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Robust strategies in nuclear-targeted cancer therapy based on functional nanomaterials

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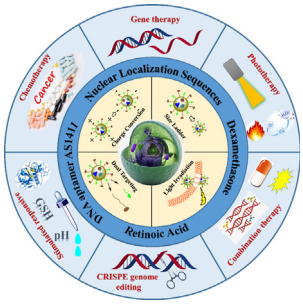
HIGHLIGHTS

- Recent advances of functional nanomaterials in cancer therapy are overviewed.
- Many nuclear targeting ligands are introduced to understand nuclear entry mechanism.
- The robust strategies are summarized to improve the nuclear delivery of nanocarriers.
- Current challenges in the clinical applications and future perspectives are discussed.

GRAPHICAL ABSTRACT

Schematic illustration of several nuclear-targeted drug delivery strategies, such as charge conversion, size ladder, dual targeting, light irradiation and stimulated responsive, for enhanced gene therapy, chemotherapy, phototherapy, combination therapy and CRISPE genome editing based therapy.



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ABSTRACT

Nucleus, as the machinery for genome transcription, play prominent roles to support the fundamental cellular functions, the destruction of any of these specific parts would significantly modulate the cell function. Therefore, troumendous drug delivery systems with enhanced nucleus targeting ability have been studied for nucleus-related disease regulation. The purpose of this review is to sort out the fundamental nuclear targeting strategy, especially the active mechanism of various nuclear targeting ligands and their extensive applications based on cancer targeting therapy. Various nuclear targeting ligands are first introduced to understand their nuclear entry mechanism. Next, to overcome biological barriers and avoid the serum protein absorption, diverse robust delivery strategies based on different nuclear targeting ligands are discussed. Moreover, other sophisticated carrier systems with enhanced nuclear entry, while without nuclear targeting ligands are also assembled. At the end the challenges and future opportunities in the field of nuclear targeting nanotherapeutics are tentatively proposed, to speed up their clinical translation.

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1. Introduction

Cellular organelles like cytomembrane, lysosome, mitochondrion, Golgi apparatus, endoplasmic reticulum and nucleus play important roles in the normal functions of cells. Subcellular dysfunction can lead to a series of diseases, including cancer, Parkinson's disease (PD), Alzheimer's disease (AD), and diabetes [1,2]. Organelles can be treated as potential therapeutic targets for the treatment of a variety of diseases, Many previous studies showed that the delivery of nanocarriers into the cytosol could achieve their goals, the encapsulated agents will find its active site by simple diffusion and interaction with various structure of the cell [2–5]. Generally, the mechanisms of cellular entry by nanocarriers include phagocytosis, clathrin-mediated endocytosis, caveolae-dependent endocytosis, RhoA-dependent, Arf6-associated, flotillin-assisted, fast endophilin-mediated endocytosis and transporter passively mediated [6]. Various nanocarriers are developed to help therapeutic agents not only in increasing retention time in both intra- and extracellular environments, but also for escaping a lysosomal/endosomal barrier in the intracellular environment, thereby protecting the sensitive drug agents from degradation [6]. These nanocarriers could be fabricated as stimuli-responsive polymers to release cargo from the endosome into the cytoplasm by endoosmolytic mechanism, which induce endosomal disruption and release by exploiting different pH or redox environment [2,5]. However, increasing studies have emerged indicating that the direct cytosol transportation is not enough for most targeted drug delivery approaches. The cytosol is a dynamic environment that contains specific components including water, ions and proteins, these macromolecules with high concentration make the cytosol as a high viscous structure that forms a significant diffusion barrier for targeted drug deliver nanocarriers [7]. In the cytoplasm, therapeutic drugs face many challenges including acidic and enzymatic degradation. Moreover, due to the multidrug resistance (MDR) that overexpression of drug efflux transporters, even though the encapsulated anticancer agents could be successfully delivered into cytosol, they could be pumped out of the cancer cells, thereby hampering their pharmacodynamics effect [8,9]. Many anticancer agents are known to be activated on a subcellular localization, such as doxorubicin (DOX) is most widely studied anticancer drug that not only can act on mitochondria but interact with DNA of nucleus to induce the cell death [2]. Therefore, the development of nanocarriers capable of subcellular level targeting is considered as promising strategy to resolve the MDR and regarded as the third generation of nanomedicines [2,3].

Currently, organelle targeted nanocarriers, especially for the nucleus, with the high-efficiency in anticancer therapy, may have great potential applications in this field [10]. Nucleus exhibits important functions in cellular metabolism and in determining cell survival and death, thus regarded as one of the most popular targets in nanocarriers-associated organelle-targeted therapy [2,5]. In the case of anticancer drug delivery, more and more investigators have mainly pay attention to the *in vivo* tumor microenvironment as well as intracellular organelle targeting [2]. Nanotechnology as a powerful tool for drug delivery and organelles targeting, however, the nuclear targeting process could be obstructed due to numerous factors, such as the intrinsic physicochemical properties (size and charge) of nanocarriers, and several biological barriers like extracellular matrix, the cell and subcellular membranes also inhibit the penetration of nanocarriers into the nucleus. Accordingly, the importance and key technical challenge in nuclear targeting process can be generalized into four main categories: i) dual ligands targeting to facilitate the nuclear entry, ii) stimulation-triggered charge conversion to avoid the serum protein adsorption, iii) stimuli-responsive size/morphologies-changeable nanoplatforms to actively target nuclei, vi) light irradiation strategy to achieve nucleus targeted drug delivery [11,12].

In this review, the organelles structure and the function of nucleus and various nuclear targeting ligands modified nanotherapeutics will be fully discussed. We highlighted the smart design multifunctional nanocarriers for therapeutic treatments. The current strategies for engineering targeting nanocarriers to nuclear are summarized, basic principles and methods for designing nuclear-targeted nanocarriers are discussed in detail. Various therapies, including chemotherapy, phototherapy, gene therapy and synergistic therapy rely on the nanotechnology are comprehensively reviewed to overcoming MDR and improve their efficiency, which could provide a new perspective for potential clinical applications.

2. Nuclear structure and the ligands targeting mechanism

2.1. Nucleus structure and function

The nucleus is separated from the cell cytosol by the double lipid bilayer of the nuclear envelope, which consist of inner and outer membranes, an underlying nuclear lamina, and lots of nuclear pore complexes (NPCs) [13]. The nucleus also has nucleoplasm with the gel-like matrix, DNA, chromosomes, and small bodies nucleolus play an important part in the synthesis of RNA and proteins. NPCs have complex cylindrical structures that perforated the membranes for the trafficking of small polar molecules and macromolecules. The core structure of NPCs with a central tube of around 30 nm diameter and 50 nm long that are associated with many proteins known as nucleoporins (Nups) [14]. Numerous unstructured multiple repeats of phenylalanine-glycine nucleoprins (termed as FG Nups) line the inner walls of NPCs which formed a disordered filamentous cloud or hydrogel to interfere larger macromolecules transport [15,16].

The nucleus is the control center which regulates the cell growth, reproduction and metabolism in eukaryotic cells. It is also the site for the expression of selected subsets of the genetic information encoded in the double-stranded, spiral-shaped DNA. Majorly nucleus is involved in cell division and protein synthesis that required for cell physiology, growth, multiplication, death *etc*. The functional machinery is coordinated by various biochemical processes and a slightest variation in its structure and function may cause serious genetic disorders [2].

2.2. Nucleus targeting for cancer therapy

Since a large amount of genetic information such as DNA are existed in the nucleus and the dysfunction of nucleus may cause genetic disorders like cancer. Thereby the direct damage to DNA or inhibition of the enzymes involved in DNA replication in the nucleus could result in efficiency anticancer treatment [17]. Many first-line DNA-toxin chemodrugs such as doxorubicin (DOX), cisplatin, anthracycline and camptothecin (CPT) can interact with nuclear DNA or its associated enzymes to damage DNA or inhibit the related enzymes activities [18,19]. However, due to the overexpression of drug efflux pumps (*e.g.*, P-gp), drug sequestering to acidic compartments, drug deactivation, metabolism and detoxification, the anticancer efficiency of drugs are limited and only a small percentage of drugs reached to the targeted site of nucleus [2,5]. It is expected that intra-nuclear transport of chemodrugs/PSs by nuclear targeting ligands modified NPs could direct interact with nuclear DNA or in situ ROS generation for DNA damage, thereby enhancing the anticancer therapy. For instance, the direct nuclear delivery of DOX by nanocarriers successfully overcome MDR in cancer cells *via* the drug's bypassing the P-glycoprotein

(P-gp) drug efflux pump and improved the therapeutic index by enhancing apoptosis of cancer cells [20]. Gene therapy is also a promising therapeutic strategy for combating a cancer and other genetic disorders. The fragile DNA/RNA molecules are efficient transported into the nuclei of the targeted cells by nanocarriers for protecting against the nuclease degradation, resulting in knocking down or correcting disease related genes, eventually eradicating various diseases at their origin [5]. Moreover, the generation of cytotoxic reactive oxygen species (ROS) from photosensitizers (PSs) or radiotherapy base oxidative destruction of DNA helix that lead to the tumor cells apoptosis [5,21].

2.3. Nuclear ligands targeting mechanism

Normally, ions and small molecules can passively diffuse to NPCs freely, while larger macromolecules with large size and charge could be hindered enter of the nucleus by the steric permeability barrier of NPCs [15]. For the larger ones such as NPs, the successfully active pass through the NPCs can rely on a translocation signal, the nuclear localization signal (NLS), which is a short stretch of basic oligopeptide that can interact with a cytoplasmic transporter importin α and further binds to importin β to form the complex, finally, the complex interact with Nups of NPC for translocation through the pore with requiring ATP and/or GTP hydrolysis (Fig. 1a) [22]. Besides, utilizing different types of NLS to directly bind with importin β also achieved for nuclear entry (Fig. 1a) [15].

Interestingly, many nuclear proteins do not harbor a recognizable NLS, but docking with small molecules to mediate their nuclear translocation [23]. As reported, cellular retinoic acid-binding protein type II (CRABP-II), a cytosolic protein that moves to the nucleus by interacting with importin α upon binding of retinoic acid (RA), in the nucleus, CRABP-II further binds to RA receptor to form a complex through which RA is channeled to the receptor (Fig. 1b) [24]. Therefore, RA is an active intranuclear transport small molecule. Except importin α/β or importin β pathways, it has been reported that, glyco-dependent nuclear import is independent of importins where nuclear shutting lectins may interact with glycosylated NPs for mediating the nuclear import [25]. Nuclear receptors, including glucocorticoid receptors (GR) which expressed in many types of cancer cells that also offered a means of nuclear entry. Dexamethasone (Dex), a potent glucocorticoid steroid, can bind with the GR to form Dex-GR complex that induce the dilation of nuclear pores up to 60 nm, thus Dex modified NPs may use the GR for nuclear import (Fig. 1b) [26].

