Precise design strategies of nanomedicine for improving cancer therapeutic efficacy using subcellular targeting

Xianglei Fu1, Yanbin Shi2, Tongtong Qi1, Shengnan Qiu1, Yi Huang1, Xiaogang Zhao3, Qifeng Sun3 and Guimei Lin1

Therapeutic efficacy against cancer relies heavily on the ability of the therapeutic agents to reach their final targets. The optimal targets of most cancer therapeutic agents are usually biological macromolecules at the subcellular level, which play a key role in carcinogenesis. Therefore, to improve the therapeutic efficiency of drugs, researchers need to focus on delivering not only the therapeutic agents to the target tissues and cells but also the drugs to the relevant subcellular structures. In this review, we discuss the most recent construction strategies and release patterns of various cancer cell subcellular-targeting nanoformulations, aiming at providing guidance in the overall design of precise nanomedicine. Additionally, future challenges and potential perspectives are illustrated in the hope of enhancing anticancer efficacy and accelerating the translational progress of precise nanomedicine.

INTRODUCTION

Nanoparticle-based drug delivery systems (NDDSs) are extensively employed in the therapy, diagnosis, and imaging of cancer due to their characteristics of high cancer-targeting efficacy, low toxicity, and controlled release properties.1 An efficient drug delivery system must avoid the clearance of the reticuloendothelial system, penetrate across blood vessel walls and be enriched at cancer sites to exert their pharmacological effects.2 For this purpose, an ever-increasing number of preclinical studies have reported a large number of engineered nanoformulations with unique physical and chemical properties, with the goal of delivering chemotherapeutic agents, photosensitizers, genes, and other biomolecules to cancer cells in specific and efficient manners.3 However, due to the problems of multidrug resistance (MDR), high variability, and poor patient prognosis, NDDSs have still faced tremendous challenges. It is therefore necessary when designing new treatment strategies to study in-depth the pathogenesis of cancer.

With the development of precision medicine, researchers have realized that variations in key intracellular biomolecules (genes and proteins), which are usually at the subcellular level, play a critical role in carcinogenesis and cancer development.4–6 Designing drug candidates based on molecular-level pathogenesis has become a new pattern and trend of drug discovery. For example, Ying et al. found that the expression level of sterol o-acyltransferase 1, which is responsible for transforming cholesterol into cholesterol ester-storage granules, is closely related to the poor prognosis of patients with liver cancer. Based on this, the research team proved that avasimibe, a small molecular inhibitor of sterol o-acyltransferase 1, had a good antitumor effect on patient-derived tumor tissue xenograft model of hepatocellular carcinoma, and provided new treatment strategies for tumor patients.7 Moreover, high-profile gene therapies also have to deliver the therapeutic genes into the cytoplasm or nucleus, where they can function. As a result, effective NDDSs should not only carry the therapeutic agents to the target tissues and cells but also deliver the drugs to distinct subcellular sites which mean organelles as targets accurately. They are considered to be one of the most promising approaches for cancer treatment. Through their proper design and specific modifications, subcellular-targeting nanoformulations are enriched in tumor cells, are internalized by endocytosis across the subcellular barriers (such as inner body embedding and lysosomal degradation)8 and target-specific subcellular structures (as shown in Fig. 1). This is then followed by the controlled release of therapeutic agents at the target sites, thus improving their antitumor efficacy, reducing their toxic and side effects, and overcoming the most critical limitation of intracellular drug delivery—MDR.9

In this review, based on the latest research progress over the past 5 years, we will focus on the important aspects of subcellular-targeting nanoformulations for cancer therapy. First, relevant knowledge including the specific endocytosis pathway of different nanoformulations taken up into cells and the pathological characteristics of tumor cell organelles are the key elements for guiding the construction of NDDSs, especially for the selection of targeting ligands. Next, according to the different subcellular targets of commonly used anticancer therapeutic strategies (chemical therapy, gene therapy, photodynamic therapy (PDT), etc.) applied after surgery, this article will elaborate on how to achieve precise subcellular targeting by functionalizing the surface of nanoparticles (NPs) with ligands and other means in the order of lysosome, nucleus, mitochondria, endoplasmic reticulum (ER), and Golgi apparatus. Furthermore, we will point out that multiple targeting and controlled release are crucial to the design and overall construction of the subcellular-targeting NDDSs. Finally, two challenges and potential directions to pursue in order to...

1Department of Pharmaceutics, Key Laboratory of Chemical Biology (Ministry of Education), School of Pharmaceutical Sciences, Cheeloo College of Medicine, Shandong University, Jinan 25012 Shandong, China; 2School of Mechanical and Automotive Engineering, Qilu University of Technology (Shandong Academy of Sciences), Jinan 250353 Shandong, China and 3The Second Hospital, Cheeloo College of Medicine, Shandong University, Jinan 250033 Shandong, China

Correspondence: Guimei Lin (guimeilin@sdu.edu.cn)

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boost precise subcellular targeting are illustrated, which will benefit the transformation of NDDSs from laboratory research to clinical practice.

MAIN
NDDSs can achieve the enrichment of tumor microenvironment, cell internalization, and intracellular delivery through passive or active targeting. In passive targeting, the size, shape, and surface charge of NPs can affect penetration and retention, thus significantly affecting their cell internalization and subcellular localization. For example, positively charged ultrasmall NPs have a higher affinity to the organelles such as mitochondria and nuclei, thereby promoting their intracellular permeability.10 Active targeting usually relies on the modification of localization group such as antibodies, ligands, etc., which have specific interaction with the receptor, thus leading to more significant effect than conventional treatment strategies. In intracellular transport and targeting, we still focus on these two aspects to explore design strategies of subcellular-targeting nanoformulations.

