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Self-Therapeutic Nanomaterials for Cancer Therapy: A Review

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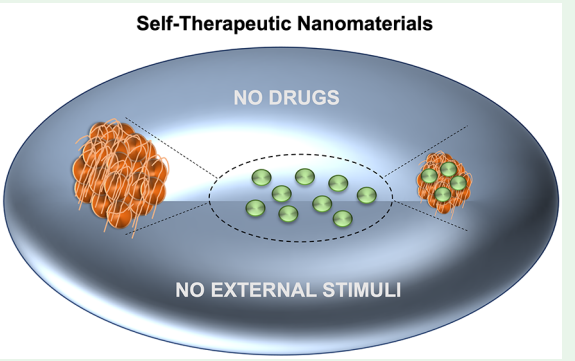
ABSTRACT: Cancer is a commonly lethal disease that causes many deaths every year around the world. Many strategies have been applied to treat cancer, such as surgery, radiation, and chemotherapy, but all of these therapeutic approaches are limited. Nanotechnology could provide a tremendous platform to boost the efficacy of therapeutic systems from the bench to clinical applications. The current trend of using nanomaterials for therapeutic applications is limited to drug delivery and external stimuli-responsive systems. However, several nanomaterials can reduce the growth of aggressive tumors through their self-therapeutic properties. In this review, we discuss the self-therapeutic nanomaterials that can kill cancer cells without the need for any external stimulation (heat, light, radiation, or a magnetic field) or the loading of any extra therapeutic compounds. These nanomaterials can produce reactive oxygen species, act as deoxygenating agents, or produce free radicals at tumor sites. Self-therapeutic peptide-based and other organic nanomaterials that are used to inhibit multidrug resistance (MDR) proteins, e.g., P-glycoprotein (P-gp), are also discussed. This review discusses the possible mechanisms of action of self-therapeutic nanomaterials for cancer inhibition, highlighting critical and future aspects.



KEYWORDS: *cancer, self-therapeutic nanomaterials, drug delivery, prodrug, drug*

1. INTRODUCTION

Cancer is the second most common cause of death around the globe. It killed 9.6 million people in 2018. According to the WHO, one in five men and one in six women will develop cancer in their life and one in eight men and one in 11 women will die from this serious disease.[1] Several methods have been developed for treatment, but there are still no available approaches that can completely eradicate this life-threatening disease. Cancer therapy is currently mostly limited to surgery, radiation, and chemotherapy, but they each have several disadvantages and often fail to cure the condition.[2]

Recently, nanomaterials have attracted much attention from scientists interested in cancer therapy because of their versatile physical and chemical properties.[3] Many reports have focused on the use of nanomaterials as carriers of therapeutic compounds. These therapeutic systems have been extended by introducing external stimuli (e.g., light, magnetic waves and heat) to improve drug release at the tumor sites. These approaches can be further subdivided into photodynamic, photothermal, magnetic, and neutron-capturing systems. Unfortunately, the use of nanomaterials as carriers of therapeutic compounds has some flaws, which preclude these therapeutic systems from clinical applications. The major challenges are a low drug loading efficiency, low solubility in an aqueous media, poor ability to cross in vivo barriers and penetrate inside the tumor (less than 1% reach the tumor), problematic physical and chemical interactions of hydrophobic therapeutic compounds with nanomaterials, in vivo instability, a suboptimal biodistribution, low tumor targeting ability, and a suboptimal drug release profile.[4] To minimize all of these issues and bring nanomaterials from the bench to clinics, scientists are trying to develop optimized self-therapeutic nanomaterials that can work like a "magic nano bullet" without the loading of additional therapeutic compounds or external stimuli dependency to make these systems practical for clinical applications.