In the dense fibrillary core and granular regions of the nucleolus, nucleolin is the most abundant nucleolar phosphoprotein which is highly expressed in exponentially growing eukaryotic cells, it is a RNA-binding protein that plays important roles in the regulation of cell proliferation and growth, replication and nucleogenesis [27]. In addition, nucleolin is also present on the cell surface that acts as a surface receptor. Importantly, one of its diverse roles is to serve as a shutting protein that actively migrate from cytoplasm into nucleus, endowing nucleolin with natural nuclear targeting function [27]. AS1411, a 26-mer DNA aptamer, have been confirmed to selectively bind to nucleolin (important in AS1411 nuclear internalization and transport) with a high binding affinity. Moreover, the AS1411 has been tested as a chemotherapeutic agent that involved in the inhibition of cell proliferation *via* BCL-2 mRNA destabilization and NF-κB inhibition [28]. Therefore,

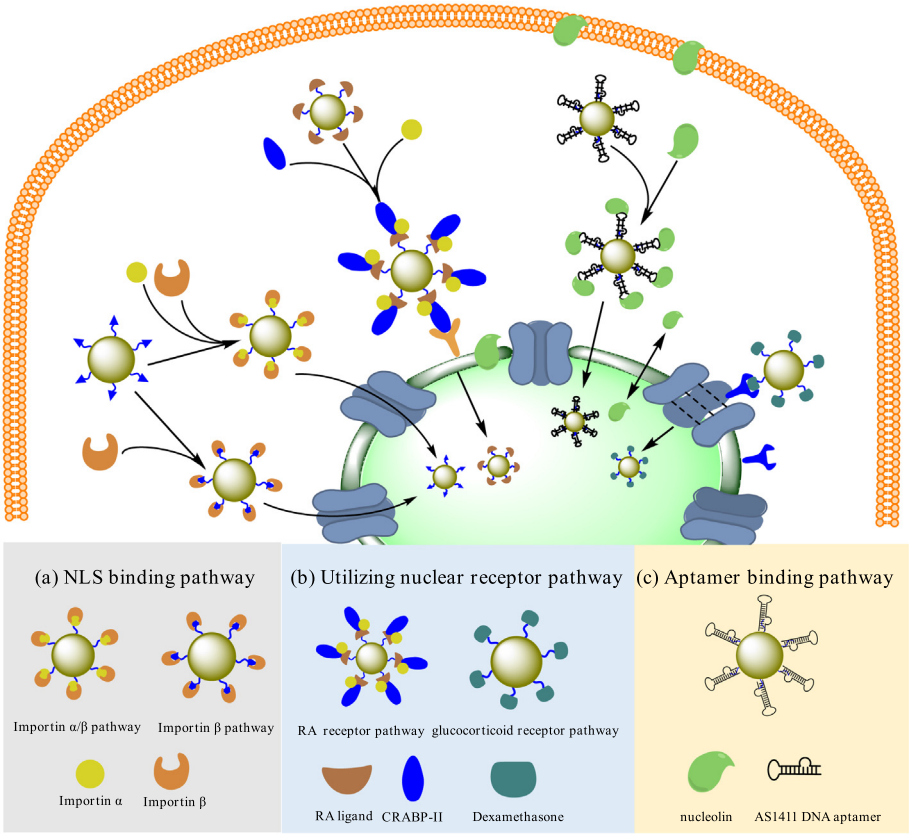

Fig. 1. Schematic illustration of nuclear targeting mechanism. a) The NLS modified NPs bind to importin α and then binds to importin β or directly bind to importin β to form the complexes, the complexes transit through the NPC by interaction of importin β with Nups of the NPC. b) Some ligands decorated NPs may utilize nuclear receptors for nuclear import. For instance, Dex labeled NPs use the glucocorticoid receptors for nuclear entry, and RA modified NPs bind to CRABP-II, which further binds to RA receptor to form a complex to active nuclear transport. c) AS1411 DNA aptamer conjugated NPs recognize the nucleolin to facilitate the nuclear delivery.

the design of nuclear targeting drug delivery system based on aptamer AS1411 and nucleolin had been investigated wildly in the field of anticancer therapy (Fig. 1c) [29].

In summary, the conventional transport of NPs between the cytoplasm and the nucleus *via* the interaction of NLS and the importin superfamily of nuclear transporters, followed by translocation through the NPCs, are regarded as efficiency pathway for promoting the nuclear import of NPs. Several other importin-independent nuclear import pathways, including the interaction with nuclear receptors, directly binding to the components of the NPC or permeabilizing the nuclear membrane by electrostatic interaction, tumor cell division, and a sugar-dependent process, supplying alternative approaches that facilitate the nuclear transport of NPs. More details on the NLS sequence and non-conventional nuclear transports mechanisms have been reviewed elsewhere [30,31].

3. Robust strategies for the design of nucleus targeting nanocarriers

Notably, the conjugation of nanocarriers to nuclear targeting ligands could facilitate their nuclear entry, however, due to the intrinsic physicochemical properties of nanocarriers (*eg.*, size and charge), and several biological barriers the nuclear penetration efficiency could be severely limited [32]. For instance, even though large nanocarriers with size range of 50–200 nm can accumulate around leaky regions of the tumor vasculature through the enhanced permeability and retention (EPR) effect, it is extremely challenging for these large NPs tumor cells penetration because of trapping in perivascular regions [32]. In addition, the nanocarriers modified with NLS exhibit positively charge which could adsorb serum protein and lead to short blood circulation time. On the other hand, the negatively charged nanocarriers hardly adsorb serum protein but exhibit low capacity of lysosome escape [11]. Thus, robust strategies are urgently needed to improve the nuclear delivery of various nanosystems. In this section, various strategies, including dual ligands targeting, "size ladder" changeable, stimulation-triggered charge conversion, and light irradiation strategy are comprehensively discussed (Fig. 2).

3.1. Dual ligands targeting strategy

Normally, dual ligands targeting strategy has been applied for more precisely nuclear localization of nanocarriers. Especially for the tumor cells, nanocarriers could be incorporated with cell receptor targeting ligands (*e.g.*, folic acid, hyaluronic acid), cell penetrating peptide (*e.g.*, RGD) or antibody (*e.g.*, Herceptin, transferrin) to specifically bind with receptors of the cancer cell membrane, then the nanocarriers were further decorated with nuclear targeting ligands to avoid the high levels of reticule-endothelial system (RES) clearance, allowing enhancement of penetration cross sev-

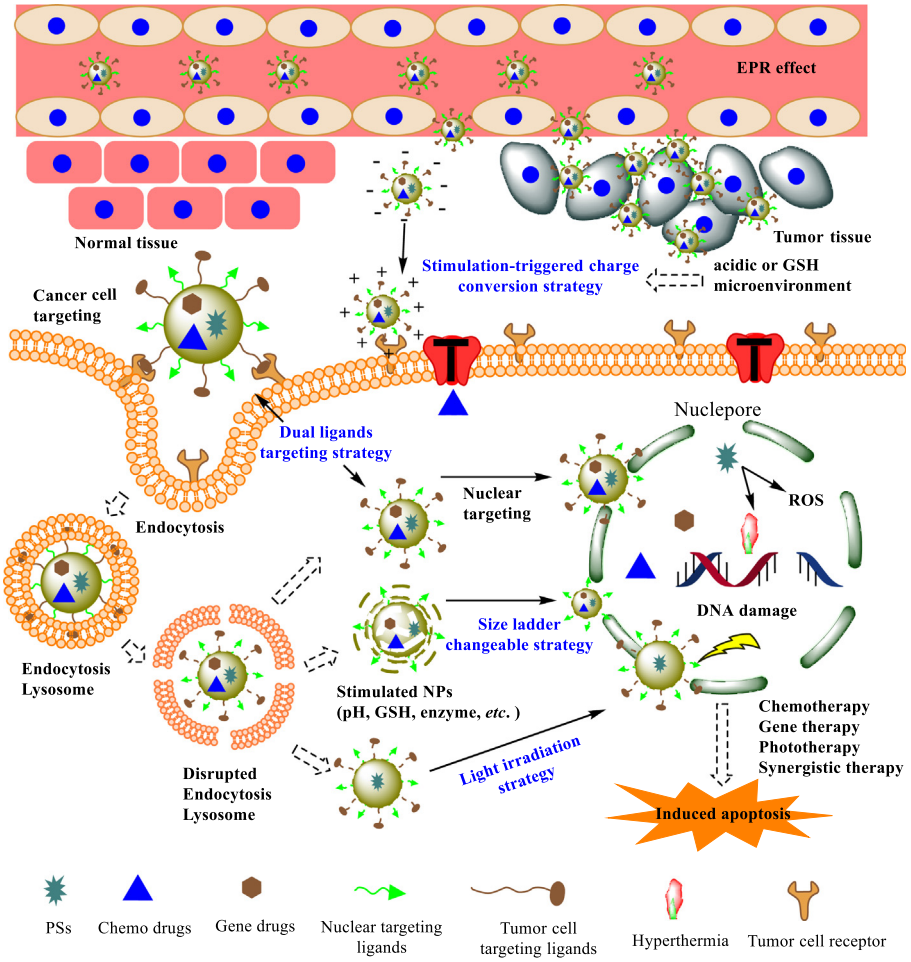

Fig. 2. Schematic illustration of the robust strategies for delivery of various drugs loaded NPs into nucleus. Different materials based nanocarriers were internalized to cells through the specific cell receptors. Based on endocytic pathways and escape from endo/lysosome, the nanocarriers could target to subcellular organelles by nuclear targeting ligands. Finally, various nanocarriers/drugs are delivered into the desired organelles sites and display multifunction to damage the nuclear DNA, resulting in cell apoptosis.

eral biological barriers and distribution of bioactive drugs at the nuclear target site [2,5,33].

3.2. "size ladder" changeable strategy

The "size ladder" changeable strategy is also smart way to enhance the nanocarriers subcellular delivery upon the stimulated-responsive condition. Under certain stimulus, their size can be adjusted to penetrating into the nucleus and enhancing the efficacies of tumor therapy [12,34]. Normally, the large sized NPs accumulate in tumor site by ERP effect but stimulated to decrease their size in the cells for improving subcellular especially nuclear entry [35–37]. For example, Guo *et al* designed a size changeable pH and reductive dual sensitive polymer mPEG-PLA-ss-PEI-DMMA based micelle system (PELEss-DA) that directly delivered Dox to the nucleus of MDR MCF-7/ADR tumor cells [35]. This micelle masked with polyethylenimine (PEI) shell that was conjugated with polylactide (PLA) *via* disulfide bonds. The results showed that the size of PELEss-DA increased from 42.1 to 87.9 nm when the pH decreased from 7.4 to 4.5, and escaped from the lysosomes through the proton sponge effect of PEI. Furthermore, the disulfide bonds between PLA and PEI were broken under the GSH condition, inducing the micelles size decreasing and finally nuclear entry [35].

3.3. Stimulation-triggered charge conversion strategy

To address the problem of serum protein nonspecific adsorption with positively charged nanocarriers, stimulation-triggered charge conversion (STCC) strategy has been proved as an efficient approach to solve this dilemma [11]. Generally, the positive charged NPs are coated with the negative charged out shell, these out shell could be hydrophilic polymers or small molecules such as succinic anhydride (SA) or methacrylic acid, therefore, the STCC strategy could minimize protein adsorption, prolong circulation time and reduce nonspecific cytotoxicity and interactions of nanocarriers [38]. The out shell could be further dissociated in response to intracellular tumoral signals, such as acidity, redox potential (GSH), ROS, and specific enzymes, subsequently, the positive NLS conjugates would be exposed and escaped from lysosome to bind with negative membrane of nucleus [39–41].

3.4. Light irradiation strategy

Typically, plasma membrane as the protective barrier of cells that maintain cellular homeostasis and regulate nutriments transport. On the other hand, plasma membrane as the biological barrier that limits the nanocarriers targeted delivery at cellular level. Interestingly, recently studies found that the disruption of the plasma membrane resulted the membrane permeability that enhanced cellular uptake and nuclear membrane penetration of NPs [42]. More important, the disruption of cell membrane usually was induced by the ROS in situ generation upon light irradiation, therefore, light irradiation strategy is regarded as the powerful way to enhance the nuclear translocation of exogenous NPs. Recently, Cheng *et al* designed a dual-stage light irradiation strategy to improve the endo/lysosomal escape of chimeric peptide (consist of a PS of PpIX and NLS) engineered exosomes (Chip-Exo) and enhance the nuclear translocation [43]. Importantly, once entry of the Chip-Exo into cancer cells through endocytosis, the lysosomal escape of Chip-Exo triggered by the first-stage light, and facilitated the photochemical internalization and nucleus targeted translocation. Furthermore, the plasma membrane rupture and nucleus destruction occurred under the second-stage light irradiation because of the in situ ROS generation. (Fig. 3a) The results showed that Chip-exo successfully translocated into nucleus, (Fig. 3b), eventually causing the tumor cells death and inhibiting the tumor growth due to the presence of light irradiation to some extent (Fig. 3c, d) [43].