Endocytosis and intracellular trafficking of nanoformulations
There are many targets (such as folate receptors, transferrin (Tf) receptors, antigens) which are usually overexpressed on the surface of cancer cells, and targeting them to maximize the drug accumulation around cancer cells have become a focus research to cancer therapy in recent decades. When NPs reach the cell surface through passive or active targeting, endocytosis is the main mechanism by which they are taken up by cancer cells. Different types of NDDSs rely on different cell endocytosis mechanisms to enter the cell, which ensures they internalize in specific intracellular regions.11 We will briefly review the classic endocytosis pathways for better prediction of the intracellular fate of nanoformulations. Endocytosis can be divided into clathrin-mediated endocytosis (CME), caveolae-mediated endocytosis (CVME), macropinocytosis, and phagocytosis (as shown in Fig. 2). Among these, CME and CVME are the major uptake pathways of various nanoformulations. Generally, large NPs (<120 nm) are internalized mainly through CME, and specific ligand-modified nanoformulations (e.g., epidermal growth factor, folic acid, chemokines, and Tf) can significantly improve the efficiency of this endocytosis pathway. Following CME, the nanoformulations are trafficked through the early endosomes—late endosomes—lysosomes pathway and arrive in the lysosomal lumen, where they may be degraded by lysosomal hydrolases.13 For those nanoformulations whose action sites are other subcellular localizations in the cytoplasm, they are supposed to be designed to avoid endosome/lysosome degradation and retain their biological activity. Using carrier materials that are stable in acidic environments and solution with pH buffering properties can alleviate degradation problem to a certain extent.14 Endosome/lysosome escape capability is a more effective prerequisite.15 The commonly recognized mechanisms of lysosomal escape include proton-sponge effect, membrane fusion, the
generation of gas, and the application of CPPs and PCI. Some examples and applications used in nanomedicine are listed in Table 1. On the other hand, nanoformulations with a small particle size (<60 nm) usually rely on CVME to enter cells. These NPs coated by caveolae usually do not enter lysosomes and are directly transferred to the Golgi or ER. Other endocytosis processes are shown in Fig. 2. As is apparent, the endocytosis process of antitumor NPs is the key step to achieve subcellular enrichment. Deep understanding and exploration of these endocytic pathways are rather significant for developing new delivery strategies for subcellular targeting.

Lysosomal accumulation
Many nanoformulations mediated by CME can actively accumulate in lysosomes at the end of the endocytosis pathway. Taking full advantage of this accumulation to delivery antitumor drugs that act on lysosomes can greatly simplify the complexity of the carriers’ design. Second, recent reports have demonstrated chloroquine and its derivatives, rapamycin, HSP70 antagonist, and cathepsin B can act on the lysosomes and their components to trigger lysosomal membrane permeabilization (LMP), which can bypass the classical caspase apoptosis pathway and thus produce antitumor effects on drug-resistant cells. Third, the lysosomal pathological features lay a foundation for precise drug release. Given the evidence discussed above, lysosomal targeting and destruction could represent potential pharmacological delivery strategies.

Lysosomal characteristics. Lysosomes are single-membrane acidic vesicles (pH 4.5–5.0) that contain more than 60 hydrolytic enzymes that can break down biomolecules (such as proteins, lipids, carbohydrates, and nucleic acids). They play important roles in maintaining cellular homeostasis, inducing cell apoptosis, nutrient sensing, and immune responses. However, malignant transformation usually leads to changes in lysosomal volume, composition, and subcellular localization. In cancer cells, increased lysosomal fragility caused by increases in sphingomyelin makes lysosomes more vulnerable to LMP in response to stimuli, such as surfactants, heat, and reactive oxygen species (ROS), thus causing cell death.

Delivery strategies of lysosomal precise therapy. Receptor-mediated endocytosis can usually increase the possibility of the NPs’ final arrival in lysosomes, so ligand modifications play important roles in lysosomal targeting. When NDDSs are modified by the specific aptamer of receptors on the surface of tumor cells, such as Tf and the anti-human epidermal growth factor receptor-2 monoclonal antibody, the receptor–ligand complex is mediated by receptor–ligand interactions, collected into transport vesicles and delivered into the early endosome-late endosome-lysosome pathway, resulting in its accumulation in lysosomes. Owen et al. reported NPs modified by different anti-HER2 mAbs (trastuzumab and 73J) that bind to different epitopes on HER2 have variable amounts reaching the lysosome. Lysosome-targeting fragments can also be used to promote lysosomal accumulation. For example, alkylated piperidine fragments could target lysosomes and then self-assemble to construct anticancer prodrug molecules. In addition to surface modification, other physicochemical properties of NPs affect the efficiency of lysosomal accumulation. Lysosomal accumulation of internalized NPs is related to NP rigidity, size, and surface charge, and smaller and softer NPs with certain positive and negative charges have much greater uptake rates into lysosomes in cancer cells. Therefore, the main means of delivering drugs to lysosomes is to design and develop the appropriate targeting sequences, assisted by optimizing the physical and chemical properties of nanof ormulations.