Most of the organic nanoparticles (liposomes, micelles, exosomes, lipids, PLA, PLGA),[5] inorganic nanoparticles (gold, silver, silica, iron, graphene, carbon quantum dots), and composites (metal−organic frameworks (MOF), transition metals dichalcogenide (TMD)) were designed as carriers in drug-delivery systems[6] or for use in external stimuli-based systems such as photodynamic therapy (PDT),[7] photothermal therapy (PTT),[8] magnetic therapy,[9] and boron neutron-capturing therapy (BNCP).[10] All of these external dependencies and low loading efficiency of therapeutic compounds are shortcomings, which has led to the failure of these systems at

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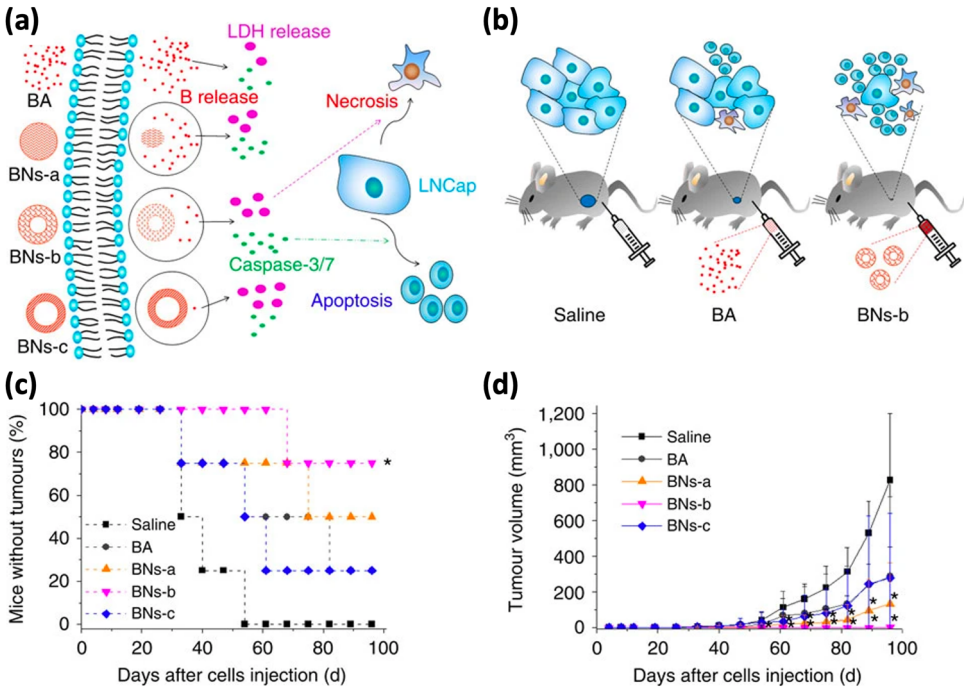

Figure 1. In vitro and in vivo effects of boron nitride nanospheres (BNs). (a) Different levels of necrosis (LDH) and apoptosis (caspase 3/7) in prostate cancer cells due to the release of boron from BA or hollow BN spheres. (b) BNS, BA, and saline effects on LNCap mouse tumor models. (c) Effect of different formulations of boron on the inhibition of tumor growth and (d) tumor volume in mice models. Reproduced with permission from ref 23. Copyright 2017 Springer Nature.

the clinical level. Additionally, these therapeutic systems need specific special equipment that is difficult to use and requires confining the patient in the hospital.

In this review, we will go over the available data on nanotherapeutic systems derived directly from nanomaterials through some specific mechanisms (using the intrinsic properties of the materials) and discuss the possible future uses of these systems.

2. DIRECT CANCER THERAPY DRIVEN BY NANOMATERIALS

The application of nanotechnology to cancer therapy could extend beyond drug delivery into the creation of new therapeutics able to destroy the tumors with minimal damage to healthy tissues and organs, as well as the detection and elimination of cancer cells during the initial stage of tumorigenesis. These relatively small particles can also be functionalized with ligands, nucleic acids, peptides or antibodies that bind to specific target molecules. Because of certain intrinsic properties of nanomaterials (reaction with oxygen species, heat and hazardous gas producers) and biocompatibilities, they are quite interesting to use directly for therapeutic purposes. Herein, we summarized self-therapeutic nanomaterials that were successfully used to target and eradicate cancer cells along with their possible mechanism of action in cancer treatment.