4. Nuclear targeting peptides modified nanotherapeutics for cancer therapy

Nuclear targeting peptides, including nuclear localization signals (NLS) and other oligopeptides, have frequently been employed as bioconjugated ligands that either decorated on the surface of nanocarriers or modified with other polymers to gain access to the nuclear compartment. These peptides contain precisely tuned

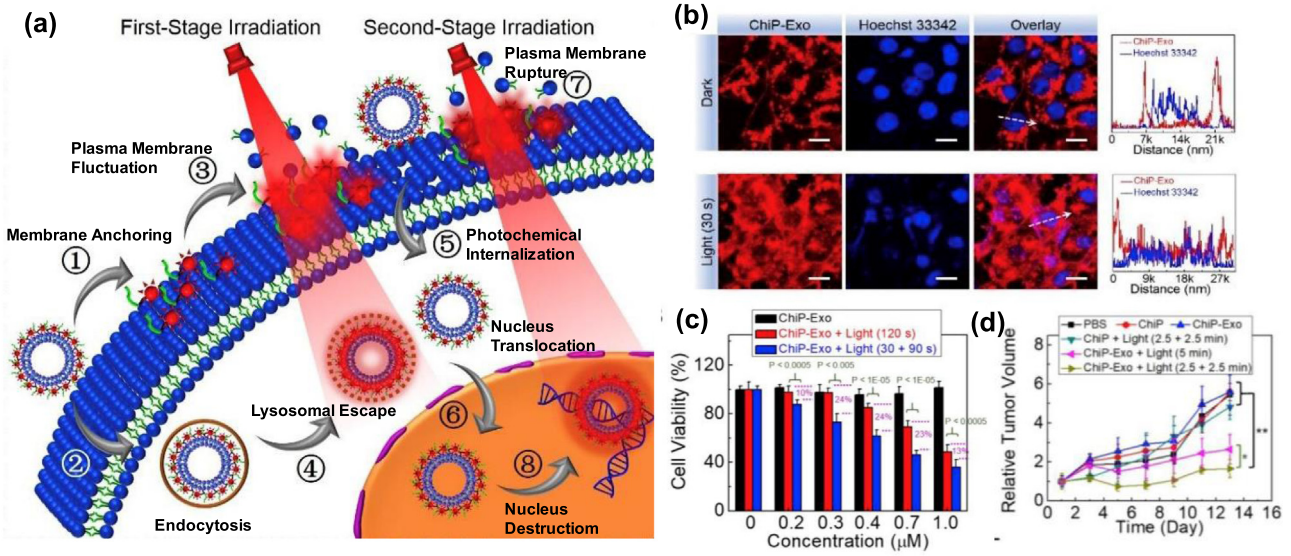

Fig. 3. a) Schematic illustration of ChiP-Exo for dual-stage light guided plasma membrane and nucleus targeted photodynamic therapy. b) CLSM images and fluorescence intensity profiles analysis of 4T1 cells treated with ChiP-Exo in the presence or absence of light. c) Cell viability of 4T1 cells after treatment with Chip-Exo in the presence or absence of light. d) The relative tumor volume changes of the mice after various treatments. Reproduced with permission[43]. Copyright 2019 Elsevier ltd.

binding affinities for nuclear transport receptors or proteins that located in the cell nucleus.

4.1. NLS decorated nanocarriers for chemo drugs therapy

NLS, including human immunodeficiency virus-1 transactivator of transcription (TAT) peptide, SV40T antigen, adenoviral, *etc.* is a type of the most classical ligand that modified with nanocarriers for the nuclear transport *via* the importin α/β pathway. TAT is most frequently used NLS peptide that consists of 86 amino acids, which could be recognized by NPC and actively deliver nanocarriers into nucleus. With the aid of TAT, various materials-based nanocarriers (mesoporous NPs, nanodiamonds, magnetic NPs, gold NPs, polymeric NPs and dendrimers) are designed for effective transportation of chemical/gene drugs into nucleus [41,44–49]. Until now, different-sized or NLS intensity NPs have been extensively studied to investigate their nuclear targeting ability and drug therapeutic efficiency [45,50–52]. Shi's group firstly developed TAT decorated mesoporous NPs (MSNs) with uniform particles sizes (25, 50, 67 and 105 nm) and found that only smaller sized TAT-MSNs (25 and 50 nm) loaded with DOX could be transported across the nuclear membrane and exhibited higher anticancer efficiency of Hela cells than larger sized TAT-MSNs (67 and 105 nm) (Fig. 4a) [45] They also observed that the more TAT peptides on MSNs of 30 nm (106, 293, and 377 peptides per MSN), the higher cellular uptake of MCF-7/ADR and nuclear penetration (Fig. 4b) [52] Furthermore, they developed dual-targeted MSNs that conjugated with RGD and TAT to specifically deliver DOX to tumor tissues, cancer cells, and finally to cellular nuclei, thereby enhancing chemotherapy efficacy *in vitro* and *in vivo* (Fig. 4d, e) [44] In order to investigate the MDR-overcoming mechanisms of DOX@TAT-MSNs, the same group utilized global gene expression analysis to clarify the cell death pathways and molecular mechanisms of MDR-overcoming [53]. In the detail report, compared with DOX and DOX@MSNs which could up-regulate DNA repair-related biological processes and p53 signal negative feedback section, DOX@TAT-MSNs induced the up-regulations of apoptosis-related genes (BCL2A1, BCL10, and CAP2), down regulation of the apoptosis inhibitor proteins Bcl-2, and down-regulated drug intracellular transport inhibitor gene LRP11 expression [53].

Normally, the NLS decorated nanocarriers could facilitate the delivery of therapeutic agents into the nuclear targeted site. However, Tammam *et al* drew different conclusion about the effect of chitosan (CS) NPs size and NLS density for nuclear targeting [50,51]. In these studies, two different sized CS NPs (S-NPs ≈ 25 nm; L-NPs ≈ 150 nm) were prepared and modified with different densities of the NLS, they found that unmodified S-NPs exhibited 5-fold higher nuclear localization rates than NLS modified NPs, but L-NPs modified with a low-intermediate NLS density providing better nuclear delivery than those with higher one in different kinds of cells. They suggested that the saturation of importin α with excess NLS would result in the NLS-L-NPs-importin α aggregates and hindering nuclear allocation [50,51]. Therefore, the NPs with optimized NLS density modification is necessary to obtain the highest efficiency of nuclear localization and drug therapy.

4.2. NLS decorated nanocarriers for gene therapy

Therapeutic genes play an important role in successful gene therapy. And nuclear-targeted gene delivery nano-systems shows higher stability, internalization efficiency and better diseases treatment efficiency. For example, Li *et al* developed AuNPs-based

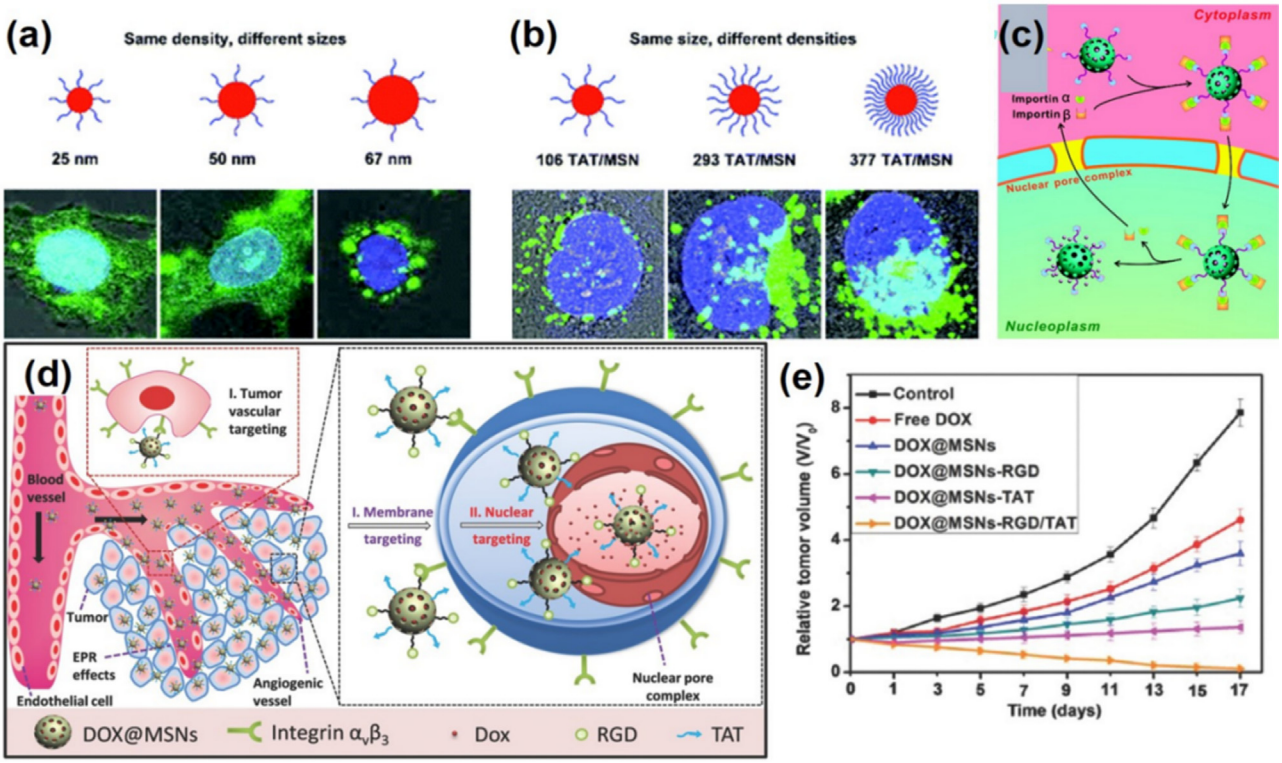

Fig. 4. a) Schematic diagrams MSNs with sizes of 25, 50, and 67 nm with TAT peptides on their surface and CLSM images of HeLa cells treated with these differently sized MSNs-TAT. b) Schematic description and CLSM images indicate the localization of MSNs-TAT with different numbers of TAT peptides on each particle surface in MDR MCF-7 cells. c) Schematic illustration of transport of DOX@MSNs-TAT across the nuclear membrane. d) Schematic illustration of vasculature-to-cell membrane-to-nucleus sequential targeted drug delivery based on DOX@MSNs-TAT/RGD for effective cancer therapy. e) *In vivo* behavior of the MSN drug carriers in mice. Reproduced with permission [5,44,45]. Copyright 2012 American Chemical Society. Copyright 2014 Wiley-VCH Verlag GmbH &Co. KGaA. Copyright 2018 The Royal Society of Chemistry.

siRNA delivery systems for long-term gene silencing in cancer cells [54]. The siRNA, was designed to target the promoter of thymidine kinase 1 (TK1) and trigger the RNA-directed DNA methylation, that was delivered into the nucleus by the NLS decorated AuNPs. The results showed that NLS decorated nanocarriers exhibited longer time TK1 mRNA suppression in MCF-7 and Hela cells to 10–17 % at 30 days than unmodified nanocarriers with the gene silencing in the cytoplasm [54]. The MSNs usually contain small pore size of ≈2-3 nm, which limited the nucleic acids internalized into the pore but could be adsorbed onto the outer surface of MSNs. Using the as-hydrolyzed bis[3-(triethoxysilyl) propyl] tetrasulfide (BTES) to penetrate into the hydrophobic domains of CTAC micelles and enlarge pore size, Shi's group designed mesoporous organosilica nanoparticles (MONs) with small size (≈30 nm) but with large pore size (8–13 nm), the model gene plasmid DNA was successfully encapsulated into the pore of MONs, which could be protected from enzymatic degradation while pDNA was completely degraded in the MSNs. Finally, the TAT decorated PEI-MONs can promote the endosome escape and deliver the pDNA through NPCs, resulting in enhancing gene transfection and potential for clinical application [55]. Recently, a deformable polymer Fe^{3+} coordinated tLyp-1-NLS decorated low molecular weight polyethylenimine (LMW-PEI) based NPs were reported for shortening the gap between *in vitro* and *in vivo* gene transfection efficiency [56]. In this system, LMW-PEI aggregated through Fe^{3+} coordination with deformation ability that can squeeze out through RES filter holes when trapped in the spleen. In addition, Fe^{3+} could trigger the endogenous hydrogen peroxide (H_2O_2) decomposition to generate O_2 that may play a positive role in cancer treatment. Moreover, tLyp-1, a truncated form of LyP-1 (CGNKRTRGC), has been regarded as tumor cells targeting and penetration ligand used for binding to the Neuropilin receptors. Therefore, a bifunctional peptides tLyp-1-NLS and the multifunctional dual targeting nanosystems were constructed that exhibited the potential for effective *in vivo* gene delivery [56].

