Biomedical Applications of Bimetallic Coordination Polymers

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Bimetallic coordination polymers (CPs) have two different metal ions as connecting nodes in their polymer structure. The synthesis methods of bimetallic CPs are mainly categorized into the one-pot method and post-synthesis modifications according to various needs. Compared with monometallic CPs, bimetallic CPs have synergistic effects and excellent properties, such as higher gas adsorption rate, more efficient catalytic properties, stronger luminescent properties, and more stable loading platforms, which have been widely applied in the fields of gas adsorption, catalysis, energy storage as well as conversion, and biosensing.

Keywords: bimetallic ; coordination polymers ; synergistic effects

1. Bimetallic Coordination Polymers Based on Anticancer Drugs

Among the traditional chemotherapeutic agents, platinum (Pt)-based drugs, mainly including cisplatin (cis-diamine dichloroplatinum (CDDP)), oxaliplatin, and carboplatin, are one of the major clinically used anticancer drugs due to their potent cytotoxicity that disrupts DNA replication [1]. However, due to the drawbacks of rapid in vivo clearance, weak tolerance, and poor targeting of free CDDP molecules, clinical use often brings about side effects such as poor chemotherapeutic efficacy or even severe systemic toxicity [2]. Therefore, recent research is focused on finding efficient delivery vectors for CDDP with high loading rates, stability as well as targeting capability. Ma and co-workers have prepared sub-50 nm CDDP-loaded hollow mesoporous organosilica (HMOS) nanoparticles (termed as Pt@HMOS), which were subsequently decorated with the bimetallic Zn^{2+}/Cu^{2+} co-doped MOF (termed as Pt@HMOS@ZC) to plug the pores of nanoparticles for efficiently preventing the premature leakage of CDDPs and improving the loading and delivery capacity of HMOS [3]. When Pt@HMOS@ZC entered the tumor cells, the acidic environment would cause the decomposition of outer MOF to release CDDP for the chemotherapy of cancer. Simultaneously, free Cu^{2+} can be released in this process, which can deplete large amounts of reduced glutathione (GSH) in cancer cells and catalyze the decomposition of hydrogen peroxide (H_2O_2) into highly toxic ·OH in tumors via a Fenton-like reaction, which acted synergistically with CDDP for chemodynamic therapy of tumors. The combination of bimetallic MOF and HMOS helps to create systems that intelligently unlock nanomedicines, a concept that offers new designs and ideas for the precise release of tumor drugs.

2. Bimetallic Coordination Polymers Based on Cancer Vaccine

Cancer vaccines with easy mass production and a favorable safety profile are increasingly being explored for the immunological treatment of cancer [4]. In terms of immune mechanisms, tumor vaccines spatiotemporally coordinate antigen transport to lymph nodes (LNs), cytoplasmic delivery, and cross-presentation of antigen in dendritic cells (DCs) with innate immune stimuli to activate specific T cell responses [5]. However, limitations in the body's own immune stimulation and DC spatiotemporal coordination (for example, DC recruitment, activation, and migration to LNs) severely affect their antitumor utility [6]. Therefore, there is an urgent need to develop an effective delivery system to solve the dilemma of cancer immunotherapy. Liu and co-workers developed a bimetallic organic framework, Mn/Zr-MOF, equipped with a biomimetic nanovaccine targeting Ythdf1 to create an in situ pro-inflammatory immune ecosystem for enhanced DC spatiotemporal coordination [7]. Plasmids expressing short hairpin RNA (shRNA) against Ythdf1 (shY1, downregulating Ythdf1 expression) and liposome-modified tumor cells membrane (CM) would be packaged and squeezed through a polymeric membrane in an extruder to form shY1-CM nanoparticles as a Ythdf1-targeted biomimetic nanovaccine. Mn/Zr-MOF-shY1-CM was fabricated by adsorbing shY1-CM nanoparticles onto Mn/Zr-MOF, which greatly enhanced the stability and targeting action of the vaccine. The results from cellular and animal experiments revealed that the cancer vaccine exhibited a strong preventive effect in delaying B16-OVA and MC38 tumorigenesis. Additionally, it demonstrated a robust therapeutic effect of inhibiting postoperative MC38 tumor recurrence and heterochronic liver metastasis. This well-

designed bimetallic MOF-loaded cancer vaccine provides an efficient strategy for the fabrication of personalized scaffold cancer vaccines.