Metalloid Boron as an Enzyme Inhibitor. Neutron-capturing therapy is usually done with compounds containing boron. Locher was the first to report on the biological effects and therapeutic possibilities of boron neutron-capturing therapy (BNCT).[11] BNCT is based on nuclear capture and fusion reactions when nonirradiated boron-10 (B^{10}) is irradiated with low energy neutrons to form $^{4}He+^{7}Li+$ fusion energy (E). The reaction mechanism is presented below:

$$^{10}B + n \rightarrow {}^{11}B^{*}$$

$$^{11}B^{*} \rightarrow {}^{4}He + {}^{7}Li + E$$

These nuclei produced closely spaced ionizations (the production of alpha particles and heat) of a path length of approximately one cell dimension (5−7 μm) that is used to destroy cancer cells.[12] The neutron-capturing property is limited only to boron-containing cells and external neutron radiation bombardment.[13] Several boron therapeutic compounds such as sodium borocaptate and boronophenylalanine are in clinical trials for neutron-targeted therapy,[13] but there is still a need for external stimuli by neutron bombardment to produce $^{4}He+^{7}Li+E$.

In the literature, there are some reports in which boron-based compounds were directly used for the growth inhibition of different cancer cells. The biological roles of boron include the regulation of gene expression, growth, and proliferation.[14] Boron is used in synthetic chemistry because of its unique characteristics that allows it to form a covalent bond with carbon. Mostly, trivalent boron reagents are electrophiles and when they get a pair of electrons from nucleophiles, they adopt a tetrahedral configuration (sp^3) to satisfy the octet rule. Generally, the conversion of sp^2 carbonyl carbon to sp^3 tetrahedral carbon inhibits the activity of enzymes. Therefore, the substitution of carbon by boron is a good transition state analogy for the suppression of hydrolytic enzymes. Additionally, boron has a strong affinity for oxygen-forming borates that are involved in the inhibition of enzymes.[15]

Bortezomib is an FDA-approved drug for treating multiple myeloma and mantle cell lymphoma.[16] The clinical development of bortezomib (trade name Velcade) occurred after the

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discovery of the ability of boron to reversibly inhibit the proteolytic/chymotryptic activity of the 26S proteasome subunit in mammalian cells.[17] Suppression of the intracellular protein degradation pathway (proteasomes) changes the levels of multiple intracellular signaling and regulatory proteins in addition to altering the regulation of cellular processes that can lead to growth arrest or apoptosis. In vitro studies showed that bortezomib is oxidatively metabolized primarily through multiple cytochrome P450 enzymes. The main metabolic pathway is deboronation to create two metabolites that are hydroxylated to inactive metabolites.[18]

Recently, boron compounds have gained interest as protective and therapeutic agents for prostate cancer and other cancers.[19−22] Boric acid (BA), the predominant form of boron in plasma, shows boron-mediated anticancer mechanisms in prostate cancer by reducing intracellular calcium signals and calcium storage, decreasing enzymatic activities (serine protease, NAD-dehydrogenases, etc.) and finally inhibiting cancer cell proliferation.[23]

In 2004, Barranco et al. used boric acid for the treatment of human prostate cancer cells.[14] Boron depleted media was prepared by its treatment with boron specific ion-exchange resin, which was added to the supplemented media of the DU-145 and LNCaP prostate cancer cell lines. The growth of the cancer cell lines were inhibited in a dose-dependent manner. For nontumorigenic cells, the required dose to inhibit growth was much higher.[14]

Recently, an interesting report was published by Ciofani et al. about the synthesis of hexagonal boron nitride nanoparticles for prostate cancer therapy. The authors synthesized hexagonal boron nitride nanoparticles by a tube furnace method at a high temperature (1300 °C) while using boric acid and ammonia as precursors for boron and nitrogen sources, respectively.[24] The synthesized hexagonal boron nitride nanomaterials were degradable in an aqueous media and showed a high cellular internalization profile. The mechanism of action was explained by the production of reactive oxygen species (ROS), which results in damage to membrane lipids, protein, and DNA as critical cell components, and mitochondrial dysfunction, which activates the apoptotic processes.