4.3. NLS decorated nanocarriers for phototherapy

The nuclear matrix is one of the most thermolabile structures in the cells, it can undergo denaturation at temperatures as low as 43–45 °C, followed by aggregation of nuclear matrix proteins and inhibition of DNA supercoiling transformation, inducing cell death. On the other way, the cell nucleus is a hyper-sensitive site for the effective photo-induced DNA damage to occur, direct targeting at the nucleus and damaging the DNA by ROS are considered as promising pathways of photodynamic therapy (PDT) [57]. Therefore, the development of novel nuclear targeting photothermal/photodynamic agents is highly desired for providing selective and enhanced cancer cell ablation [2,5,58].

Gold NPs with different shapes, including nanorods, nanocages and nanoshells, have been widely studied in El-Sayed's group to discover their effect in minimally invasive cancer therapy. After conjugation of RGD and NLS on the PEGylated AuNPs, El-Sayed's group found AuNPs successfully targeted to nucleus of cancer cells that induced DNA damage, causing cytokinesis arrest, enhancing nuclear stiffness and slowing cancer cell migration, and eventually result in cell apoptosis [59–62]. Furthermore, this group demonstrated that non-NIR absorbing plasmonic gold nanospheres (AuNSs) aggregated as NIR photoabsorbers at the nuclear region of the cells *via* surface destabilization, showing promises in plasmonic photothermal therapy (PTT) [59]. Compared with AuNPs which could absorb the 808 nm laser and induce photothermal ablation of all types of cells, the AuNSs absorb light mostly in the visible region but increase the NIR absorption efficiency as the aggregated AuNSs, thereby avoiding the nonspecific heating of healthy tissues and inducing destruction of cancer cells.

Gold nanoclusters (AuNCs) with ultra-small size possess fascinating optical properties and appreciable biocompatibilities. In the field of biological application, recent studies have shown that TAT decorated gold nanoclusters (AuNCs) could produce ROS to induce the cell apoptosis [63,64]. For instance, Vankayala *et al* designed TAT modified AuNCs to perform *in vitro* and *in vivo* fluorescence imaging, gene delivery and NIR activated PDT for anticancer treatment [64]. Under NIR (980 nm) light excitation, the singlet $^1O_2$ was generated from TAT-AuNCs for the destruction of cancer cells [64]. Au_{25}NCs, the core of each NC is composed of 25 gold atoms, with ultra-small size (∼1.2 nm) facilitates their entrance into the cell nucleus through nuclear pores. Furthermore, due to their unique fluorescence properties, they have shown promising potential for imaging the nuclei of living cells [63]. With these advantages, Zhao *et al* prepared TAT conjugated Au_{25}NCs and found that the nucleus-targeting Au_{25}NCs induce the production of ROS, resulting in the oxidative degradation of mitochondrial components, and leading to apoptosis process [63].

Besides gold NPs or gold nanorodes which have been used in phototherapy applications [65]. some other metal-based NPs such as copper sulfide NPs and iron oxide NPs that surface modification of tumor targeting ligands (RGD or transferrin) and nuclear targeting peptides exhibited significantly photothermal effect to totally kill cancer cells [66,67].

To enhance the drug-resistant cancer therapy with NIR activated multiple ROS, Yu *et al* fabricated a nuclear targeted dual-PSs based upconversion@TiO_2 NPs, molecule-PS Ce6 combined with nano-PS UCNPs@ TiO_2-TAT generated multiple ROS ($^{\cdot}OH$, $O2^{-}$, and $^1O_2$) through 980 nm NIR excitation that could break the DNA double strands and destroy the function of the nucleus, showing excellent therapeutic effect *in vitro* and *in vivo* [68]. In comparation with NIR-Ⅰ biowindow (750–1000 nm), NIR-Ⅱ biowindow (1000–1350 nm) exhibited more efficient tissue penetration and could overcome the thermos resistance caused by heat shock protein. Recently, Cao *et al* synthesized TAT modified 2D vanadium carbide quantum dot (V_2C-TAT) with photothermal effect at the NIR-Ⅱ biowindow and encapsulated V_2C-TAT into RGD engineered endogenous exosomes for cancer cell and nucleus organelle dual-targeting (Fig. 5a, b) [69]. In this systems, V_2C QDs exhibit good abilities for fluorescent imaging, photoacoustic imaging and MRI, and exosomes display the properties of good biocompatibility and protecting from the immune system for long circulation times. With irradiation by a 1064 nm laser at a power density of 0.96 W cm^{-2}, the V_2C-TAT@exosomes-RGD realized multimodal imaging-guided tumor cell nucleus-targeted PTT at low temperature (∼45 °C), leading to attractive anticancer therapeutic efficiency *in vitro* and *in vivo* (Fig. 5c, d, e) [69].

Excited PSs undergo type-I (electron transfer) and/or type-Ⅱ (energy transfer) reactions through light activation. And most type-Ⅱ based PSs are frequently utilized to produce singlet oxygen from O_2. However, lack of O_2 in the ubiquitously aberrant microenvironment of solid tumors could limit the effort of type-Ⅱ based PSs. Type-I PDT would be an appealing option to overcome the limitations of traditional type-II PDT due to the highly reactive radical generation and stronger hypoxia tolerance. Recently, Tang *et al* fabricated type-I PSs with aggregation-induced emission (AIE) characteristics for high-performance tumor therapy with less-oxygen-dependent [70,71]. To maximize the PDT effect of this NIR-emissive AIE luminogens (AIEgens), a pH-activated TAT-peptide-modified amphiphilic polymer was developed as an encapsulation nanocarriers to transport PSs, meanwhile, the STCC strategy was also applied for precisely delivering AIEgens into cell nuclei of tumor [71]. In this nanosystems, TAT was modified with SA to mask the TAT nonspecific interaction activity, the SA-modified TAT was further decorated to the terminal of maleimide-end capped poly(ethylene glycol)-*block*-poly(lactic acid) to obtain the

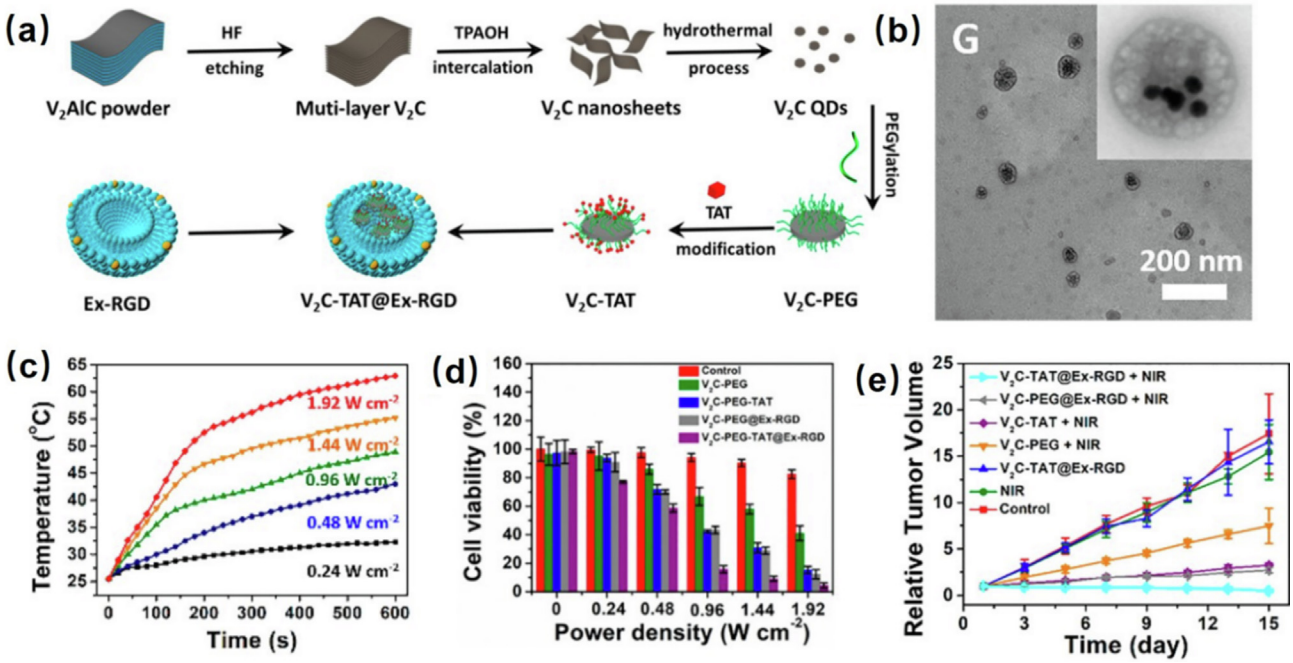

Fig. 5. a) Preparation procedure of the V_2C-TAT@Ex-RGD. b) TEM images of V2C-TAT@Ex-RGD. c) Photothermal conversion cycling test of V_2C-TAT@Ex-RGD under 1064 nm laser irradiation at a power density of 0.48 W cm^{-2}. d) Cell viability of MCF-7 cells after being incubated with different groups under 1064 laser irradiation at different laser power densities. e) Relative tumor growth curves of the MCF-7 tumor-bearing mice in different groups. Reproduced with permission [69]. Copyright 2019 American Chemical Society.

self-assembly nanocarriers, finally, the AIEgens type-I PSs was encapsulated into the nanocarriers with excellent performance in NIR-fluorescence-imaging-guided nucleus-targeted PDT application.

4.4. NLS decorated multi-drug delivery nanocarriers for combination therapy

Nowadays, combination therapy is emerging as an advanced technique that utilized in nucleus-targeted nano delivery system to maximize synergistic effect of chemodrugs, therapeutic genes and PS agents [72]. Integrating all nanotechnology that mentioned in the above section of 3, such as dual-targeting, stimulated-responsive and co-delivery technology to improve intranuclear drug delivery. For example, Han *et al* designed galactose and TAT dual-targeted, pH and redox-responsive multilayered MSNs for DOX and vascular endothelial growth factor (VEGF) siRNA co-delivery [73]. In this multilayered nanocomplexes (MLNs), the DOX was encapsulated into TAT-MSNs as the cationic core, poly(allylamine hydrochloride)-citraconic anhydride (PAH-Cit) as the anionic inner layer to interact with cationic core and inhibit the DOX free released at non-targeted site, furthermore, galactose-modified trimethyl chitosan-cysteine (GTC) conjugate as the cationic outer layer to encapsulate siRNA. Then the MLNs could protect siRNA from degradation in the blood and tumor microenvironment, facilitating the internalization of MSNs by galactose-mediated endocytosis and triggered disassembling MLNs by STCC approach. Afterwards, the disassembled MLNs escaped to cytosol and siRNA was stimulated released through cleaving disulfide bonds in GTC layers, resulting in high silencing efficiencies, Finally, the exposed TAT peptide transported DOX-loaded core into nuclei and DOX sustained released, thereafter leading to maximize synergistic effect of anticancer therapy.

Recently, Li *et al* developed dual-targeted mesoporous silica coated F_3O_4 NPs to achieve the cancer stem cell (CSC) apoptosis through combined thermotherapy and hypoxia-activated chemotherapy [74]. The specific targeting agent CD133 was conjugated with PEG-azo linker that was modified on the surface of NPs to promote the NPs internalization in CSCs, the thermo-sensitive azo linker was broken under an alternating magnetic field (AMF). Furthermore, the appeared TAT peptide could guide the NPs into nucleus, the anticancer drug tirapazamine (TPZ) was released and eliminate the CSCs through generating a transient oxidizing radical in hypoxic cells, moreover, the F_3O_4 NPs core can generate the heat under AMF to display thermo-therapy (Fig. 6a, b). Both thermal and TPZ-mediated chemotherapy can induce cell apoptosis and eliminate the hypoxic CSCs by inhibiting the expression of hypoxia-inducible factor 1-alpha and attenuating the hypoxia signaling pathway (Fig. 6c, d, e).

4.5. NLS decorated Stimulated-responsive nanocarriers in combating tumors

Nowadays, vast efforts have been put into the design smart stimuli-responsive subcellular delivery systems for enhancing therapeutic efficacy of cargoes [75]. As mentioned above in section of 3, STCC and "size ladder" changeable strategies could be applied in the NLS decorated stimulated-responsive nanosystems to resolve the problems of serum protein adsorption, RES clearance and non-specific internalization into all cells. Generally, the positively charged NLS peptides were shielded *via* conjugation of stimuli-responsive compounds/enzyme responsive linker to inhibit their nonspecific interactions, then the positively charged NLS such as TAT are appeared by responding to either internal and intrinsic environments of tumor (*e.g.,* pH, GSH and certain enzymes), thereby resulting in enhancing cellular internalization, endo/lysosome escape and nuclear targeting [36,40,41,46–48,76–79].

