MINI-REVIEW

Bioactive nanomaterials for ion-interference therapy

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Abstract
Ions with biological actions have been exploited to perform a wide range of tasks, including antitumor therapy, termed ion-interference therapy (IIT). However, single ions or ion-containing small molecules possess serious limitations for in vivo therapeutic applications due to their short circulation duration, weak discrimination between healthy and tumor tissues, and dose-limiting systemic toxicity. Bioactive nanomaterials, not only successful targeting tumors but also sufficient generation/release of active species for cell death induction, have attracted enormous interest in IIT due to their potential to tackle the challenges, and are largely the focus of this review.

KEYWORDS
active targeting, biocatalysis, ion balance, ion-interference therapy, ion messenger

1 INTRODUCTION

High cytotoxicity to cultured cancer cells is viewed as a sign of general toxicity, but not anticancer activity, and indeed, some very promising antitumor candidates are abandoned due to their severe side effects, including hepatotoxicity, nephrotoxicity, neurotoxicity, immunotoxicity, developmental toxicity, and genotoxicity. Regarding ideal anticancer drugs should largely avoid toxicity problems, not only the successful targeting of tumors but also the sufficient generation/release of active species for cell death induction. Some metal/nonmetal ions (eg, Na+, Cl−, Ca2+, Zn2+, Cu+, Pt4+, Ba2+, and

Abbreviations: ACC, amorphous calcium carbonate; AgNC, silver nanocube; BP, black phosphorus; DSF, disulfiram; GOx, glucose oxidase; GSH, glutathione; IIT, ion-interference therapy; NP, nanoparticle; PtNC, platinum nanocomplex; SCN, sodium chloride NP; TME, tumor microenvironment.
Bioactive nanomaterials for ion interference antitumor therapy

H$_2$PO$_4^-$ and HPO$_4^{2-}$ participate in many important biological processes (Figure 1), including osmotic pressure and acid-base balance maintenance, catalysis and signal pathway activation, protein and enzyme constitution, biomolecule targeting, and so forth. Their aberrant distribution/accumulation in cells interferes with these processes, inducing irreversible physical damage to cells or the activation of biochemical reactions for cytotoxic ingredients’ generation for cell death induction. Therefore, ions can be exploited against a wide spectrum of cancers with high efficiency and without drug resistance, namely, ion-interference therapy (IIT). However, the short duration of circulation, weak discrimination between healthy and tumor tissues, and dose-limiting systematic toxicity make them unavailable for direct application in the body. Bioactive nanomaterials, including nanoparticles (NPs), nanosheets, metal-organic frameworks, nanopolymers, and metal-ligand nanocompounds, have attracted enormous interest in IIT due to their potential to tackle the challenges that are otherwise difficult for single ions or ion-containing small molecules, and may become a new subdiscipline of rapidly developing nanomedicine, as this review will demonstrate.

Here, we will primarily focus on the selection of therapeutic ions, the design and preparation of bioactive nanomaterials, and the proposition of anticancer principles to present an overview of IIT. Our discussion begins with an introduction to the biological properties of ions, then summarizes the recent representative studies (Table 1), and finally illustrates the great guidance and reference meanings for further development of nanomaterials in IIT.

## 1.1 Interfering osmotic pressure

In animals, cells are generally soft without a firm extracellular barrier such as the rigid cell walls of plants, and the plasma cell membrane is too fragile to produce enough tension to counteract substantial osmotic pressure. Usually, cells sustain low ratios of intracellular to extracellular sodium and chloride and a high ratio of potassium to maintain their normal structure and physiological properties. Once these asymmetric ionic gradients are disturbed beyond cell autoregulation, the changed osmolarity may cause cytoskeleton destruction, cell cycle arrest, and even cell lysis. Therefore, interfering ion balance can lead to efficient antitumor treatment without systemic/accumulative toxicity. In 2018, Vasiljeva et al constructed the positive-charged Al hydroxide crumpled nanosheets (Alloahene) to interfere ions imbalance in the tumor environment by selectively adsorbing extracellular anionic species (e.g., Cl$^-$ and HCO$_3^-$) to strongly inhibit tumor growth.

