechanism of PRMT5 in NSCLC chemotherapy resistance, and develop efficient and safe specific inhibitors for PRMT5. This will provide new ideas and methods for the treatment of NSCLC, and is expected to improve the therapeutic effect and quality of life of patients. At the same time, we also believe that with the deepening of research, the potential of PRMT5 in tumor treatment will be more fully tapped and applied.

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