After reaching lysosomes, NDDSs need to respond to the lysosomal microenvironment effectively to release their cancer therapeutic agents, which need to act rapidly on the lysosome and trigger LMP. This response mainly relies on some pH-sensitive liposomes and stimulus-responsive polymers containing specific pH-triggered switches (such as disulfide bonds, hydrazone bonds, acrylic acid, and diethylaminophenyl units) and enzyme...
### Table 1. The mechanisms and applications of lysosomal escape used in nanomedicine

| Mechanism of lysosomal escape | Device | The key structure for lysosomal escape | Cargoes | Cell line | Reference |
|-----------------------------|--------|--------------------------------------|---------|-----------|-----------|
| Proton-sponge effect        | catHDL/PA | Polyanions bearing both pendant carboxylate groups and alkyl chains | DOX and curcumin | T24 | [117] |
| N-quadernary ammonium-chitosan | Quaternary amine groups | Brucine | HepG2 | [70] |
| MPN-Coated NPs             | The phenolic molecules in the metal-phenolic networks(MPNs) | Calcein | MDA-MB-231 | [118] |
| FL-C6-NH2-Modified CRP@dOSN | pH-responsive imine bonds | Chitosan | HeLa | [119] |
| Polymeric-drug conjugate solid NPs containing encapsulated superparamagnetic iron oxide NPs (IO@PNP) | Poly(ethylene glycol)-block-poly(histidine) | DOX | PC3MM2 | [120] |
| Polyurethane micelles      | Hydrazone bonds | | | | |
| mPEG-b-PLA-PHi-ss-OB        | Disulfide bonds | DOX and siRNA | MCF-7/ADR | [122] |
| Surface-modified single-walled carbon nanotube | Polyethyleneimine (PEI)-betaine | DOX and siRNA | A549 | [123] |
| GA-loaded cp-HDL NPs (cp-HDL/GA) | The histidine in CPPs | Gambogic acid (GA) | HepG2 and HT1080 | [124] |
| Guanidino HPMA copolymer    | Guanidine group | KLA peptide | B16F10 | [125] |
| TPH/PTX nanomicelles        | The positively charged nanomicelles and HA | PTX | A549 | [126] |
| D-alpha-tocopheryl poly (ethylene glycol 1000) succinate and HA dual-functionalized cationic liposomes | The imidazole groups of histidine | PTX | MCF-7/MDR | [127] |
| m-HA coating PEI-PCL/shRNA complexes | PEI-PCL | PTX and KIAA1199 specific shRNA | MDA-MB-231 | [128] |
| Dextran nanogels with CAD adjuvant | Cationic amphiphilic drugs adjuvant (nonbiodegradable polymeric dextran NGS, inorganic propionylamine-functionalized MSNs, cationic LNPs, such as (PEGylated) DOTAP-DOPE liposomes, the lipofection reagent Lipofectamine RNAiMAX, and lipid NPs containing the ionizable lipid DLin-MC3-DMA) | siRNA | H1299 | [129] |
| mPEG-PHi-PSD/PLL/siRNA NP | Polyl-histidine | siRNA | NSCLC | [130] |
| Lipid NPs                   | The ionizable cationic lipid components | siRNA | HTB-177 | [131] |
| UCNP (CD/Azo) -siRNA/PEG NPs | GE11 + /TH + NP | siRNA | MDA-MB-468 | [132] |
| The cationic dextran nanogels | Cationic amphiphilic drugs | | H1299 | [133] |
| pH/redox dual-sensitive unimolecular NPs | The imidazole groups | siRNA | MDA-MB-468 | [134] |
| Poly(2-diethylaminoethyl methacrylate) around the silica nanoparticle core (PDEAEM@SNP) | The tertiary amine group of the PDEAEM shell | siRNA | MDA-MB-231 | [135] |
| siRNA biomimetic nanocomposites modified by erythrocyte membrane | Citraconic anhydride grafted poly-l-lysine | siRNA | U87MG | [136] |
| DSPE-PEG-uPA@iCaP | The CaP shell | siRNA and Pt | MDA-MB-231 | [137] |
| UA-GT/PAh-Gt/siRNA NCs | Imidazole-containing moieties | siVEGF | QGY-7703 | [138] |
| Angiopep LipoPCB(Temozolomide + BAP/ siTGF-β) | The zwitterionic lipid [diethanolamine-amine-poly(carboxybetaine) lipid] | Temozolomide and siTGF-β | GL261 | [139] |
| PCI MSNs tethered with lipid bilayers (MSN@TLB) | IR-780 | Zoledronic acid | MCF-7 | [140] |
| Photoactivatable Pt(VI) prodrug-backboned polymeric nanoparticle system (CNNP(TCP/si (c-fos)) | Azide complexes | Pt and si (c-fos) | A2780DDP | [141] |
| Glucose functionalized polydopamine NPs | Polydopamine | Bortezomib borate | MDA-MB-231 and MCF-10A | [142] |
| C60-DEX-NH2 | Fullerenes | siRNA | MDA-MB-231 and 4T1 | [143] |
| The lipoic acid and chlorin e6-conjugated pullulan micelle | Ce6 | Chlorin e6 and DOX | HepG2, HeLa and HCT-116 | [144] |
response switches (such as cathepsin B-sensitive dipeptide linker, glycosidic bond hydrolyzed by glycosidase, vSIRPα-probe activated by lysosomal endopeptidases). Additional important triggering methods are the delivery of photosensitizers and magnetic agents to lysosomes by NDDSs. When the tumor is exposed to external near-infrared light or a magnetic field, the sensitive agents will produce a considerable amount of ROS and heat, stimulating the destruction of the fragile lysosomal membrane, and induce tumor cell death. As shown by Zhang et al., their novel photosensitizer supramolecular nanogel is sensitive to lysosomal pH and aggregates in the lysosomes for enhanced PDT of multidrug-resistant cancer.