4.5.1. pH responsive nanosystems

pH responsivity is the most widely studied since pH values are different in normal tissues (pH 7.3–7.4), tumor extracellular envi-

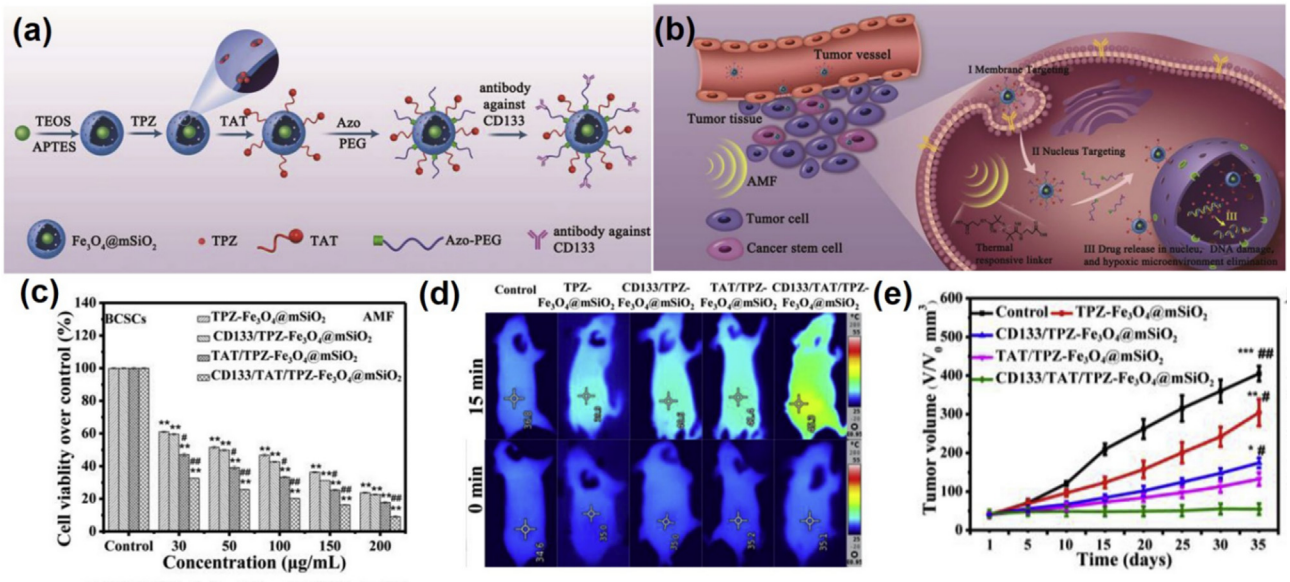

Fig. 6. a) Fabrication of antibody against CD133/TAT/TPZ-Fe_3O_4@$mSiO_2$ NPs. b) Schematic of the multistage targeting strategy for cancer stem cells targeting therapy. c) Viabilities of BCSCs after incubations with different groups for 48 h with AMF. d) The thermal imaging of the mice were treated with different groups under AMF at 0 min and 15 min. e) Relative tumor growth curves of the CSCs xenograft mice were in different groups. Reproduced with permission [74]. Copyright 2019 Elsevier ltd.

ronment (pH 6.2–6.9) and cellular endo/lysosomes (pH 4.0–6.0), thus inspiring scientists developed various STCC-based nanosystems for smart delivering cargoes to the targeting sites. For instance, the TAT peptide was masked by SA or 2,3-dimethylmaleic anhydride (DMA) and was hydrolyzed at the acidic environment, afterward the TAT was recovered and TAT modified NPs delivered drugs into cell nuclei [40,47,80]. According to the mildly acidic extracellular pH (≈6.5) of a tumor and endo/lysosome pH (≈5.0) conditions, Zhang's group successfully fabricated dual-pH sensitive poly(L-lysine)-*block*-poly(L-leucine) diblock copolymer-based micelles for tumor-triggered targeting uptake and nuclear DOX delivery [41]. In this study, N_3-TAT peptide was synthesized and reacted with SA to amidate the lysine amino residues into acid-labile β-carboxylic amides (N_3-TAT(SA)). Furthermore, the N_3-TAT(SA) was conjugated to the copolymer by CuAAC click reaction and the lysine amino groups of copolymers were amidated by DMA into another acid-labile β-carboxylic amide. Finally, PLLeu PLL(DMA)–TAT(SA) self-assembled into the negatively charged micelles. During the nuclear targeting process, the amides of DMA would be firstly hydrolyzed when the micelles arrived at the mildly acidic tumor extracellular environment (pH ≈ 6.5), the negatively charged micelles converted to positively charge and facilitated the tumor cells internalization. Once entrapping into the cellular endo/lysosomes, the SA of TAT was hydrolyzed under the lower acidic (pH ≈ 5.0) environment, then the nuclear localization function of TAT was recovered that promoted the DOX-loaded micelles targeted to nuclei, thus enhancing the tumor chemotherapy [41].

Normally, large NPs (50–200 nm) can trigger EPR effect that accumulate around the tumor microenvironment but could be also induce the diffusional hindrance in the tumor interstitial space, while small NPs (10–20 nm) could sufficiently penetrate deep into tumor tissue and induce better tumor distribution but still large enough to slow down tumor clearance. The smaller NPs (<9 nm) are facilitated to penetrate nucleus but could suffer rapid kidney excretion *in vivo*. To solve these matters, Li *et al* designed polymeric NPs with STCC and "size ladder" changeable strategies by adapting to the varying barriers in a multistage stimuli-responsive way for the transport of NLS decorated DOX-loaded NPs from blood to tumor cancer nucleus [37]. In this system, two HPMA based copolymers, DOX and R8NLS detachable subgroup hydrazone linked cationic copolymer (P-DOXR8NLS), and DMA modified anionic copolymer (P-DMA), self-assembled as stepwise size reductive and charge reverse nanocarriers (PNV) for programmed nuclear targeting of systemically administered anticancer DOX. The cationic copolymer P-DOXR8NLS was shielded with charge-reversible P-DMA to form negatively charged nanocarriers (-4.18 mV) in diameter to ≈55 nm, thereby increasing EPR effect and tumor accumulation. (Fig. 7a) After the NPs accumulated at tumor tissues, the first-stage size reduction was triggered followed by cleaving DMA from HPMA polymer with mild acidic condition, the NPs was disassembled to small linear P-DOXR8NLS (≈10 nm/39 kDa) for promoting endocytosis. At the intracellular level, the second-stage size reduction was triggered to hydrolyze DOXR8NLS from polymer under endolysosomal acidic condition, the smaller sized DOXR8NLS (≈2.4 kDa) was mediated by NLS to guarantee the successful nuclear entry (Fig. 6\7b). Finally, the nanocarriers exhibited good nuclear targeting and inhibited tumor growth by 75 % *in vivo* (Fig. 7c) [37].

4.5.2. GSH responsive nanosystems

It is widely known that the cytoplasm of tumor cell contains high concentration of GSH (2–10 mM), which is enough to cleave the disulfide bond instantly. PEG conjugated PAMAM dendrimers can increase the EPR effect and condense nucleic acids but reduce cellular uptake and decrease expression efficiency. To solve this problem, Li *et al* designed PAMAM-SS-PEG-RGD conjugate which was interacted with pDNA and a high mobility group Box 1 (HMGB1) protein containing NLS to form nanocomplexes for improving the transfection and expression efficiency in gene delivery [77]. In this system, RGD modified PAMAM could enhance the tumor cells targeting, the HMGB1 contains positively charged residues which could bind to pDNA *via* electrostatic interactions. Once the nanocomplexes enter the cytoplasm of cell, the PEG chains can be cleaved from PAMAM by the high concentration of GSH. Finally, the HMGB1 with NLS promote the nucleus uptake and transfection of pDNA.

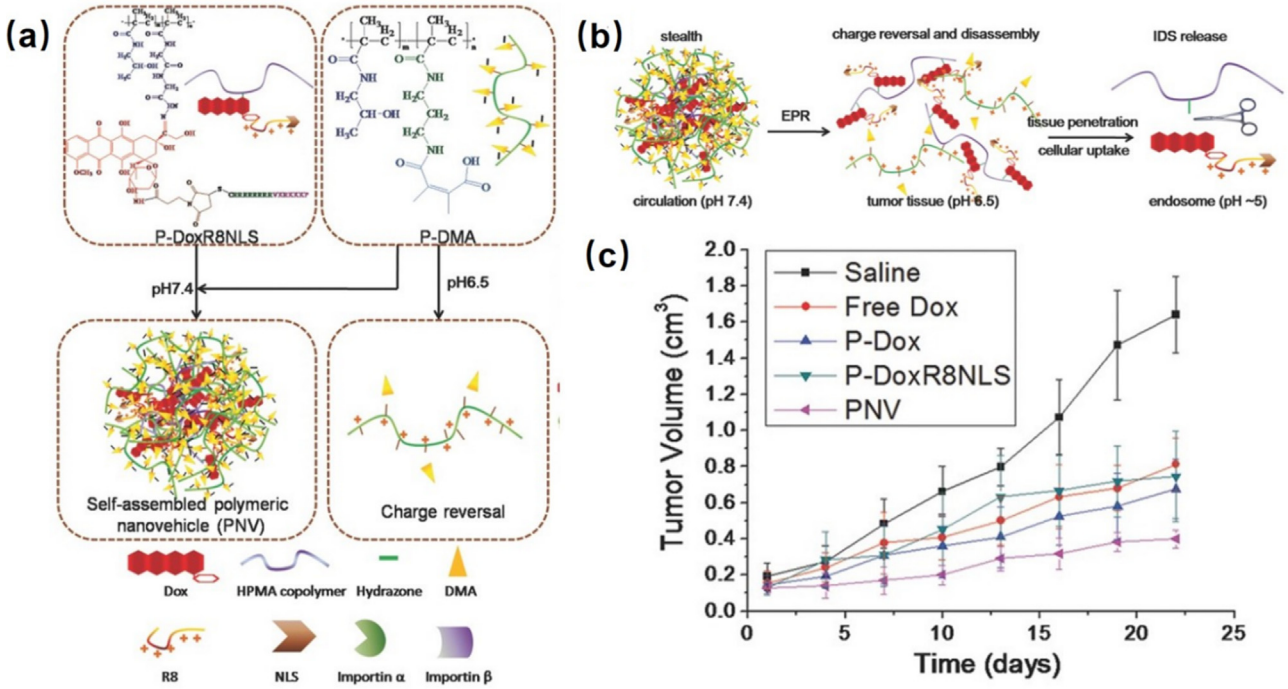

Fig. 7. a) Schematic illustration of the preparation of HPMA polymeric nanovehicle (PNV). b) Schematic mechanism of multistage size reduced PNV. c) Tumor growth curves from HeLa tumor-bearing nude mice given different Dox-loaded formulations. Reproduced with permission [37]. Copyright 2015 Wiley-VCH Verlag GmbH &Co. KGaA.

4.5.3. Enzyme responsive nanosystems

Some certain enzymes, such as MMPs (MMP-2 or MMP-7) and cathepsin B, are overexpressed in the tumor site in several malignancies. Using these enzymes as the stimuli-triggers, many stimuli-responsive NPs are designed for improving the nucleus uptake and anticancer drugs delivery [36,76,81]. For example, Anajafi *et al* prepared NLS decorated polymersomes to deliver DOX to the pancreatic cancer cell nucleus, the NLS linked with MMP-7 responsive linker and covered with oligoanionic inhibitory domain to avoid the nonselective normal/tumor cells targeting [76]. The NLS was activated only in the presence of overexpressed MMP-7, facilitating the nuclear transport of the polymersomes and releasing the DOX in response to the local reducing microenvironment [76]. Sun *et al* developed cathepsin B-sensitive TAT modified nuclear-targeted chrysin-PCL-TAT-ALAL-hyaluronic acid self-assembly polymeric micelles for enhanced 9-Nitro-20(S)-CPT (9-NC) delivery and antitumor efficacy [81]. In this drug delivery system, ALAL peptide could be cutoff in the lysosomes due to the high expression of cathepsin B, leading the lysosomal escape and further TAT peptides expose for final nuclear targeting and directly delivered 9-NC to the cell's "heart" [81].