In fact, fluctuations in ion balance are inevitably produced by cellular activity itself, such as changes in transport and metabolism. However, the smart physiological mechanisms can sense ion change and then regulate it by opening/closing ion channels and intracellular trafficking with efflux/storage processes. Therefore, transporting ions across the membrane to inverse the concentration gradient is difficult to achieve. Considering the special uptake mechanism of NPs via clathrin-mediated endocytosis and macropinocytosis, NPs can be actively transported into cells without being detected by the related ion pumps/channels. In 2012, Huang’s group first delivered a large amount of sodium ions into the cell interior with the help of nanodiamonds, inducing osmotic stress followed by cell swelling, oxidative stress, and finally, efficient killing of tumor cells. Similarly, Xie et al in 2019 synthesized sodium chloride NPs (SCNPs) as a Trojan horse to deliver sodium and chlorine ions into cells to disrupt the inherent ion homeostasis for tumor killing.

Extensive cell swelling and giant bleb formation were observed only a few hours after the co-incubation of cells and SCNPs, which eventually caused cell rupture and complete osmotic lysis. Moreover, this treatment can cause immediate and immunogenic cancer cell death. Nanomaterials can be purposefully designed with various chemical components, offering endless ways to disrupt the balance of cellular Na$^+$, K$^+$, and Cl$^-$ ions, such as selective ion absorption, responsive ion release, and cellular autoregulation inhibition, which all hold promise as effective cancer therapeutics complementary to traditional chemotherapeutics.
### TABLE 1  The classification of bioactive nanomaterials for IIT

| Classification                     | Bioactive nanomaterials       | Interfering ions | Reference |
|------------------------------------|-------------------------------|------------------|-----------|
| Changing osmotic pressure          | AI(OH) nanosheets             | Cl⁻, HCO₃⁻        | 7         |
|                                    | Na⁺-nanodiamonds              | Na⁺              | 8         |
|                                    | NaCl NPs                      | Na⁺, Cl⁻          | 9         |
| Disturbing cellular communication  | CaO₂ NPs                      | Ca²⁺             | 12        |
|                                    | CaCO₃ NPs                     | Ca²⁺             | 13        |
|                                    | ZnO NPs                       | Zn²⁺             | 15-17     |
|                                    | ZnO quantum dots              | Zn²⁺             | 18        |
| Activating the biocatalysis        | Fe⁰ NPs                       | Fe²⁺             | 20,21     |
|                                    | Fe₃O₄ NPs                     | Fe²⁺             | 22,23     |
|                                    | Cu-Cys NPs                    | Cu⁺              | 27        |
|                                    | Cu²⁺-doped SiO₂ NPs           | Cu⁺              | 28        |
| Activate targeting IIT            | Peptide-stabilized Pt NPs     | Pt²⁺             | 34        |
|                                    | Polymer-cisplatin NPs         | Pt²⁺             | 42        |
|                                    | Ag NPs                        | Ag⁺              | 48,49     |
|                                    | AgNC-GOx                      | Ag⁺              | 50        |
|                                    | BaO₂ NPs                      | Ba²⁺             | 55        |
|                                    | BN NPs                        | B(OH)₃           | 61        |
|                                    | Black P nanosheets            | H₂PO₄⁻/HPO₄²⁻⁻    | 74        |

#### 1.2 | Disturbing cellular communication

Single cells build up a tissue via cellular communication with metal ions (e.g., Ca²⁺, Zn²⁺, and Mg²⁺) as messengers or cofactors. Similarly, a tumor, as a microtissue, is made up of a heterogeneous collection of cell types, needing messengers to modulate cell signaling, cellular cooperation, and functional constraints, which are important for tumor development, including growth, differentiation, invasion, and metastasis. For example, Ca²⁺, as one of the key intracellular second messengers, rules tumor-stromal communication, angiogenesis, and tumor microinvasion. Zn²⁺ as an important messenger molecule acts in constructing the structure and function of many proteins, activating intracellular pathways and regulating cell fate. Interference with such messengers can certainly affect cell physiological functions and may even cause great damage to tumors.