In 2014, Li et al. prepared hollow boron nitride nanospheres (BNs) as a boron source for prostate cancer therapy. The authors synthesized the BNs by a traditional chemical vapor deposition (CVD) method. After the CVD reaction, the precursor of BN was collected and further heated at different temperatures (900, 1025, and 1400 °C) in an argon (Ar) atmosphere to improve its crystallinity and allow for controlled boron release. The authors examined two key damage-associated pattern protein markers: caspase-3/7 to evaluate apoptosis and lactate dehydrogenase (LDH) release to evaluate necrosis. The results indicated that apoptosis and necrosis are enhanced by BN spheres compared to boric acid in vitro. The authors also investigated the in vivo anticancer effectiveness of BA and hollow BNs in subcutaneously and orthotopically injected LNCap prostate cancer cell mouse models. It was shown that BNs and BA significantly suppressed prostate tumor growth compared with the control (Figure 1).[23] Besides, taking advantage of the hollow shape of the BNs and their maximum surface to volume ratio, paclitaxel was loaded successfully to simultaneously use the system as a traditional drug-delivery system. Significant tumor inhibition was observed with BNs loaded with paclitaxel in both in vitro and in vivo experiments.

Boron compounds can also be effectively used in Prostate-Specific Antigen (PSA) mediated tumor growth. PSA is a serine protease and is one of the most abundant proteins secreted with chymotrypsin-like activity in human prostate epithelium and it is a well-established marker of prostate cancer.[25] PSA is thought to cleave insulin-like growth factor-binding protein-3 (IGFBP-3) and lead to tumor growth by increasing local IGF-1 levels and its mitogenic capabilities.[26] Gallardo-Williams et al. used boron supplementation to inhibit the growth and local expression of IGF-1 in human prostate adenocarcinoma cells (LNCaP) implanted in nude mice.[25] Moreover, boron-enriched diets result in inhibition of different kinds of cancers such as lung, prostate, and cervical cancers because of boron's role in a variety of enzymatic inhibitions such as serine proteases, NAD-dehydrogenases, and mRNA splicing, as well as receptor binding mimicry and the induction of apoptosis.[21] All of these findings together have opened up a new way to cure cancer by synthesizing biocompatible self-therapeutic boron-based nanomaterials.

The common concept in all of these reports is that the arrest of cancer growth is mediated by boron atoms. Many boron-based nanomaterials such as boron nitride nanosheets, nanotubes, nanoparticles, and rare earth boride nanostructures have been synthesized by several different methods such as CVD, hydrothermal methods and electrochemical methods.[27] Boric acid and boron nitride are the most abundant forms and could be a good source of boron atoms for therapeutic applications. Because they are highly soluble in biological fluids,[23] nanomaterials with a certain crystallinity as a boron source would be a good choice for therapeutic applications. Mateti et al. synthesized different types of boron nitride nanomaterials and tested Saos-2 osteoblast-like cells for compatibility tests.[28] The authors claim that biocompatibility strongly depends on their size, shape, structure, and surface chemical properties and that cell death is caused by the unsaturated boron atoms located at the nanosheets edge or on the particle surface. Therefore, for therapeutic applications, boron-based nanomaterials should have a structure and chemical and surface properties where plenty of unsaturated boron atoms are present. The structure should be not too amorphous because boron atoms will dissolve in biological fluids before reaching the tumor sites, and not too stable since it needs to be biodegradable and provide enough boron to arrest the tumor growth, regardless of any method of synthesis. Additionally, the replacement of other atoms such as carbon with boron could be another choice to inhibit cancer-related enzymes as previously discussed.

Oxygen-Capturing Approach. Though it is obvious, the primary tumor or metastasis can grow to a size of about 1−2 mm^3 if provided a sufficient supply of oxygen and nutrients by diffusion, but tumor growth beyond this size requires vascularization, a process called angiogenesis.[29] When tumors switch to an angiogenic phenotype, which refers to a phenotypic change in an early stage of tumor development necessary for growth beyond 2−3 mm in size, an angiogenic switch is triggered and attracts the growth of blood vessels.[30]

Angiogenesis is controlled by the upregulation of stimulators and the downregulation of inhibitors, which could trigger the angiogenic transduction pathway, which plays a pivotal role in tumor growth, progression, and metastasis of cancer.[31] Antiangiogenic strategies alone might not be effective enough to eradicate tumors due to the excessive compensatory mechanisms by which blood vessels will be remodeled.[32,33]