4.6. Other peptides modified nanocarrier for nucleus delivery

Except NLS peptides which were frequently utilized for nanocarriers nuclear localization, some novel nuclear targeting peptides were identified that either bind with nuclear membrane protein or proteins which located in the cell nucleus [82,83]. For example, Integrins β3 (αvβ3 and αIIbβ3) are an important cell adhesion molecular family, and integrin αIIbβ3 presents on cancer cell surface and in the perinuclear region of prostate cancer cells. Zhang *et al* developed Arginine-Tryptophan-(D-Arginine)-Asparagine-Arginine (B3int), as an integrins β3 specific ligand, modified liposomes for selectively deliver DOX into prostate cancer cell nucleus [82]. Due to the high affinity and specificity of B3int to intergrins β3 with the K_d value of 0.2 nM, the DOX could be selectively delivered into nucleus, thereby significantly inhibiting tumor growth with low dose of 1.5 mg/Kg [82]. Recently, Liang *et al* designed drug-peptide nanomedicines induced by enzyme-instructed self-assembly (EISA) [83]. In this nanosystems, the peptide ligand PMI (TSFAEYWNLLSP) was capable of activating the p53 gene by binding with the MDM2 and MDMX that located in the cell nucleus, thus enhanced cellular uptake and nuclear accumulation capability of optimized nanomedicines formed by EISA mechanism at a low temperature of 4 °C.

5. Single-stranded DNA aptamer AS1411 decorated nanocarriers for nucleus-targeted drug delivery

AS1411, a single-stranded, G-rich DNA aptamer with the sequence of 5′- GGTGGTGGTGGTTGTGGTGGTGGTGG, exhibits high affinity for binding nucleolin which is the most abundant nucleolar phosphoprotein and is overexpressed on the cancer cell membrane and nucleus [28,84]. Many studies report that nucleolin/AS1411-mediated targeting is an effective strategy for nucleus-localized drug delivery and cancer theragnostics [85–91]. Recently, Zhang *et al* designed aptamer functionalized upconversion nanotheranostic agent for the highly effective DOX drug delivery [92]. In this work, anti-proliferating cell nuclear antigen (anti-PCNA) aptamer and AS1411 aptamer were used as the DNA nanotrain to load DOX, then DOX was further released in the nucleus while anti-PCNA aptamer specially bind with PCNA, finally, the fabricated nanotheranostic agent displayed 93.04 % cell apoptosis and inhibition of tumor growth [92].

DNA origami as rational nanocarriers that can be easily linked with cancer-targeted aptamers for efficient drug delivery. Recently, DNA tetrahedron was designed and linked with aptamers MUC-1 and AS1411 for successfully delivering anticancer metal complex $[Ir(ppy)_2phen]^+PF_6$ (IrPP) or DOX into nucleus for enhanced cancer therapy [87,88]. For instance, Tian *et al* prepared the dual-targeted aptamers modified DNA tetrahedron (MUC-1/AS1411 DNA-Td) that encapsulated the anticancer metal complex IrPP *via* a strong

stacking interaction and specifically targeted the MUC-1 overexpressed U251 cells, inhibiting glioma migration by blocking VM-associated signaling pathways and inducing mitochondrial fragmentation and apoptosis in U251 cells [88]. For effect monitoring the targeting ability and imaging the distribution of DOX@MUC-1/AS1411 DNA-Td in MUC-1 positive cells, Liu *et al* utilized activated aptamer probe strategy that conjugated activatable MUC1 aptamer probe with complementary sequence with quencher for imaging MUC-1 protein on cytomembrane [87]. The complementary sequence with quencher release and fluorescence recovery when MUC-1 probe of DNA-Td binds MUC-1 protein and causes conformational change of aptamer. DOX@MUC-1/AS1411 DNA-Td exhibited more effective to against DOX-resistant MCF-7 cells after binding to nucleolin selectively, providing great potential in cancer diagnosis and therapeutics.

Furthermore, the single-stranded DNA AS1411 could be integrated into DNA nanostructures *via* Watson-Crick base-pairing interactions, applying in biosensor, bioimaging and nuclear targeted cancer therapy. More specifically, theses G-rich DNA aptamers could incorporate hemin, an iron-containing porphyrin, to form G-quadruplex-hemin DNAzyme that exhibited high catalase-like activity, based on these properties, Yang *et al* designed Ce6 loaded DNA AS1411 G-quadruplex-based nanocarriers for improved cancer therapy [85]. In this study, hemin and Ce6 both are inserted into G-quadruplex-forming region. Afterwards, calcium ions (Ca^{2+}) and poly(L-histidine)-polyethylene glycol (pHis-PEG) are mixed with G-quadruplex to obtain Ca-AS1411/Ce6/hemin@pHis-PEG (CACH-PEG) nanoscale coordination polymer-based nanocarriers (Fig. 8a). The study showed that the nanocarriers was dissembled at pH 5.5 because of the protonation of imidazole groups to weaken the binding of pH and Ca^{2+}. The multifunctional nanocarriers displayed catalase-mimicking DNAzyme function that could in-suit produce O_2 by triggering the decomposition of endogenous H_2O_2 (Fig. 8c), the Ce6 was delivered into nucleus and generated ROS by AS1411 aptamers, moreover, the AS1411 inhibited antiapoptotic protein Bcl-2 expression (Fig. 8b), all these functions of nanocarriers synergistically enhanced PDT by overcoming the hypoxia-associated resistance and finally improving anticancer treatment (Fig. 8d, e) [85].

6. Small chemical molecules modified nanocarriers for nucleus-targeted drug delivery

In general, NLS and AS1411-tagged nanocarriers are most common approaches to nuclear targeting. However, peptides and DNA aptamer nuclear targeting ligands are fragile, considering the vulnerability of these ligands, small chemical molecules are more stable and easy to be modified.

6.1. Dexamethasone decorated nanocarriers for nucleus-targeted drug delivery

Dexamethasone (Dex), a potent glucocorticoid steroid, can bind to the glucocorticoid receptor which expressed in almost every cell nucleus, then the formed Dex-glucocorticoid complex is actively transported from the cytoplasm into the nucleus, during the transportation process, the glucocorticoid can dilate nuclear pores up to 60 nm, therefore, many studies are reported to utilize Dex-conjugated nanocarriers for the translocation of gene or chemodrugs into the nucleus [26,93–95]. For instance, Wang *et al* employed a cooperative, dimensional strategy for improving intranuclear drug delivery. Specifically, they prepared dual-pH/redox responsive amphiphilic polymeric hybrid micelle and combined with a "size ladder" changeable strategy to achieve effective nucleus-targeted anticancer drug delivery *in vitro* and *in vivo* [94]. In this study, amphiphilic blocks (P_{123}) conjugated to charge-reversible block (DMA-PEI) *via* redox responsive disulfide bond, which further interacted with Dex conjugated P_{123} to form size tunable hybrid micelles (PSPD/P_{123}-Dex) (Fig. 9a). The smaller sized NPs could be achieved through pH/redox-triggered structural variation to enhance charge-mediated endocytosis and promote Dex regulated nuclear transportation (Fig. 9b, c). Finally, the DOX was successfully delivered into nucleus and the efficacy of anticancer treatment was significantly improved (Fig. 9d.e). Recently, Zhou *et al* designed Dex decorated nanocomposite for diagnostic imaging and enhancing PTT/PDT efficacy [96]. In this nanosystem, not only WS_2 NPs have been used as NIR absorbing agents for PTT ablation of cancer *in vitro* and *in vivo*, but also act as drug delivery carriers because of their sheet-like structures, therefore, the photosensitive AuNCs were absorbed on large surface of WS_2 NPs through electrostatic interaction. Taken together, these nuclear targeting nanocomposite exhibited promising X-ray computed tomography imaging and synchronous PTT/PDT activities [96].

6.2. Retinoic acid modified nanocarriers for nucleus-targeted drug delivery

As mentioned above in section of 2.3, RA can easily bind to CRABP-II and further shows excellent affinity for the nuclear RA receptor [23,24]. According to this, RA was utilized as the nuclear targeting ligand to prepare multi-drug delivery nanosystem for the nuclear transportation [97,98]. For instance, Yang *et al* designed RA-modifed N–(2-hydroxypropyl) methacrylamide (HPMA) copolymer based micelles for co-delivery of two payloads (docetaxel and CPT) for tumor therapy. The results showed that RA-conjugated CPT facilitated the nuclear transport of CPT, the dual drug loaded micelles exhibited superior synergic cytotoxicity and *in vivo* tumor inhibition (87.1 %) [97]. Similar experiment has also been performed by You *et al*. [98]. In this experiment, two antitumor drug cisplatin and celastrol were modified with RA and mitochondria targeting ligand triphenylphosphine (TPP) respectively, finally, a multistage targeted-delivery method was applied in synergistic therapy for cancer treatment [98].

7. Functional nanocarriers for CRISPE/Cas9 delivery in cancer therapy

As a raising genome editing technology, the RNA-guided Cas9 nucleases from the CRISPR (clustered regularly interspaced short palindromic repeat)-Cas systems have emerged as versatile genome editing platforms for treatment of a wide spectrum of disease. Until now, various nanocarriers, such as lipid and polymeric NPs could deliver CRISPR-based genome editing systems including Cas9 protein/sgRNA complexes [99], Cas9 mRNA/sgRNA complexes and Cas9/sgRNA plasmids into cells [100,101]. Among these genome editing systems, Cas9/sgRNA plasmids exhibited greater stability than other systems, but the large size limited their application in treatment diseases. To address this issue, many delivery vectors decorated with nuclear targeting ligands for Cas9/sgRNA plasmids were designed [102,103]. For instance, Cheng's group fabricated AS1411/TAT-functionalized genome-editing nanosystems on suppression of tumor development [103,104]. The Cas9/sgRNA plasmids were compacted by protamine in the presence of calcium ions to form nanosized cores, which were further decorated by TAT and AS1411 conjugated hyaluronic chains, then the genome editing system could be translocated into malignant cell nuclei, inducing β-catenin knockout and suppress Wnt/β-catenin pathway, resulting in downregulated programmed death-ligand 1 (PD-L1) proteins involved in tumor progression and immunosuppression. This provides a facile strategy

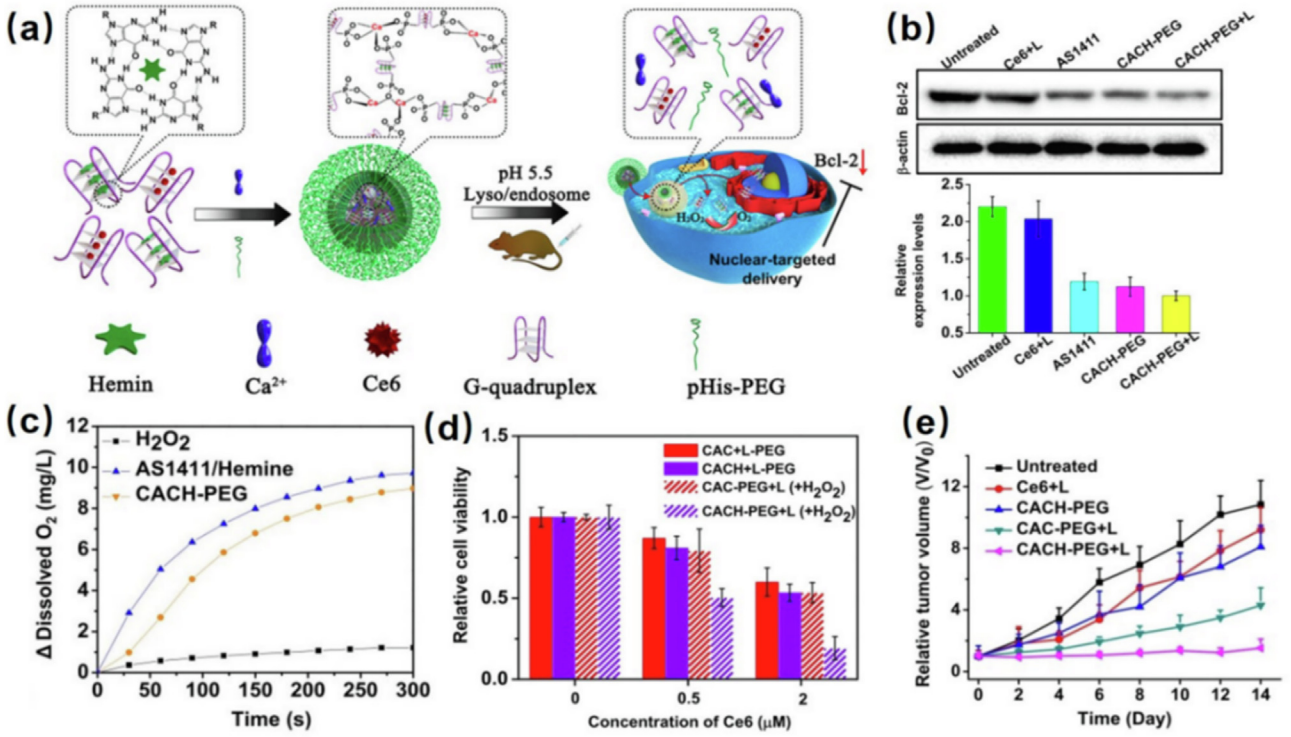

Fig. 8. a) A schematic illustration for synthesis of CACH-PEG. b) Western blot and quantified Bcl-2 expression levels for cell lysates of 4T1 cells after various treatments. β-actin was used as an internal reference. c) Oxygen generation in 2 mM of H_2O_2 solutions after the addition of AS1411/hemin complex or CACH-PEG NPs at room temperature. d) In vitro PDT treatment of 4T1 cells after being incubated with CAC-PEG or CACH-PEG under exposure to 660 nm light irradiation. e) The tumor growth curves of4T1-tumor-bearing mice after various treatments are indicated. Reproduced with permission [85] Copyright 2018 American Chemical Society.