Nucleus targeting
Chemotherapy is still the cornerstone of cancer treatment and the vast majority of conventional chemotherapeutic drugs need to work in the nucleus of cancer cells to induce apoptosis. Alternatively, cancer gene therapy, which transfers genes (such as the CRISPR/Cas9 nuclease system, nucleic acid aptamers, DNA, and siRNA) to the chromosomes of tumor cells to regulate or replace abnormal genes, is gradually emerging. Their efficacy depends on the efficient transfer of the drugs or complete therapeutic exogenous gene into the nucleus. In recent studies, the nucleus has been commonly used as the site of action for free radicals and heat to cooperate with chemotherapy or gene therapy to improve the antitumor effect, which means transporting photosensitizers or theranostics to the nucleus to produce ROS with potentially damaging effects. However, the NDDSs targeting the cancer cell membrane generally only release foreign genes or anticancer agents into the cytoplasm, and then they can only enter the nucleus through free diffusion. The efficiency of diffusion is limited, and <1% of the therapeutic agents in the cytoplasm enter the nucleus and reach the final target. Therefore, enhanced therapeutic agent efficiency by nuclear targeted delivery is anticipated to be necessary for efficient cancer treatments and overcoming MDR.

Nuclear characteristics. The nucleus is the site of storage, replication, and transcription of genetic material and it plays important roles in cell proliferation, metabolism, growth, and differentiation. Due to the strong shielding effect of the bilayer nuclear membrane, nuclear pore complexes (NPCs) with lengths of ~90 nm and transverse diameters of 70 nm are the only channels for bidirectional exchange between the cytoplasm and nucleoplasm. The inner walls of NPCs are tethered with phenylalanine-glycine nucleoporins (FG Nups), thus limiting the inner diameter to only ~40 nm. As a result, the low efficiency of nuclear membrane penetration has greatly hindered applications of nuclear targeting NDDSs.

Construction strategies of cancer cell nucleus-targeting NDDS. In general, the NDDSs’ ability to efficiently access the cancer cell nucleus from the cytoplasm arises from three aspects: passive diffusion, active targeting, and pore formation in the nuclear envelope membrane (as shown in Fig. 3).

Passive diffusion: The structure of the NPCs limits the translocation of nanoformulations into the nucleus by passive diffusion. Based on principles of Brownian motion, the key influencing factors of passive cancer cell nucleus-targeting NPs such as size, shape, and charge have been extensively studied as follows.

Size is the critical factor affecting the passive diffusion of NPs into the nucleus. Lim’s group has demonstrated that ions and small molecules with molecular weights <40 kDa can diffuse freely through the NPCs. For NDDSs, NPs capable of passive nuclear diffusion are generally smaller than 9 nm. Therefore, it is necessary for nucleus-targeting NPs to regulate their size by rational preparation or to achieve size reduction of large NPs.
activated by special pH conditions or enzymes. In particular, how to compress and fold gene macromolecules to minimize the size of the gene nanocarrier system should be considered. The existing research has mainly focused on how to condense DNA/RNA into stable complexes through the electrostatic interactions between cation nanocarriers and anion nucleic acids.

Although small NPs are able to diffuse into the nucleus, the charge and shape of the NPs also play important roles in nuclear uptake. Positively charged NPs are more favorable for passage into the nucleus, but intravenous injection of positively charged NPs may induce hemolysis. To address this problem, a charge reversal strategy from negative to positive in endosomes and lysosomes has been applied. NDDSs that recover a positive charge in lysosomes can not only promote lysosomal escape but also enhance nuclear targeting, thus enhancing the cytotoxicity of the anticancer drug compared with free drugs. Other studies have shown that NPs with a higher aspect ratio (shaped like rods or worms) achieve higher nuclear concentrations compared with the lower aspect ratio NPs, which can be ascribed to the structure of the NPCs.

Active targeting: Although the ultrasmall NPs can carry therapeutic agents into the cancer cells’ nucleus, most of the marketed NDDSs, whose sizes are usually between 100 and 200 nm, are excluded from the nucleus. Fortunately, NPs larger than NPC can realize nuclear active targeting by surface ligand modification after lysosomal escape.

Nuclear localization signal sequences (NLSs), including from the SV40 T antigen, adenovirus, transactivator of transcription (TAT) peptide, NF-κB, KRRRR et al. are the most classical ligands used for nuclear targeting. NLSs can be recognized by karyopherins (Kaps) and rapid binding between Kaps and FG Nups cause FG Nups to shrink back into more malleable forms. Therefore, NLSs modified NPs with a large particle size could enter the nucleus via active translocation. Thus far, most reported sizes of active nuclear targeting NDDSs were extended to 50 nm, which means gold NPs and mesoporous silica NPs (MSNs) have been extensively used in nuclear active targeting because of their advantages of easy control of particle size and surface modification. For example, Tang et al. synthesized copper sulfide NPs encapsulated by a silica shell layer, which were modified by RGD and TAT peptides at the same time. Mediated by RGD to enter cancer cells, these NPs can effectively target the nucleus with the help of TAT. When illuminated by a 980 nm laser, copper sulfide NPs release heat to rapidly increase the temperature and damage the DNA. Li et al. developed a kind of gold NPs with simultaneous surface modification of siRNA and NLSs. The NLS-mediated NPs translocated to the nucleus and the siRNA acted on gene promoter DNA methylation, thus inducing long-term gene silencing in the nucleus of cancer cells. Meanwhile, a promising strategy to transfer larger NPs to the nucleus involves optimizing the NLS density. For instance, compared to the high density of 2 NLS2/nm, NPs modified with the intermediate density of 0.9 NLS2/nm can achieve a 3.7-fold increased nuclear accumulation.