As a typical case, an abnormal accumulation of intracytoplasmic Ca²⁺, named calcium overload, will induce severe oxidative stress, causing cell damage and death in numerous cell types. The underlying mechanism is vigorous mitochondrial respiration, which boosts a cascade of reactive oxygen species (ROS) generation, mitochondrial membrane damage, cytochrome C release, and caspase family activation. In 2019, our group exploited this destructive process for efficient antitumor therapy with CaO₂ NPs prepared via a simple and large-scale process. By concurrent introduction of massive exogenous Ca²⁺ and H₂O₂ in cells, the constant oxidative stress by H₂O₂ desensitizes calcium-related channels followed by an uncontrollable cellular accumulation of Ca²⁺, which hinders the accurate transmission of calcium signals and induces cell death. Notably, the concept of IIT, using the bioactive Ca²⁺ ions to disturb the important biological processes for cell death induction, was first proposed in this paper. Afterward, Yuan et al synthesized amorphous calcium carbonate (ACC) preloaded with curcumin (Cur) for effective Ca²⁺ generation by ACC in the acidic tumor environment and selective inhibition of Ca²⁺ expulsion by Cur, triggering persistent intracellular calcium overload for cancer-specific therapy.

As a pioneer study, Xing et al localized the Nd-sensitized core-shell upconversion nanoparticles (UCNPs) on cell surface via metabolic glycan biosynthesis strategy for optogenetic activation of ChR2 for Ca²⁺ influx-triggered apoptosis occurrence in Hela cells. Zn²⁺ shares some common characteristics with Ca²⁺, and thus, ZnO NPs or quantum dots have been synthesized to interfere with zinc ion homeostasis for selective cytotoxic effects against a broad range of cancer cell lines.

Though these essential metal ions are required for physiological functions, they can cause cytotoxicity, acute inflammation, and even an immune response in excessive concentrations. Disturbing cellular communication in situ without introducing exogenous ions is an ideal method for safe and effective antitumor therapy, but still remains a challenge. The endoplasmic reticulum is the largest store of releasable calcium in the cell, whose Ca²⁺ pumps can be regulated by redox conditions. Developing bioactive nanomaterials to regulate intracellular redox for calcium
overload in cancer cells is potential for tumor-specific therapy with high efficiency, without systemic side effects to the body.

1.3 | Activating biocatalysis

Biocatalysis has been viewed as an important technology in the pharmaceutical industry, driven by the increasing need for new and more effective medicines to patients. This is because biocatalysis offers substantial benefits, including reducing the cost of goods, number of synthetic steps and environmental impact, as well as improved safety and selectivity. Considering malignant tumors, cells change the nature of the microenvironment, and conversely, the microenvironment affects how a tumor grows and spreads. Although the structure and composition of the tumor microenvironment (TME) varies among different types of cancers and between patients, some common characteristics exist, such as mildly acidic conditions, hypoxia, and overproduction of \( \text{H}_2\text{O}_2 \) and glutathione (GSH). Therefore, using immobilized biocatalysts in tumors to enable the implementation of biocatalysis for the in situ generation of toxic drugs may be an ideal way for highly specific and selective tumor therapy. To attain this goal, a remarkable and attractive aspect of biocatalysis is the ability to rapidly generate catalysts that can then be optimized for a given substrate and reaction environment in tumor. Focusing on TME, \( \text{H}_2\text{O}_2 \) is a strong oxidant, but it is not very reactive because of its slow reaction kinetics with the majority of biomolecules. Thus, it can accumulate in cells and tissues at relatively high concentrations. However, in the presence of some catalysts, \( \text{H}_2\text{O}_2 \) can be activated to be more reactive oxidants, leading to severe oxidative stress and cell death. In 2015, our group successfully synthesized amorphous elemental Fe\(^{0}\) NPs with a disordered atomic structure that can rapidly ionize in mildly acidic conditions into Fe\(^{2+}\) and subsequently catalyze the reaction of \( \text{H}_2\text{O}_2 \) into the highly toxic \(-\text{OH}\). A series of Fe-based nanomaterials have since been prepared as potent biocatalysts for interfacial antitumor therapy.