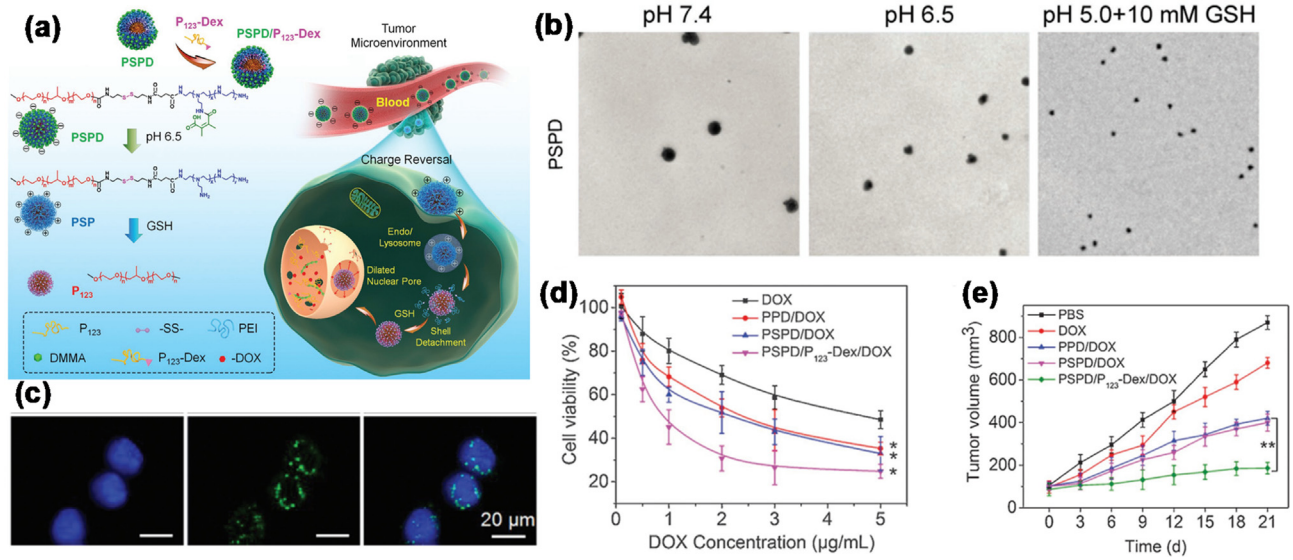

Fig. 9. a) Schematic illustration of the STCC and "size ladder" changeable strategies for Dox nucleus delivery mediated by hybrid micelle PSPD/P123-Dex. b) TEM images of PSPD micelles under different conditions. c) CLSM images of Hela cells incubated with PSPD/P_{123}-Dex/FITC-P_{123}.d) Cell viabilities of Hela cells after incubations with specified formulation. e) Tumor growth curve of BALB/c nude mice with HeLa xenografts treated with the specified formulation. Reproduced with permission [94]. Copyright 2017 Wiley-VCH Verlag GmbH &Co. KGaA.

for effective immune restoration through reversal of PD-L1-mediated cancer immunosuppression [104].

The heat generated from AuNPs not only could be used for PTT but also utilized to trigger the release of therapeutic agents. Recently, Wang *et al* prepared lipid (PEG2000-DSPE) coated TAT modified AuNPs to deliver Cas9-sgPlk-1 plasmids into tumor nuclei for effective knock-outs of *Plk-1* gene of melanoma and inhibition of the tumor both *in vitro* and *in vivo* [105]. The Cas9-sgPlk-1 plasmids was condensed on TAT-AuNPs *via* electrostatic interactions but could be thermo-trigger released into nuclei through photothermal effects under proper laser irradiation (Fig. 10a, b). Afterward the *Plk-1* gene, a master regulator of mitosis often

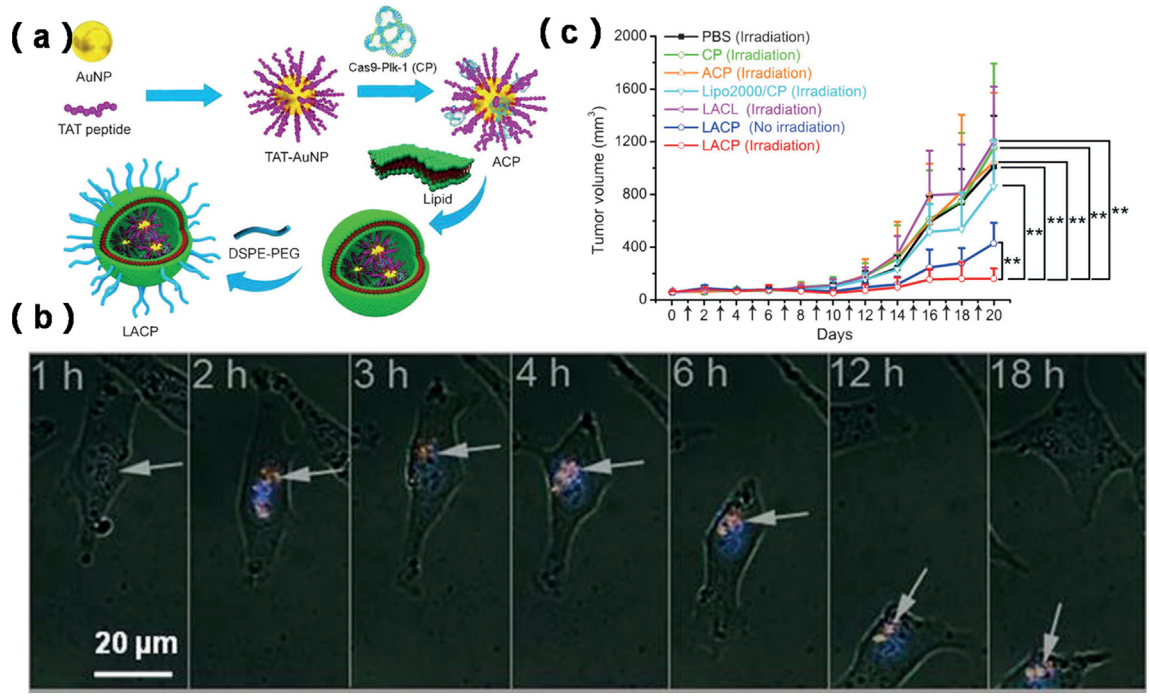

Fig. 10. a) A schematic illustration for synthesis of lipid encapsulated, AuNPs-condensed, Cas9-sgPlk-1 plasmids loaded nanocomplexes. b) Real-time tracing of the internalization process of the nanocomplexes in a cell and nucleus. c) Sizes of tumors treated with different formulations. Reproduced with permission [105]. Copyright 2018 Wiley-VCH Verlag GmbH &Co. KGaA.

overexpressed in tumor cells, was edited and about 65 % Plk-1 protein was down-regulated, indicating successful nuclear CRISPR/Cas9 delivery for treatment of cancer (Fig. 10c).

8. Other mechanisms for nuclear entry without nuclear targeting ligands

The modification with nuclear targeting ligands is an effective way to guide various nanosystems to enter the nucleus, however, the NLS functionalization of nanocarriers with positive charge may compromise the pharmacokinetic behavior as the positively charged arginine and lysine may enhance mononuclear phagocytic system recognition. Moreover, the high cost and poor stability of those ligands limit their further applications in biomedical research and clinical therapy [106]. Without the NLS assistance, the other way to enter the nucleus through nucleopores is mostly dependent on proper particles size and/or positive charge [106–110]. In addition, it is noteworthy that the efficiency of nuclear entry with different sized nanocarriers are largely depend on the materials [111]. For instance, Huo and co-workers fabricated ultra-small AuNPs with diameters of 2, 6, 10 and 16 nm and observed that only AuNPs smaller than 10 nm can enter the nucleus of MCF-7 cells, they further used 2 nm AuNPs as carriers to deliver triplex-forming oligonucleotide into nucleus directly and regulate the gene expression, finally reducing cell viability [106]. Wen *et al* prepared ultra-small Fe_3O_4 nanoparticles for nuclei targeting Dox delivery and PTT, the results showed that particles with smaller size (2.1 and 4.3 nm) can enter the nuclei, while larger ones (9.5 nm) are only located in the cytoplasm, and the nuclear targeting NPs exhibited superior toxicity to 9.5 nm NPs [110]. Hua *et al* synthesized multifunctional fluorescent carbon QDs with average diameters of 3.8 nm, after conjugating with PpIX PS, the diameters increased to 25.2 nm but still exhibited remarkable nucleus-targeting property and achieved phototherapeutic efficiency [112]. Yao and co-workers synthesized sulfonic-graphene quantum dots (sulfonic-GQDs) and found GQDs with lateral sizes of 1.8 to 3.6 nm (2.5 ± 0.5 nm on average) and thicknesses of 0.5 to 4 nm, the results showed that the sulfonic-GODs, retaining a small enough size and without any bio-ligand modification, achieved penetration through the nuclear membrane into the nucleus [113]. Due to the different materials with different properties, Chen *et al* reported that the larger sized C_5N_2 nanocarriers (36 nm) also could directly enter the cell nucleus but more large NPs could reduce the nucleus-entry capacity, the further study showed that abundant amino groups caused the rapid rupture of endosomes for effective nucleus entry (Fig. 11 a, b, c, d). Various molecular drugs/dyes/NPs (DOX, hydroxycamptothecine (HCPT), propidium iodide (Pi) and MnO_2 NPs) could be loaded on the C_5N_2 nanocarriers and were delivered to the nucleus (Fig. 11 e). Furthermore, the C_5N_2 nanocarriers are considered as photothermal/dynamic agent and loaded MnO_2 NPs could catalyze the decomposition of H_2O_2 to produce O2 in the tumor microenvironment, therefore, C_5N_2- MnO_2 NPs produced more ROS under hypoxia and enhanced PDT activity for synergistic cancer therapy (Fig. 11f) [114]. Recently, Jiang *et al* synthesized Hf-heptamethine indocyanine dye-based nanoscale coordination polymers (Hf-HI-4COOH) for low temperature PTT, in this reports, due to the proper size (average diameter of 36.7 nm) and positive charge in cancer cells, over 90 % of Hf-HI-4COOH internalized by 4T1 cells were found in the nuclei after 4 h incubation. Finally, this firstly reported nanoscale coordination polymers with intrinsic nuclear targeting exhibited strong near-infrared absorption and inhibition of breast tumors inhibition in tumor-bearing mice under low temperature (48 °C) and power density (0.3 W/cm^2) without obvious toxicity [109].