In addition to NLS ligands, boronic acid groups can also translocate anticancer NPs with a large size from the cell surface to the nucleus through the importin α/β-mediated pathway. In the future, the development and discovery of new NLSs will provide a wider range of options for targeted ligands of nuclear targeting NDDSs.

Opening the nuclear membrane: In addition to improving the physicochemical properties of the nanofORMulations to pass through NPC as readily as possible, another effective method is to open the nuclear membrane with the help of cell membrane penetrating peptides (CPPs) to enhance the nuclear translocation of antitumor NDDSs. Researchers have gradually mastered some common properties of CPPs and have synthesized a series of CPPs with stronger penetration and higher efficiency, such as CB5005, which consists of a membrane permeation sequence cascaded with the NF-κB NLS. Further study found this kind of CPP had a unique affinity to brain glioma and its application in adriamycin delivery could effectively penetrate the membranes of cancer cells and the nucleus, allowing the chemotherapy drugs to directly damage the DNA.

In short, nuclear delivery efficiency may depend on the physicochemical properties of the NPs including size, shape,
Mitochondria are double-membrane-bound organelles with independent DNA and they participate in multiple cellular functions, including energy production, calcium buffering, lipid synthesis, signaling, cell proliferation, and apoptosis. In the process of Adenosine production, calcium buffering, lipid synthesis, signaling, cell participate in multiple cellular functions, including energy production, increased ROS production, Ca$^{2+}$ overload, and the Warburg effect, which mean that mitochondria in cancer cells are more susceptible to external disturbances than normal cells.

Mitochondria in cancer cells show greater susceptibility than those in normal tissues. Thus, there is the potential to deliver amphipathic poly(amidoamine) dendrimer, TPP-Lonidamine-DOX (MTSs). Similarly, disturbing the mitochondrial membrane integrity by CPPs also helps NPs penetrate into mitochondria (as shown in Fig. 4).

**Active targeting:** DLCs, including 4-carboxybutyl triphenylphosphonium (TPP), quaternary ammonium salts, nitrogen-containing heterocycles, and localized lipophilic cations (DLCs) and specific mitochondrial-targeting sequences (MTSs). Similarly, disturbing the mitochondrial membrane integrity by CPPs also helps NPs penetrate into mitochondria (as shown in Fig. 4).

**Construction strategies of cancer cell mitochondria-targeting NDDSs.** In view of the large negative MMP and the precise membrane structure of mitochondria in cancer cells, cancer cell mitochondria-targeting NDDSs usually achieve active subcellular targeting with the aid of two different targeting ligands: delocalized lipophilic cations (DLCs) and specific mitochondrial-targeting sequences (MTSs). Similarly, disturbing the mitochondrial membrane integrity by CPPs also helps NPs penetrate into mitochondria (as shown in Fig. 4).
The Golgi apparatus is closely linked to the ER. It is usually comprised of three different compartments, including the cis-Golgi network, medial-Golgi, and trans-Golgi network, which have a pH gradient from cis-Golgi network (pH 6.7) to trans-Golgi network (pH 6.0). It is an important organelle of cell secretory pathways that can modify, label, store and transport proteins, lipids, and polysaccharides. Recent studies have shown that the Golgi’s function is significantly improved in cancer cells, and its structural integrity affects certain signaling pathways, particularly those related to migration, invasion, and angiogenesis. Therefore, delivering intra-Golgi protein inhibitors to cancer cells' Golgi has the potential to block multiple molecular pathways associated with the development of cancer.

Design of ER or Golgi targeting nanoformulations. In the delivery process of therapeutic agents acting on the ER or Golgi apparatus, it is necessary to consider the different endocytosis pathways of NPs entering cancer cells. That is, mainly because the CVME pathway can actively transport NPs into the ER and Golgi. Obviously, it is very beneficial to deliver antitumor agents to achieve CVME by specific design of their nanoformulations. The other key to designing NDDSs is to enhance their retention time in the target subcellular organelles and to avoid their being discharged by exocytosis. For example, Xue et al. reported an effective strategy for IR(III) delivery targeting the ER. The IR(III) complex can not only target the ER actively but also produce ROS in response to the PDT reagent, which results in oxidative damage to proteins. E3/19K of adenovirus, phosphotetrapeptide (4P), KXX peptide, propylene oxide, the sulfonyl group, and ER-targeting photosensitizer TCPP-TER have also been applied to construct NPs targeting the ER.

In terms of Golgi targeting, Huang et al. demonstrated that L-cysteine is a kind of effective ligand for the Golgi. Carbon quantum dots and silica NPs could target the Golgi to monitor its changes when they are modified with l-cysteine. Gong’s team repeatedly proved that chondroitin sulfate (CS) nanomicelles targeted the Golgi since the glycosyltransferases in the Golgi could specifically bind to CS. However, it should be pointed out that compared with the targeting of the mitochondria and nuclei, the subcellular targeting of the ER and Golgi is still in its infancy, with not enough information available to apply comprehensive design strategies.