Similar to Fe\(^{2+}\), some transition metal ions (ie, W, Mn, Cu, Ag, and Au) can also participate in peroxide-initiated free radical formation and culminate in ion-mediated antitumor therapy. Copper, as an essential element in living bodies, is mostly found bound to proteins and is generally recognized as a cofactor in many enzyme redox reactions via valence shifts between its two states, Cu\(^{2+}\) and Cu\(^{+}\). However, excessive free copper in the body can cause severe oxidative stress and systemic toxicity. This is because the Cu\(^{+}\)-catalyzed generation of \(-\text{OH}\) can occur in weakly acidic and neutral media, a distinct difference compared to the strong dependence of Fe\(^{2+}\) on acid (pH 2-4). Therefore, it is important to spatiotemporally restrict Cu\(^{+}\) in tumors and not in circulation for the effective generation of \(-\text{OH}\). To realize this, Li et al synthesized copper-amino acid mercaptide self-assembled NPs (Cu-Cys NPs) for GSH-activated and \( \text{H}_2\text{O}_2 \)-reinforced Cu\(^{+}\)-ion-mediated therapy. After endocytosis into tumor cells, the Cu\(^{2+}\) in the Cu-Cys NPs is reduced to Cu\(^{+}\) by GSH, and Cu\(^{+}\) will catalyze the reaction of \( \text{H}_2\text{O}_2 \) into \(-\text{OH}\). GSH depletion and \(-\text{OH}\) generation will lead to DNA damage, protein inactivation, lipid peroxidation, and ultimately cell apoptosis. Similarly, Shi’s group exploited Cu\(^{2+}\) for enhanced disulfiram (DSF)-based cancer chemotherapy. In mildly acidic conditions, the co-released Cu\(^{2+}\) and DSF from Cu\(^{2+}\)-doped, DSF-loaded hollow mesoporous silica NPs generated toxic dithiocarbamate-copper complexes, and concurrently, the immediately generated Cu\(^{+}\) will catalyze the reaction of high levels of \( \text{H}_2\text{O}_2 \) in tumors, resulting in the production of \(-\text{OH}\), which further enhances DSF-based cancer chemotherapy. These metal ion-included nanomaterials with biocatalytic effects indeed provide an alternative strategy for cancer treatment with high specificity and efficiency, and can promote the development of inorganic nanodrugs in biomedical science.

1.4 | Active targeting to DNA/proteins

The common side effects of chemotherapy invariably bring great suffering to patients and treatment delay due to gradually acquired drug resistance, dose reduction, or even discontinuance of chemotherapy. Anticancer targeting, which not only targets the whole tumor, individual cells, specific organelles, or molecules but also releases the active species at certain times or sites, is promising for enhanced chemotherapy with reduced side effects. Nanomaterials with the natural advantage of passive targeting (enhanced permeability and retention effect) have been developed with various extra targeting approaches, including targeting specific tumor conditions, active targeting, multistage targeting, and targeting by external stimuli. Active targeting is usually achieved by the addition of targeting components on/in nanomaterials for preferential accumulation in tumor itself, individual cancer cells, intracellular organelles, or certain molecules in cancer cells, based on specific interactions such as ligand-receptor, avidin-biotin, or antibody-antigen. In fact, realization of active targeting is possible by the use of specific ions to sense tumors and then to open the door for severe cytotoxicity. Therefore, specific ion-containing nanomaterials have been constructed for active targeting IIT.

1.4.1 | Platinum

Typically, platinum-containing drugs, as the most widely used anticancer chemotherapeutics, represent one of the great successes in the field of medicinal inorganic chemistry.
Studies have proven that the N7 atoms of purine residues guanine and adenine in DNA are the most nucleophilic sites, which are preferentially platinated, causing DNA structure distortion and cell death. So the platinum(II)/platinum(IV) complexes have been developed to actively target DNA for enhanced IIT. However, most of them usually show weak discrimination between healthy and tumor tissues, and are accompanied by drug resistance, a major hurdle to the success of chemotherapy.33 Constructing platinum-containing nanosystems to preserve their anticancer activity in circulation and targeting drug release in tumors is an effective approach. A peptide-stabilized platinum nanoparticle (PtNP) was developed against hepatic cancer cells (HepG2), but was not active, or only barely active, against other cancer and non-cancerous cells.34 Peptidic ligands enable the preparation of stable monodisperse PtNPs with average diameters of 2.5 nm, which can benefit their uptake into tumors. The high oxidative environment in HepG2 cells is the key to unleashing the cytotoxicity of PtNPs by oxidizing inert Pt0 to cytotoxic PtII.

