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Hybrid nanoparticles for combination therapy of cancer

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ABSTRACT

Nanoparticle anticancer drug delivery enhances therapeutic efficacies and reduces side effects by improving pharmacokinetics and biodistributions of the drug payloads in animal models. Despite promising preclinical efficacy results, monotherapy nanomedicines have failed to produce enhanced response rates over conventional chemotherapy in human clinical trials. The discrepancy between preclinical data and clinical outcomes is believed to result from the less pronounced enhanced permeability and retention (EPR) effect in and the heterogeneity of human tumors as well as the intrinsic/acquired drug resistance to monotherapy over the treatment course. To address these issues, recent efforts have been devoted to developing nanocarriers that can efficiently deliver multiple therapeutics with controlled release properties and increased tumor deposition. In ideal scenarios, the drug or therapeutic modality combinations have different mechanisms of action to afford synergistic effects. In this review, we summarize recent progress in designing hybrid nanoparticles for the co-delivery of combination therapies, including multiple chemotherapeutics, chemotherapeutics and biologics, chemotherapeutics and photodynamic therapy, and chemotherapeutics and radiotherapy. The *in vitro* and in *vivo* anticancer effects are also discussed.

1. Introduction

Our understanding of cancer biology has significantly advanced in the past two decades [1], spurring much investment in the development of new cancer therapies. However, the survival rates for many common cancers have remained largely unchanged in the same period, calling for new and disruptive technologies for cancer treatment. Nanoparticle drug delivery potentially represents such a disruptive technology for enhancing therapeutic efficacies and reducing side effects by improving the pharmacokinetics and tumor deposition of the payloads via the enhanced permeability and retention (EPR) effect [1]. In animal models, the therapeutic efficacies of nanomedicines were further enhanced by attaching active targeting ligands on the particle surfaces to increase tumor selectivity and drug deposition in cancer cells. Unfortunately, in the clinic, nanomedicines have largely failed to achieve better therapeutic outcomes of chemotherapeutic interventions.

A number of reasons have been proposed to account for the gap between preclinical animal results and clinical human trial data, including the less pronounced EPR effect in human tumors, the heterogeneity of human tumors, and the high propensity of developing resistance to therapies in human tumors. Several strategies have been pursued to overcome the barriers to delivering nanoparticles to human tumors, such as designing nanoparticles with superior pharmacokinetics [2] and multi-stage delivery systems [3] and enhancing the EPR effects using high intensity focused ultrasound (HIFU) [4] and X-ray radiation [5,6]. Combination therapies provide a potential solution to addressing the tumor heterogeneity and drug resistance issues by taking advantage of distinct mechanisms of action of the multiple therapeutics/modalities to hit multiple targets and to overcome cross-resistance [7]. After a number of setbacks with monotherapies, several ongoing clinical trials are evaluating the therapeutic efficacy of combining chemotherapeutic nanomedicines with radiotherapy or small molecule drugs [8,9].

To optimize their synergistic therapeutic effects, combination nanomedicines need to be rationally designed to accommodate multiple therapeutic drugs or modalities with temporally controlled release of individual cargoes. In this review, we will summarize the recent progress in the design of hybrid nanoparticles for combination therapy of cancers. Hybrid nanoparticles composed of both inorganic and organic components can be prepared using a number of strategies. The ability to combine a multitude of organic and inorganic components in hybrid nanoparticles in a modular fashion should allow for systematic tuning of their properties for combination cancer therapy. Optimally designed hybrid nanoparticles can combine the beneficial features of both purely inorganic nanomaterials (e.g., quantum dots (QDs) [10], gold nanoparticles [11], and metal oxides [12–14]) and purely organic nanoparticles (e.g., liposomes [15], dendrimers [16], micelles [17], and polymeric hydrogel nanoparticles [18]).

In this review, we will confine our discussion to four classes of hybrid nanomaterials: nanoscale coordination polymers (NCPs) and nanoscale metal-organic frameworks (NMOFs) that are built from metal ions or clusters bridged by organic linkers, polysilsesquioxane (PSQ) nanoparticles that are synthesized from condensation of silanol-based monomers, and inorganic nanoparticle/organic polymer

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composite systems that are prepared by mixing mesoporous silica, gold, or iron oxide nanoparticles with biodegradable polymers or biomacromolecuels. After briefly introducing synthetic strategies for various hybrid nanoparticles, we will discuss their recent applications in the co-delivery of multiple therapeutics/modalities to synergistically enhance the anticancer efficacy. We will only focus on combination therapy using multiple chemotherapeutics or by combining chemotherapy and other therapeutic modalities. We will also provide an outlook for potential clinical applications of hybrid nanoparticles.

2. Synthesis of hybrid nanomaterials

2.1. Synthesis of NCPs or NMOFs

NMOFs and NCPs are a new class of molecular nanomaterials that are built from connecting metal ions or metal clusters with bridging ligands. In the past 15 years, bulk MOFs and coordination polymers have been extensively explored for various applications, such as gas storage and separations [19–23], nonlinear optics and ferroelectrics [24,25], catalysis [26–31], sensing [32,33], and light-harvesting and photocatalysis [34–37]. On the other hand, NMOFs/NCPs possess several interesting properties that make them potential nanocarriers for anticancer drug delivery: (1) compositional and structural tunability allows for the fine tuning of physicochemical properties of the nanoparticles; (2) highly porous and oriented structures accommodate efficient loading of diverse cargos; (3) intrinsic biodegradability due to the relatively labile metal-ligand bonds [38–44].