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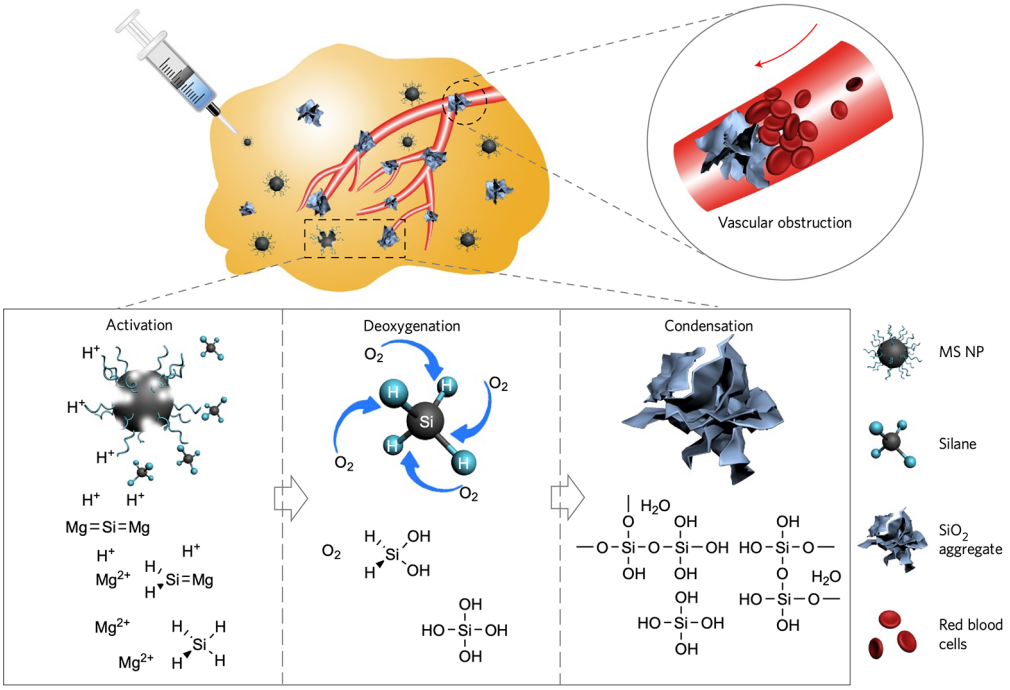

Figure 2. A schematic illustration of intratumoral deoxygenation utilizing magnesium silicide nanoparticles (MS NPS): Reproduced with permission from ref 38. Copyright 2017 Springer Nature.

Most antiangiogenic small molecule drugs cause toxicity and require the development of new strategies in a suitable delivery system.[34] Moreover, abnormal or leaky tumor vasculature during tumor angiogenesis results in poor delivery of angiogenic inhibitors, exhibiting a poor pharmacokinetic profile within the tumor stroma. In this respect, nanomedicine plays a crucial role.[35] Because of the small size and high surface volume ratio of nanotheranostic-based antitumor agents, they can be used to more effectively target tumor endothelial cells.[36] In this scenario, several investigators demonstrated novel nanotechnology-based diagnostic and therapeutic approaches for the treatment of cancer. Mukherjee and Patra provided some examples of new nanomaterials including copper, carbon, silver, gold, silica, chitosan, and peptides conjugated with antiangiogenic properties.[37] The limits of these approaches are their dependence from external drugs and stimuli and the accumulation of toxic metals or byproducts in the human body. To overcome these hurdles, Zhang et al. developed nanomaterials that can not only stop the growth of unwanted blood vessels by blocking them with their soluble byproducts but could also deprive tumor cells of oxygen, resulting in the inhibition of tumor growth.[38] It was also reported that magnesium silicide nanoparticles (MS NPS) could be used as deoxygenation agents for cancer therapy (Figure 2).[38]