Extensive studies have also focused on the development of functional nanodeliveries of platinum as active targeting anticancer prodrugs.35-41 Zhang et al first reported a polymer-cisplatin conjugate NP, Bi(PEG-PLA)-Pt(IV), with well-controlled drug loading yield, excellent acid-responsive drug release, and potent cytotoxicity against ovarian cancer.42 As an environmentally sensitive drug delivery vehicle, Bi(PEG-PLA)-Pt(IV) can potentially minimize Pt loss during circulation in neutral blood, trigger rapid intracellular PtIV release under acidic conditions, and further reduce PtIV to toxic PtII by overexpressing GSH in tumors. In fact, nanodeliveries with precise spatiotemporal drug release are highly desired for achieving potent cancer therapy with minimal adverse side effects. This drug release targeting may be achieved by applying external stimuli such as light, ultrasound, or electric or magnetic fields. As an example, Yang’s group synthesized a bifunctional platinum nanocomplex (PtNC) consisting of a zero valence Pt core surrounded by a bivalent PtII shell with tunable ratios through the facile and controllable reduction of a PtIV-coordinated polycarboxylic nanogel.53 Upon near infrared (NIR) light irradiation, these PtNCs achieved the rapid release of cytotoxic PtII due to the photothermal effect of the Pt core, thereby leading to light-reactive synergistic therapeutic damage to tumor cells.

1.4.2 | Silver

Silver (Ag) is another star element in the field of biomedical inorganic chemistry that has been proven with well-documented antimicrobial properties and has been widely used in treating wounds, burns, and catheter-related infections.44,45 Ag NPs have gained increasing interest as antiviral and anticancer agents.46,47 The underlying mechanisms include active targeting of Ag+ to proteins/DNA to disrupt cellular functions.48,49 To promote the degradation of Ag NPs into toxic Ag+ for ion-interference anticancer therapy, Huang et al reported a strategy that combined glucose oxidase (GOx) with silver nanocubes (AgNCs) (denoted as AgNC-GOx), which can oxidize the high concentration of intratumoral glucose into gluconic acid and H2O2 for the subsequent dissolution of AgNC into Ag+, to achieve synergistic cancer starving-like/metal ion therapy.50

1.4.3 | Barium

Identifying novel anticancer targets can undoubtedly put forward the development of new anticancer strategies, which may tackle previously unsolvable problems. Ion channels contribute to virtually all basic cellular processes and are also involved in the malignant phenotype of cancer cells.51 Among them, potassium channels show the highest variability and the most frequently altered expression in many tumor types and have been repeatedly proposed as potential anticancer targets.52,53 Ba2+, as a stable divalent metal ion, can strongly bind to potassium channels to prevent the outflux of K+, which can further affect cell membrane potential and osmotic homeostasis, and finally induce inhibition of cell proliferation and death. Therefore, Ba2+ has great potential for IIT, but its acute and chronic toxicity due to common channel targeting in normal tissues should be seriously considered.54 In 2019, our group rationally designed N, N-bis(carboxymethyl)-L-glutamic acid tetrasodium salt (GLDA) chelator-modified barium peroxide NPs (GL-BaO2 NPs) for combined Ba2+-IIT and radiotherapy with increased therapeutic efficacy and specificity and reduced side effects.55 In normal tissues, GLDA can strongly bind to the leaked free Ba2+, thus reducing unwanted side effects. In tumor tissue, the generated -OH upon X-ray irradiation breaks the chemical structures of the chelators, and consequently, the released Ba2+ will bind to potassium channels to contribute to tumor radiotherapy. Such interference effects might substantially improve the currently available treatments, offering a new window for cancer treatment.