Four general methods have been utilized to synthesize NCPs or NMOFs: surfactant-free nanoprecipitation at room temperature and solvothermal reactions at elevated temperatures (Fig. 1) and surfactant-based reverse microemulsion and solvothermal reactions (Fig. 2). Amorphous particles from these reactions are called NCPs, while crystalline materials are categorized as NMOFs. Surfactants are used to control particle morphologies in reverse microemulsions and surfactant-templated solvothermal reactions.

In nanoprecipitation, precursor solutions are mixed to allow for particle nucleation and growth at room temperature. After the reaction, the resultant nanoparticles are precipitated out of the suspension by adding a poor solvent [45,46]. For example, the NCP composed of the anticancer prodrug *c,c,t*-Pt$(NH_3)_2Cl_2$(succinate)$_2$ (disuccinatocisplatin, DSCP) and Tb^{3+} ions was synthesized by adjusting the pH value of an aqueous solution of $TbCl_3$ and $[NMeH_3]_2$DSCP to 5.5, and adding methanol to the precursor solution to precipitate the NCP [45].

Surfactant-free solvothermal synthesis is carried out by heating a solution of metal ions and ligands to control particle nucleation and growth. For example, a crystalline Fe^{3+} NMOF of the formula $Fe_3(\mu_3\text{-}O)Cl(H_2O)(BDC)_3$ was synthesized by heating a solution of $FeCl_3$ and terephthalic acid (BDC) with microwave [47]. This NMOF displayed octahedral morphology with a diameter of 200 nm and adopted a highly crystalline MIL-101 structure. In another example, the UiO NMOF of the formula of $Zr_6(\mu_3\text{-}O)_4(\mu_3\text{-}OH)_4$(amino-TPDC)$_6$ was synthesized by heating a DMF solution of $ZrCl_4$ and amino-triphenyldicarboxylate (amino-TPDC) at 80 °C for 5 days to afford hexagonal-plate particles with a diameter of ~100 nm and a thickness of ~30 nm [48].

In reverse microemulsions, surfactants are used to control nucleation and growth kinetics of particles. A crystalline $Gd(BDC)_{1.5}(H_2O)_2$ nanorod was synthesized by mixing two microemulsions containing either $GdCl_3$ or $[NMeH_3]_2$[BDC] [49]. The particle morphologies could be controlled by adjusting the water to surfactant molar ratio (*w* value) of the microemulsion. More recently, 30 nm Zn-bisphosphonate NCPs containing the cisplatin prodrug (Zn-cis) and oxaliplatin prodrug (Zn-oxali) were synthesized by vigorously stirring a mixture of $Zn(NO_3)_2$ and corresponding prodrugs in the presence of 1,2-dioleoyl-sn-glycero-3-phosphate sodium salt (DOPA) in the Triton X-100/1-hexanol/cyclohexane/water reverse microemulsions [50].

Surfactant molecules can be used to template the NMOF synthesis under solvothermal conditions. For example, a reverse microemulsion of $GdCl_3$ and $[NMeH_3]_6$[BHC] (BHC = benzene hexacarboxylic acid) was heated at 120 °C to afford block-like crystalline Gd-BHC NMOFs of 25 × 50 × 100 nm in dimensions [49]. This method was also used to synthesize other DOPA-capped NCPs and NMOFs, including Zr-methotrexate (MTX) NMOFs, Zn-MTX NMOFs, and La-DSCP NCPs [46,51].

By taking advantage of the porous NMOF/NCP structure and the functionality of bridging ligands, several different strategies have been adopted to incorporate high loadings of therapeutic agents into

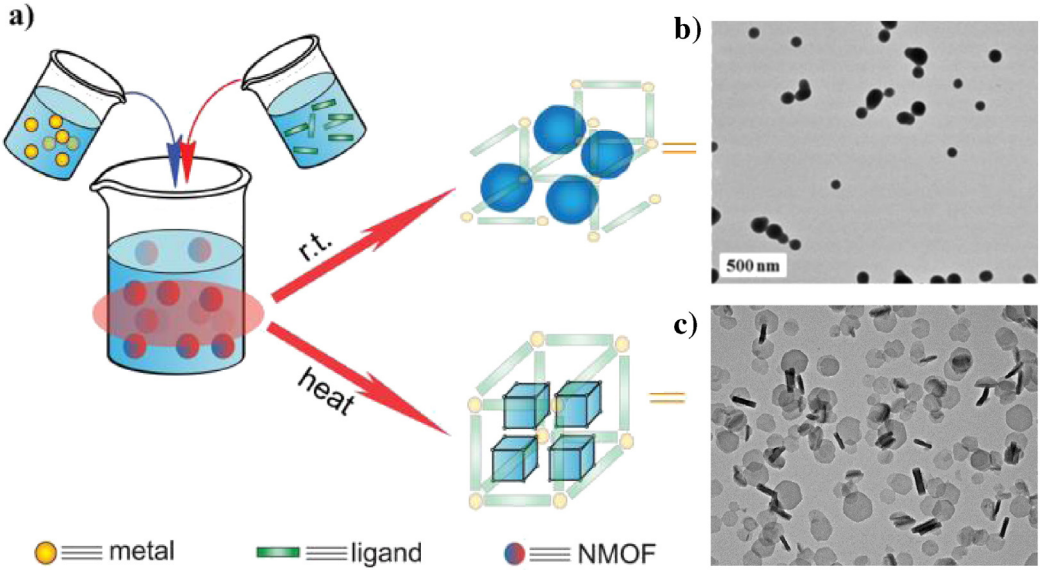

Fig. 1. (a) Surfactant-free synthesis of NMOFs [39]. (b, c) Representative TEM image of NMOFs synthesized by nanoprecipitation (b) [45] and SEM image of NMOFs synthesized by solvothermal method (c) [48].
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