In this report, the authors synthesized injectable MS NPs by self-propagating high-temperature synthesis in an O_2/Ar mixed-gas atmosphere. The excess of O_2 exothermally reacted with the excess of Mg followed by a subsequent combination reaction between Mg and Si, yielding Mg_2Si/MgO mixed particles with a core−shell morphology (Mg_2Si core within a thin outer MgO shell). The product (Mg_2Si/MgO) was purified to obtain Mg_2Si and remove the MgO particles (because it could inhibit the unwanted growth of grains) and was further modified with polyvinylpyrrolidone (PVP) to rapidly absorb molecular oxygen from cancer cells by acting as a deoxygenation agent (DOA) and to block tumor capillaries from being reoxygenated. In a mouse model, tumor growth was significantly inhibited. It was claimed that the byproducts (waste) of the nanomaterials were used to cover the blood capillaries that provided oxygen to the tumor. The possible mechanism of action is presented below:

$$Mg_2Si + 4H^+ \rightarrow 2Mg^{2+} + SiH_4$$

$$SiH_4 + 2O_2 \rightarrow 2H_2O + SiO_2$$

Here, the Mg_2Si nanoparticles capture oxygen from the tumor and leave the bioproduct SiO_2, which is useful to cover up the ends of unwanted tumor vessels and maintain intratumoral hypoxia without any long-term toxic effects. Hence, synthesizing these kinds of materials with specific properties such as oxygen capture together with the blockage of extra blood vessels by their byproducts could bring about advances in antiangiogenesis therapy.

The synthesis of other biocompatible nanomaterials for use as deoxygenation agents based on SiO_2 and manganese-based materials is demanding in the current therapeutic systems. Any technique adopted to synthesize these type of materials as deoxygenation agents is worthwhile provided that the byproducts are biocompatible or safely eliminated from the body and the material (composite) has the ability to absorb certain levels of oxygen from the tumor microenvironment (one mole of material in its composite byproduct form could have the ability to consume two moles of oxygen molecules or even more).[38]

Highly Toxic Hydroxyl Radical Ions for Cancer Cell Death. The Fenton chemical reaction mechanism is utilized in cancer by converting H_2O_2 (present at a much higher concentration than in normal cells, ranging from 100 μM to 1 mM in the tumoral microenvironment) into highly toxic hydroxyl free radicals ($OH^{\cdot}$) to efficiently kill cancer cells and suppress tumor growth.[39−43] Several research groups have

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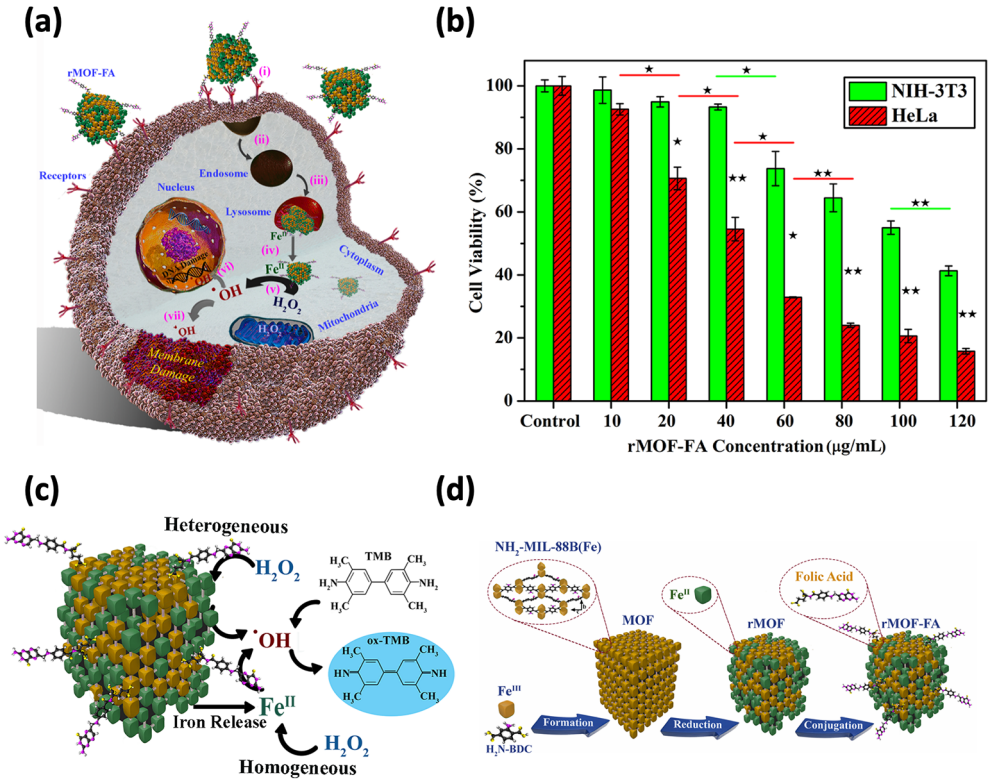