Other subcellular-targeting nanoformulations
Apart from the above, there are several other important subcellular structures that are also susceptible to therapeutic agents. The mutation of and abnormal expression of cytoskeleton-associated proteins play important roles in cancer cell migration, so targeting the cytoskeleton may be a potential anticancer therapy. For drugs (such as PTX and vincristine) acting on the cytoskeleton, the current delivery strategy is mainly to design NDDSs that are degraded in the lysosome, releasing the therapeutic agents into the cytoplasm through lysosome escape, and then achieve the drug targeting by the interaction between the drug molecules and the protein targets.
As a complex of RNA and protein, many key molecules and proteins in ribosomes are secondary regulators of epigenetic regulation and cancer progression. In recent years, ribosomes have been gradually regarded as a potential target in the development of anticancer drugs. Discovery and delivery of drug molecules acting on ribosomes remains in a preliminary stage. Delivery of antitumor drugs to ribosomes will also be an important branch of subcellular targeting in the near future.

Key factors in the rational design of subcellular-targeting anticancer nanomedicine

The above has described different strategies of precise delivery of antitumor agents to subcellular organelles in cancer cells. To guide the rational design and clinical transformation of subcellular-targeting anticancer nanomedicine comprehensively, we will emphasize below two key factors and principles that need to be considered when constructing efficient nanomedicine.

**Dual targeting and multiple targeting.** The initial premise of the subcellular-targeting NDDS discussed above is that they have overcome the first step of initial delivery and tend to accumulate in the region of the tumor. Therefore, in the rational design of subcellular targeting anticancer nanomedicine, we need to use dual-targeting strategies, taking into account both cancer cell targeting and subcellular targeting. For example, Qu’s team designed folate and TAT-modified Fe₃O₄ core/mesoporous silica shell NPs to deliver camptothecin, López et al. developed mesoporous silica particles with asymmetric modification of folate and TPP, and Xie et al. constructed hollow carbonitride nanospheres modified by hyaluronic acid (HA) and mitochondrial localization peptide D. These NDDSs achieved the organic combination of cancer enrichment and subcellular level targeting, which greatly improving the efficiency of the antitumor agents. Furthermore, it should be noted that the overlapping interactions between two target ligands and their relative densities may have influences on their targeting ability. Meanwhile, scientists are also making efforts to synthesize multifunctional targeting sequences, such as one sequence having both cancer-targeting and subcellular targeting functions or having both navigation and imaging functions.

In many cases, targeting only one organelle may not be able to reach the expected therapeutic effect. One solution chosen by scientists is to simultaneously target multiple subcellular organelles or structures. For example, Yao et al. have developed HA-modified hydroxyapatite (HAP) NPs (HAP-HA), HA acts as a tumor-targeting active ligand and can bind to the CD44 receptor overexpressed on the surface of cancer cells. HAP can load and deliver DOX to the nucleus and mitochondria of tumor cells to maximize the expected therapeutic effect. Multiple targeting is based on the principle of organelle interaction network and functional synergy. Achieve simultaneous targeting of mitochondria and nucleus, ER and nucleus, as well as ER and mitochondria is of great significance for enhancing therapeutic efficacy.

**Accurate response and controlled release.** The differences between nanoformulations and free drugs lie not only in the protection and transport by the carriers but also in the controllable release of the cargoes in specific locations. Thus, subcellular-targeting nanoformulations are supposed to release their payload in a controlled manner to ensure that the goods cannot be released before reaching the specific target, but only be released on demand when they reach the target successfully. This response relies on the characteristics of the microenvironment in different organelles, such as the acidity of lysosomes, the weak basicity of the ER, the weak acidity of the Golgi, and the high expression of ROS and H₂O₂ in the mitochondria. In-depth explorations of intracellular environments, components, and functionality will drive innovation in the development of promising subcellular-targeting NDDSs in the field of anticancer nanomedicine. It needs to be emphasized that in some programmed stimulus-response drug delivery systems, the use of two or more stimuli in sequential or coordinated action also requires comprehensive tests in vivo to achieve accurate spatiotemporal control of each trigger factor.

**CONCLUSIONS AND PERSPECTIVES**

With the development of medical biology and nanotechnology, research into and applications of subcellular-targeting NDDSs have become hot topics and trends over the past 5 years. Great advances in nanotechnology have stimulated the quick development of various subcellular-targeting nanoformulations as listed in Table 2. They are generally modified with subcellular-targeting function groups to efficiently cross through the intracellular obstacles and reach the molecular target, where they control their payloads release in response to the specific subcellular micro-environment (e.g., the acidic environment of the lysosome and Golgi). This direct delivery of therapeutic agents to their final destination maximizes the therapeutic efficacy of various cancer therapies. Although progress in preclinical studies has been made, we have to point out that some limitations still remain. Here, we list the current challenges and potential future directions of this topic.