3. Bimetallic Coordination Polymers for Chemodynamic Therapy (CDT)

Chemodynamic therapy (CDT) has gained widespread attention for its use in cancer therapy by inducing reactive oxygen species (ROS) in tumor cells and disrupting the balance of the redox state in cancer cells [8]. CDT is driven by Fenton reactions which are based on the generation of highly toxic ROS from intracellular H_2O_2 catalyzed by Fe^{2+}/Fe^{3+} redox pairs [9]. The resulting ROS has a strong oxidation capability and can cause severe oxidative damage to organelles and biomolecules. However, the Fenton reactions progress is overly dependent on the tumor microenvironment conditions such as pH and concentration of H_2O_2, hence the anticancer effect of CDT is greatly limited [10]. A novel cascade nanozyme (Co-Fc@GOx) combining nanoscale Co-ferrocene MOF and GOx was fabricated and showed remarkable cascade enzymatic/Fenton activity [11]. Owing to the synergistic effect of Fe^{2+} and Co^{2+}, the prepared Co-Fc MOF can not only possess high Fenton activity but also bind more firmly to GOx. The results showed that the loaded GOx catalyzed a large amount of glucose in the tumor environment to produce abundant gluconic acid and H_2O_2, which significantly facilitated the Fenton reaction and accelerated the in situ induction of ROS, particularly ·OH, thereby enhancing the therapeutic effects on cancer cells. This Co-Fc@GOx can effectively regulate the tumor microenvironment through a cascade reaction and may serve as an alternative CDT platform to promote tumor therapy. Qu and co-workers have designed bimetallic CuZn-MOF (Cu/ZIF-8) wrapped with DNAzyme for intracellular in situ synthesis of tumor drugs and DNAzyme-based gene therapy [12]. The synthesized DNAzyme@Cu/ZIF-8 can release Cu^{2+}, Zn^{2+}, and DNAzyme upon decomposition in the acidic environment of tumor cells. The released Cu^{2+} underwent reduction to Cu^{+} through ascorbic acid, subsequently, these ions catalyzed the synthesis of chemotherapeutic drugs via the copper-catalyzed azide-alkyne cycloaddition (CuAAC) reaction. Moreover, the released Zn^{2+} can act as a cofactor to activate the cleavage activity of DNAzyme. Both the synthesis of anticancer drugs and the activation of gene therapy took place within the tumor cells, which could destroy the cancer cells in situ to minimize the side effects on normal organisms.

4. Bimetallic Coordination Polymers for Radiotherapy

Radiotherapy is the most commonly used clinical treatment strategy for early and intermediate-stage tumors [13]. However, radiotherapy is often ineffective due to factors such as variations in the radiosensitivity of different types of tumor cells and infections in solid tumors [14]. Moreover, the potential resistance and side effects of radiotherapy (for example, esophagitis, enteritis, radiation cystitis, pulmonary fibrosis, bone marrow injury, and other side effects) seriously damage patients' health [15]. Therefore, increasing the sensitivity of cancer cells to radiotherapy as well as reducing the impact of side effects of radiotherapy have become important directions in the development of radiotherapy. Gold nanoparticles as emerging radiosensitizers can both damage cells by generating free radicals through the photoelectric and Compton effects, as well as improve the efficiency of radiation therapy by inhibiting DNA repair processes [16]. The composite system of AuNPs and bimetallic MOFs achieved significant radiosensitization of tumors due to the synergistic effect of multiple components [17]. The Lu group designed and synthesized a bio-functional bimetallic MOF MnRu-MOF by doping Mn^{2+} into a ruthenium (Ru) complex, followed by the incorporation of gold nanorods (AuNR) into this system to prepare the heterojunction radiosensitizer Au@MnRu-MOF with enhanced cancer radionuclide/immunotherapy [18]. Single-crystal XRD confirms that MnRu-MOF is a novel crystal structure with *P63/mmc* space group and a channel diameter of 27 Å. In this system, Au@MnRu-MOF can release Mn^{2+} under acidic conditions and modulate NK-mediated (NK = natural killer) cell therapy to overcome the proliferation of the triple-negative breast cancer cell line MDA-MB-231. Moreover, photoelectrons generated by high-energy X-ray excitation of AuNR can be transferred to the excited singlet state of Ru polypyridine complexes, promoting the accumulation of cytotoxic free radicals. As a result, the MnRu-MOF combined with AuNR was formed with a core-shell heterojunction structure and used to inhibit the proliferation of MDA-MB-231 cells, which provides ideas for the rational design of biologically functional MOFs and the combined treatment of cancer.

5. Bimetallic Coordination Polymers for Immunotherapy

Immunotherapy is a novel anti-cancer tool that can recognize and kill cancer cells by activating the host's own immune system [19]. However, acute myeloid leukemia (AML) and other malignant cells can activate a variety of immune evasion mechanisms to escape forced elimination by the autoimmune system. Among them, epigenetic alterations-mediated reduction in the antigenicity of leukemoblasts (LBs) is one of the key mechanisms of immune escape and resistance to T-cell immunotherapy [20]. Thus, the epigenome can be reprogrammed to reverse immune evasion, regarded as an emerging strategy for the treatment of multiple malignancies. Song and co-workers prepared a bimetallic MOF-based nanocomposite (called AFMMB) consisting of DNA hypomethylating agents azacitidine (AZA), leukemic stem cell (LSC)

membranes, and pro-autophagic peptides for the immunological treatment of leukemia [21]. Due to the homing ability and immuno-compatibility of LSC membranes, the constructed AFMMB particles exclusively targeted LBs and triggered autophagy by binding to the Golgi-associated plant pathogenesis-related protein 1 (GAPR-1), leading to its disassembly and the release of Fe^{3+}, Mn^{2+}, and AZA. The release of DNA hypomethylating agents effectively suppressed DNA methylation, upregulated major histocompatibility complex class I molecules, and induced RNA methylation-mediated decay of programmed cell death protein ligand transcripts, thereby restoring stimulators of the interferon gene pathway. The dual epigenetic effects of AFMMB enhanced the antigenicity of AML cells and consequently facilitated the recognition and killing of cytotoxic T cells by tumor cells. This research highlighted the promising applications of bimetallic coordination polymers (CPs) for the treatment of hematological malignancies and solid tumors.

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