Compared normal cells with tumor cells, the researcher found that intracellular substances were released into the fluid surrounding the tumor cells due to the disorder of phospholipid bilayer alignment, indicating the increased cell membrane permeability of tumor cells. Based on this information, Lei *et al* discovered a new cell membrane permeability targeting (CMPT) mechanism

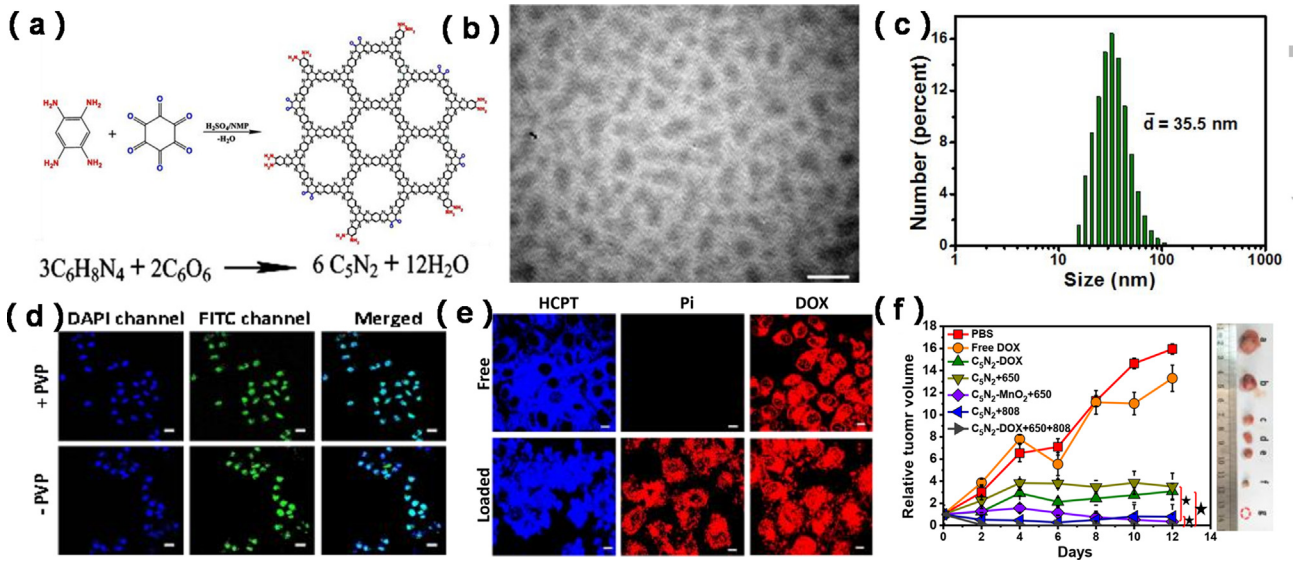

Fig. 11. a) Schematic diagram of the synthesis, b) TEM image of C_5N_2 NPs. c) Sizes distribution of C_5N_2 NPs. d) Confocal fluorescence images of Hela cells stained by DAPI after incubation with C_5N_2-FITC NPs. e) Confocal images of HCPT, Pi and DOX loaded C_5N_2 NPs or free molecules in Hela cells. f) The relative tumor volumes with different treatments Reproduced with permission [114]. Copyright 2019 Wiley-VCH Verlag GmbH &Co. KGaA.

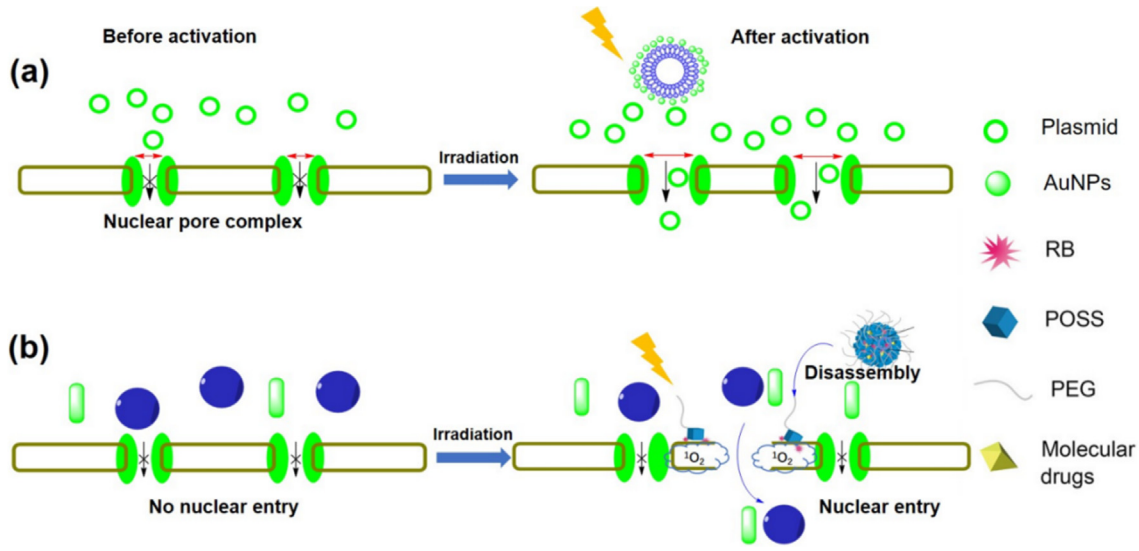

Fig. 12. a) Schematic illustration of nanomechanical transduction enhanced nuclear entry of biomolecules. A near-infrared laser pulse activates plasmonic nanoparticles to create plasmonic nanobubbles which could increase the nuclear membrane permeability and enhance nuclear entry for biomolecules. b) Schematic diagram of light-promoted nuclear entry of nanoparticles larger than nuclear pores assisted by PPR NPs.

with a graphene-based fluorescent nanoprobe (3.35 ± 0.15 nm) for tumor nuclear targeting [115]. They further found that the nanoprobe tumor targeting efficiency (≈50 %) with CMPT mechanism is much higher than EPR effect, and this nanoprobe eventually targeted to nucleus *via* binding to the DNA and histones, thus envisaging a bright blueprint for cancer therapy and diagnosis [115].

Interesting, some NPs with desired chemical composition and molecular weight can enter nucleus independent of the NPC and NLS by transiently destructing nuclear envelope and directly permeabilizing the nuclear membrane [116] Nowadays, the direct acting on the nuclear membrane to compromise the integrity of the nuclear membrane or increase the nuclear membrane permeability are reported as the promising light irradiation strategy for improving drug loaded nanocarriers nuclear delivery [117,118]. It has been reported that the nanomechanical force from plasmonic nanobubbles that produced by gold-coated plasmonic liposomes upon Near-infrared laser pulses activation, which could enhance nuclear membrane permeability and promote universal uptake of large macromolecules into the nucleus (Fig. 12a) [117]. Furthermore, Zhu *et al* developed self-assembled NPs that consist of a polyamine-containing polyhedral oligomeric silsesquioxane (POSS) unit, a hydrophilic polyethylene glycol (PEG) chain, and the PS rose bengal (RB). The results showed that the lysosomal structures and nuclear membranes were disrupted by $^1O_2$ which was generated under light irradiation, thereby promoting chemotherapeutic agents (10-hydroxycamptothecine and docetaxel) and nanomaterials (Prussian blue NPs and gold nanorods) nuclear entry (Fig. 12b) [118]. These light irradiation strategy of "rocking the nucleus" provide a new train of thought for nuclear drug delivery.

9. Summary and perspective

The effective of nanocarriers for the subcellular targeted delivery of therapeutic agents reflects the progress of nanomedicines towards the clinic. Subcellular drug targeting and delivering have become a promising strategy in future nanocarriers development, thus improving the subcellular organelles related diseases treatment. Nucleus is the most popular subcellular target in nanomaterial-associated therapy because of their vital importance in cellular metabolism and in regulation of cell survival or death. This review aims to discuss the approaches and methodologies of various nanosystems development for the effective targeted delivery of therapeutics to subcellular organelles. To overcome biological barriers and specifically target to the cells, nanocarriers are modified with cell receptor targeting ligands. Furthermore, various nuclear targeting ligands, including NLS, AS1411 aptamer, Dex and RA are utilized to facilitate the drugs nucleus delivery. Therefore, different therapeutic agents such as chemodrugs, gene agents and PSs are successfully encapsulated into nanocarriers with multistage targeting ability for delivering them into the subcellular targeted site, thereby resolving the problem of MDR and improving their bioactivity. Moreover, the co-delivery nanosystems are rapidly developed to obtain synergistic activity and amplify the combination therapy. Interestingly, various strategies, including dual ligands targeting, size ladder changeable, STCC and light irradiation strategies are applied for effectively nuclear targeting and drugs delivery. Therefore, with the new goals of subcellular targeting, the field multitargeted and stimulated responsive multifunctional nanocarriers are moving to a higher level of complexity. Nonetheless, to speed up the future clinical applications of subcellular targeted therapy, there remain many hurdles and issues that need to be addressed.

1) The mechanism of NPs trafficked through the cells are different that depend on the cell types. Therefore, the surface modification of nanocarriers to facilitate the cells internalization and subcellular targeting should be carefully designed to meet the requirement of suitable cells.
2) The evaluation of the efficient subcellular targeting of NPs are largely applied by confocal laser scanning microscopy (CLSM) or by testing the final effect of the loaded therapeutic agent. However, the qualitatively analysis of how many NPs and how much cargo are delivered into the targeted site to achieve the maximum therapeutic effect are still unclear, so that the novel analysis methods need to discover to promote NPs progress of clinical utilization.
3) The co-delivery of drugs is developed so fast to enhance the synergistic effect. However, the multiple subcellular organelles targeting strategies are emerging as powerful way to reach the expected therapeutic effect but rarely reported. In this sense, the multiple subcellular targeting NPs by the combination of various agents are urgently needed to fabricate and highly desirable.
4) Until now, most subcellular studies with sophisticated NPs designs are frequently applied in the anticancer treatment that may destroy the organellar function and finally induce the cell apoptosis. However, many disease treatments (*e.g.*, PD and AD) that need to scavenge the overexpressed ROS or restore cell functions but not lead to the cell death, these kinds of studies are rarely reported [119]. Furthermore, whether the nanocarriers, especially the metal-based nanosystems have side-effect with the functions of organelles, that are still unknown but should be cautiously evaluated and confirmed.
5) Subcellular targeted ligands intensity is crucial for NPs targeting ability, not the more targeted ligands modified on the surface of NPs, the better subcellular internalization. For example, in glioma, NLS surface coating on NPs even reduced the nuclear delivery, and CS NPs with small sized without the NLS modification exhibited 5-fold higher nuclear localization rates than NLS modified NPs in different kinds of cells [51]. Therefore, the appropriately shaped NPs, cell types and nucleus properties are important factors that need to consider when prepare ligands modified NPs to reach the maximum targeting ability [120,121].
6) Multiple surface modifications to confer several functionalities to the carriers could increase the complexity of chemical synthesis, production costs and the number of potential side effects of the system, thereby making the translation of these technologies to the clinical setting extremely difficult. Hence, there is the need for SMART/ELEGANT design of these nanocarriers. For instance, by having "multifunctional ligands", these ligands may incorporate properties that allow both targeting and intracellular delivery in the same molecule. Having an understanding of the biological process of delivery and uptake as well as an understanding of chemistry and the field of materials would enable us to do this innovatively.
7) Genome editing offers promising solutions to genetic disorders and cancer therapy, especially, the CRISPR /Cas9 is emerging as powerful technology to edit single or multiple genes in a wide variety of cell types and organisms for gene therapy. Encouragingly, using CRISPR/Cas9 technology for lung cancer therapy in clinical trial has been reported. And multifunctional nanosystems for CRISPR /Cas9 plasmids nuclear delivery are reported in our review. However, safety delivery of nanocarriers is still the main challenge for robust implementation of CRISPR /Cas9 gene editing *in vivo*, therefore, more smart and safety nanocarriers need to be developed for improving delivery of CRISPR /Cas9 system. [101]

Overall, the development of subcellular targeting nanosystems for improving therapeutic efficacy continue to be an interesting research topic. And the subcellular targeting technology will enter into the mainstream of the nanomedicine and provide new train of thought in existing clinical nanotechnologies. Nowadays, most of the nanocarriers formulations mentioned are in pre-clinical progress, the development of subcellular targeting multifunctional nanocarriers could enhance therapeutic efficiency with extraordinary advances to the next generation and accelerate the clinical translation.

Data availability

Data will be made available on request.

Declaration of Competing Interest

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

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