In terms of cell biology research, the current progress related to the fate of subcellular-targeting nanomedicine may involve some uncertainties. (1) There is controversy since different researchers have come to different conclusions about the endocytosis pathway and mechanism of the same type of nanoformulation. (2) There is a lack of support from raw data and targeted research related to the stability of most currently existing nanoformulations in lysosomes, especially regarding how to ensure subcellular-targeting groups are able to function after escaping from the lysosome. (3) The intertumor heterogeneity is currently less considered in the design of subcellular-targeting NDDSs, which are mainly based on the common pathological features of organelles. Therefore, there is an urgent need for more comprehensive studies on different types of cancer cells (such as MDR cells) at the organelle/molecular level. In addition, precision medicine is based on gene mutation information, and individualized treatment, especially in subcellular delivery of gene therapeutic agents, should pay more attention to understanding the internal regulation of living systems by combining them with gene sequencing technology.

In terms of clinical transformation, the translation efficiency of complex nanoformulations is quite low. A high targeting ability of multiple modified structures is closely related to their instability, and a high sensitivity to intracellular environmental changes is often accompanied by systemic toxicity. This imbalance between efficacy and side effects makes demands on the exploration of multifunctional targeting groups (e.g., have both cancer-targeting and subcellular-targeting functions, have both navigation and imaging functions) on the one hand, and drives the development of diversification triggering and release strategies at the subcellular level (especially the nucleus) on the other hand. Furthermore, exploiting controllable preparation of nanoformulations in combination with other novel techniques such as microfluidic technology will control or optimize their properties more accurately.