1.4.4 | Boron

Boron (B) has well-established biochemical and nutritional functions. An epidemiological study showed that boron-enriched diets can reduce the risk of cancers, including prostate, breast, cervical, and lung cancer. This protective effect seems to be independent of other risk factors, such as age, smoking, obesity, and race.56 B exists in the human body mostly in the form of B(OH)3 (boric acid, BA, 98.4%). BA has a similar structure to carbon and can act as a
competitive inhibitor to some carbon-containing substrates, such as some enzymes (peptidases, proteases, proteasomes, arginase, nitric oxide synthase, and transpeptidases). By directly inhibiting enzymatic activity, BA can control the proliferation of some types of cancer cells. Studies have proven that at an appropriate concentration, BA in the blood can lower the risk of prostate cancer by inhibiting the NAD (nicotinamide adenine dinucleotide) metabolite cADPR, and in tumor sites, BA can specifically inhibit prostate cancer cell proliferation by actively targeting a serine protease. However, the short circulation time, low bioavailability, and low fraction arriving at the tumor all largely limit the effectiveness of BA for prostate cancer treatment. Developing B-based chemicals for chemoprevention and chemotherapy in prostate cancer may be an effective solution. Golberg et al fabricated hollow boron nitride (BN) nanospheres with controlled crystallinity and B release, facilitating the passive enrichment of B in tumor sites and the specific inhibition of enzymatic activities in cancer cells to inhibit proliferation and induce apoptosis for both androgen-sensitive LNCap and androgen-independent DU145 prostate cancer cells. Additional insights into the molecular basis of cancer apoptosis will facilitate the rational design of B-based nanomedicines for specific therapeutic interventions for cancer.

### 1.4.5 Phosphorus

Phosphorus (P) is the second most abundant mineral in humans, and as an essential nutrient, it is abundant in the diet. In body fluids, P presents mainly as inorganic phosphate (P\(_i\)) in the form of H\(_2\)PO\(_4^-\)/HPO\(_4^{2-}\), which plays key roles in diverse physiological functions, such as osteoblast differentiation and skeletal mineralization. Increasing evidence indicates that P\(_i\) also acts as a global signaling molecule in modulating multiple cellular functions by altering signal transduction pathways, gene expression, and protein abundance in many cell types. Naviglio et al proved that P\(_i\) inhibited proliferation in both MDA-MB-231 breast cancer cells and human osteosarcoma U2OS cells by slowing cell cycle progression. The induction of sensitization of cells to doxorubicin was also found in P\(_i\)-treated U2OS cells in a p53-dependent manner. Notably, the serum P\(_i\) concentration is critical for the well-being of the organism. P\(_i\) deficiency can lead to bone impairment, central nervous system dysfunction, rhabdomyolysis and muscle weakness, cardiac dysfunction, and respiratory failure, whereas an increase in P\(_i\) may induce seizures, cardiac dysrhythmias, soft tissue calcification, renal failure, and even influence the ageing process and lifespan. Therefore, targeting P\(_i\) levels at local sites might represent a rationale to develop P\(_i\)-based IIT for therapeutic intervention in cancers. Black phosphorus nanosheets (BPs) have been demonstrated to have high bioactivity due to their inherent and selective chemotherapeutic effects. Yu’s study showed that BPs could degrade spontaneously in the presence of water and oxidative stress within cancer cells to release P\(_i\) in tumor sites for local retention, but this did not occur in normal cells. The acute elevation of phosphate anions could induce G2/M phase arrest and subsequent apoptosis- and autophagy-mediated cell death in different cancer cell lines, exhibiting ideal selectivity for tumors and biocompatibility with normal tissues. This study also provided insights into the development of P-containing nanomaterials as direct bioactive anticancer agents or as drug delivery systems for cooperative chemotherapy.

### 2 SUMMARY AND OUTLOOK

In summary, aberrant distribution/accumulation of ions in cancer cells will lead to cell damage and final death, which expedites a new tumor therapeutic modality, IIT. From our above discussions, several important points are summarized as follows: (a) changing cellular electrochemical potential via the absorption or direct transport of ions; (b) interference with cellular communication via the accumulation of ion messengers in cells; (c) activation of biocatalysis by the release ions in tumors for in situ cytotoxic species generation; and (d) active targeting intracellular DNA, proteins, or enzymes to open the door for severe cytotoxicity. These points are of critical importance for the design of functional nanomaterials to move this field forward. Of note, the current research has mainly focused on effects of single ion in cells, and the understanding of how these ions are integrated in the cellular milieu has not yet been considered. Future advances in IIT will require a better understanding of the interaction of all ions in the context of both tumor tissues and their microenvironments in order to fully appreciate how cells respond to the designed nanodrugs in a way that maximizes their utility and minimizes their inherent toxicity in biological systems.

### CONFLICT OF INTEREST

The authors declare no conflict of interest.

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