In terms of monitoring methods, observing dynamic nanoformulations’ behavior in vivo and in tumor cells is indispensable to the biological and medical research of nanomedicine. However, the various visualization imaging techniques in the field of nanomedicine have their own advantages and disadvantages. For instance, the analysis conducted by transmission electron microscopy is static while having high resolution. Two-photon microscopy can observe tumor tissues directly in real time and...
| Subcellular structures | Targeting molecules | Cargoes | Vehicles | Size and zeta | Cell lines | Others | Reference |
|------------------------|---------------------|---------|----------|---------------|------------|--------|----------|
| ER                     | TCPP-TER            | Porphyrin | Ds-sP/TCPP-TER NPs | 100 nm | 4T1 cells | PDT | 102 |
| Fluorescent dansyl group | Tri-substituted triazine and 5-fluorouracil | DOX | Ag NPs | 75 nm | MCF-7/KCR cells | \ | 152 |
| \ | \ | \ | \ | \ | \ | 101 |
| Phosphoric acid tetrapeptide (1P) | Phosphoric acid tetrapeptide (1P) | \ | The crescent-shaped supramolecular assemblies | \ | \ | \ | 98 |
| \ | \ | \ | \ | \ | \ | 96 |
| Adenovirus E3/19K protein | The tumor-associated antigen L6 | \ | Cancer vaccine | \ | \ | \ | 97 |
| \ | \ | \ | \ | \ | \ | 97 |
| Golgi                  | CS                  | DOX and retinoic acid | CS nanomicelles | 40.2 ± 1.42 nm | Hepatic stellate cells | \ | 104 |
| \ | \ | \ | \ | \ | \ | 95 |
| CS                    | PTX and retinoic acid | CS nanomicelles | 192.7 ± 1.8 nm | 4T1-Luc cells | \ | \ | 105 |
| \ | \ | Cyanine dyes | BSA-pH-PTT | \ | HepG2 cells | PTT | 95 |
| L-cysteine            | Carbon quantum dots | Silica NPs | 8.5 ± 3.5 nm | \ | HEP-2 cells | \ | 103 |
| Lysosome              | Anti-HER2 mAb       | \ | Antibody drug conjugate | \ | \ | \ | 28 |
| \ | Anti-HER2 aptamer (human epidermal growth factor receptor-2, HApt) | \ | Gold nanostars | 90 nm, −8.05 mv | \ | SK-BR-3 cells | \ | 27 |
| \ | \ | \ | \ | \ | \ | 26 |
| TF                    | Dihydroartemisinin  | Nanoscale Graphene oxide | 100–200 nm | EMT6 cells | \ | \ | 26 |
| \ | \ | \ | \ | \ | \ | 26 |
| EGF                   | \ | Iron oxide magnetic NPs | 14 ± 4 nm | MDA-MB-231 cells | \ | Magnetic fluid hyperthermia | \ | 24 |
| \ | \ | \ | \ | \ | \ | 24 |
| \ | Photosensitizer     | Supramolecular nanogels and organosilica nanodots | 75 nm | A549/DDP cells | \ | \ | 37 |
| \ | \ | \ | \ | \ | \ | 37 |
| Alkylated piperidine fragment | Ferrocene analogs | N-alkylamino ferrocene-based prodrugs | \ | BL-2 cells | \ | The prodrug reacts with ROS. | \ | 29 |
| \ | \ | \ | \ | \ | \ | 29 |
| Mitochondria          | HA                  | Coumarin-6 | HA/PEG/BD Nanodrugs | 150 nm | A549 cells | \ | 74 |
| TPP                   | BSA, MAO-A, Cetuximab, IgG, or anti-MITO2 | CPD−TPP−protein@BS−NPs | \ | \ | Hela, HepG2, and SH-SYSY cells | \ | 78 |
| TPP                   | Lonidamine and DOX | TPP-LND-DOX NPs | 110 nm | \ | 4T1, MCF-7, and MCF-7/ADR cells | \ | 76 |
| TPP                   | Lonidamine and α-tocopheryl succinate | poly(DL-lactic-co-glycolic acid)-block (PLGA-b)-poly(ethylene glycol)-TPP polymer | \ | \ | Hela, IMR-32, and 3T3-L1 cells | \ | 77 |
| TPP                   | α-tocopheryl succinate and obatoclax moieties | TOS-TPP-Obt-NPs | 131.6 nm, 42.9 ± 1.20 mV | \ | MDA-MB-231 cells | \ | 153 |
| TPP                   | Gd                  | TIO2(Gd) NPs | 17.6 ± 0.1 mV | MCF-7 cells | \ | Radiation therapy | \ | 66 |
| TPP                   | \ | Poly(amidoamine) dendrimer | \ | \ | Hela cells | \ | \ | 75 |
| DSPE-PEG2K-TPP        | Lonidamine and IR-780 | Thermosensitive liposomes | 125.0 ± 63.36 nm, 23.5 ± 3.12 mV | \ | Lewis Lung Carcinoma cells | PTT/PDT | 68 |
| Subcellular structures | Targeting molecules | Cargoes | Vehicles | Size and zeta | Cell lines | Others | Reference |
|------------------------|---------------------|---------|----------|--------------|------------|--------|-----------|
| Nuclear                | TPP-PEG-PE          | PTX     | Liposome | 145–175 nm,1.66 ± 5.49 mV | HeLa cells | \        | 79        |
|                        | Fenton reagent      |         | Upconversion NPs | \ | HepG2 cells | \        | 85        |
|                        | Triplex-forming     |         | Tiopronin-covered gold NPs (Au-TIOP NPs) | <10 nm | MCF-7 cells | \        | 45        |
|                        | Acridine based      |         | Acridin-9-methanol NPs | 60 nm | HeLa cells | \        | 154       |
|                        | AS1411 aptamers     | Ce6     | Ca:AS1411/Ce6/hemin+pHis-PEG (CACH-PENG) NCP | \ | 4T1 cells | PDT      | 42        |
|                        | DGR or RGD, and KRRRR | Antisense single-stranded DNA oligonucleotide | TD NCP/ASO-NPs | 76–198 nm | MDA-MB-231 cells | Gene interference therapies | 52 |
|                        | FA and TAT          | Camptothecin | MSNs | \ | HeLa and A549 cells | \        | 112       |
|                        | H1 peptide          | HA2     | Cross-linked N-(2-hydroxypropyl)methacrylamide copolymer micelles | \ | MCF-7 cells | \        | 145       |
|                        | Membrane-permeable  | DOX     | \ | \ | Human glioma cells (U87) | Coordinately administered | 62 |
|                        | sequence (CB5005M)  | sRNA    | Au NPs | \ | MCF-7, HeLa, and HepG2 cells | \        | 58        |
|                        | NLS                  | Iridium (III) | LNPdePEG-FA | 150 nm | HeLa cells | \        | 46        |
|                        | NLS                  | PPAP-DMA | 150.6 ± 15.6 nm | HeLa cells | \ | PDT  | 43        |
|                        | NLS                  | Photosensitizer | Exosomes | 132.6 nm | 4T1 cells | PDT | 41        |
|                        | NLS                  | Albumin-Rhodamine | Chitosan NPs | 150 nm | L929 cells | \ | 59        |
|                        | RGD and NLS         | DOX     | Au NPs | \ | HSC-3 cells | \        | 55        |
|                        | TAT                  | DOX     | MSNs | 43 nm | MCF-7/ADR cells | \        | 155       |
|                        | RGD and TAT          | Cu5     | Cu5@MSN-TAT-RGD NPs | 40 nm, –23.9 ± 0.7 mV | HeLa cells | PTT | 57        |
|                        | TAT                  | DOX     | MSNs | 25/50/67/105 nm | HeLa cells | \ | 56        |
|                        | TAT                  | DOX     | NaYF4:Er@NaGdF4–PEG | 58.8 nm | HeLa cells | \ | 54        |
|                        | TAT                  | anti-p65 antibody and TAT peptide | MSNs | 40 nm | 4T1 cells | \ | 156       |
|                        | HA and TAT           | 9-Nitro-20(S)-camptothecin | CHR–PCL–TAT–ALAL–HA (HATPC) micelles | 121.6 ± 5.79 nm | SKOV3 tumor cells | \ | 51        |
| Nuclear and mitochon     | HA and HAP           | DOX     | Hydroxyapatite NPs | 179.50 ± 24.50 nm | HepG2 cells | \ | 115       |
|                        | HA and KLA           | DOX     | Carbon nitride nanosphere | 236.5 nm | A549 cells | \ | 114       |
in vivo, but it is limited by the imaging depth and the resolution at the subcellular level. Most of the organelle fluorescent dyes need to be used after cell membrane rupture and inactivation. To solve these problems will require complementation with numerous technologies on the basis of the existing tools, especially imaging methods for visualizing the actual process of nanoformulations entering single cancer cells. In addition, subcellular pharmacokinetics also affect the final efficacy of nanomedicine and should be paid more attention to, since it can be used for screening and transformation.

In general, subcellular-targeting NDDS are expected to play a greater role in cancer treatment and, where appropriate, of other diseases. It is also an inevitable trend in the field of personalized cancer medicine and precision nanomedicine. This review emphasizes the importance of subcellular targeting in the precise treatment of tumors, and encourages the development of novel subcellular-targeting strategies. The application of multidisciplinary and more concentrated efforts in the research into subcellular-targeting NDDS and clinical transformation can further enhance our understanding of personalized cancer medicine for precise treatment and effectively guide the future design of nanoformulations.

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ADDITIONAL INFORMATION

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