Figure 3. Fenton chemical approach to OH· ion therapeutic systems. (a) Schematic illustration of rMOF-FA nanoparticles for cancer therapy. (b) rMOF-FA effects on HeLa and NIH-3T3 cells. (c) Peroxidase-like activity of rMOF-FA nanoparticles. (d) Synthesis scheme of rMOF-FA nanoparticles. Reproduced with permission from ref 39. Copyright 2017 American Chemical Society.

published the synthesis of different nanomaterials such as Fe_2O_3, $MnFe_2O_4$,[44] FeOx-MSNs,[45] silver,[46] gold,[47] and α-Fe_2O_3[48] that take advantage of the Fenton reaction mechanism to kill cancer cells.

Zhang et al. developed amorphous iron nanoparticles (AFeNPs) as cancer theragnostics while taking advantage of overproduced H_2O_2 in the tumor using the Fenton chemical process. The AFeNPs were synthesized by a hubble-bubble technique where Fe^{3+} was designed to occur in a bubble film constructed from an amphiphilic block copolymer F-127 (Pluronic). The precursor solution was confined in the small space between the F-127 bilayers to limit the long-range diffusion of iron atoms and to suppress the nucleation and growth of the crystalline phase of FeNPs. The addition of PVP to increase the viscosity and a citrate chelator to decrease the concentration of free iron ions further controlled the formation of FeNPs. Finally, a freeze-drying technique was used to obtain fragments of the bubble film.

The amorphous structure and the ionization of AFeNPs enabled the on-demand release of a ferrous ion into the tumor, which led to the production of an excessive amount of OH· free radicals in the tumor microenvironment.[49] The Fenton chemical reaction with iron ions (Fe^{2+}, Fe^{3+}) in the presence of H_2O_2 to produce free radicles (OH·) is shown below.

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^{\cdot} + OH^{-}$$

$$Fe^{3+} + H_2O_2 \rightarrow Fe^{2+} + HO_2^{\cdot} + H^{+}$$

Ranji-Burachaloo et al. synthesized a reduced iron-based metal−organic framework attached to folic acid (rMOF-FA) as a controlled released source of iron in an acidic environment (characteristic of tumor sites). The rMOF-FA was synthesized by a simple hydrothermal method where Pluronic F-127 as a surfactant and ferric chloride ($FeCl_3 \cdot 6H_2O$) as precursor solutions were mixed followed by the addition of acetic acid and the precipitate was transferred into an autoclave. For the reduction of iron-based MOF, it was treated with hydroquinone that was further functionalized with folic acid (FA) by EDC/NH chemistry to obtain rMOF-FA and used for the controlled release of iron in acidic conditions. The released iron reacted with H_2O_2 in tumor sites to produce OH· ions that further oxidized protein lipids and DNA to decrease cell viability. The in vitro experiments showed that rMOF-FA is highly toxic to cancer cells (HeLa) because of the production of free radicals (OH·), whereas they are much less toxic for normal cells (NIH-3T3) (Figure 3).[39]

Because the Fenton mechanism suffers from low-level production of free radicals OH· ions, many research groups have improved this approach by combining it with other therapeutic systems such as sono-fenton,[50] photofenton,[51] photothermal therapy (PTT), and chemotherapy.[52] Several other research groups also proposed different compounds besides iron, which could produce Fenton-like reactions using cations such as Mn^{2+}, Cu^{1+}, Cr^{4+}, and V^{2+}.[53] The overall compound should have the capacity to release cations gently to start a Fenton-like reaction and the material should be biodegradable enough to provide cations in the tumor microenvironment.

Self-Therapeutic Organic Nanomaterials. Organic materials such as peptide-based nanomaterials are used in medicine for therapeutic applications. The major advantage of peptide-based therapeutic systems is that they could target

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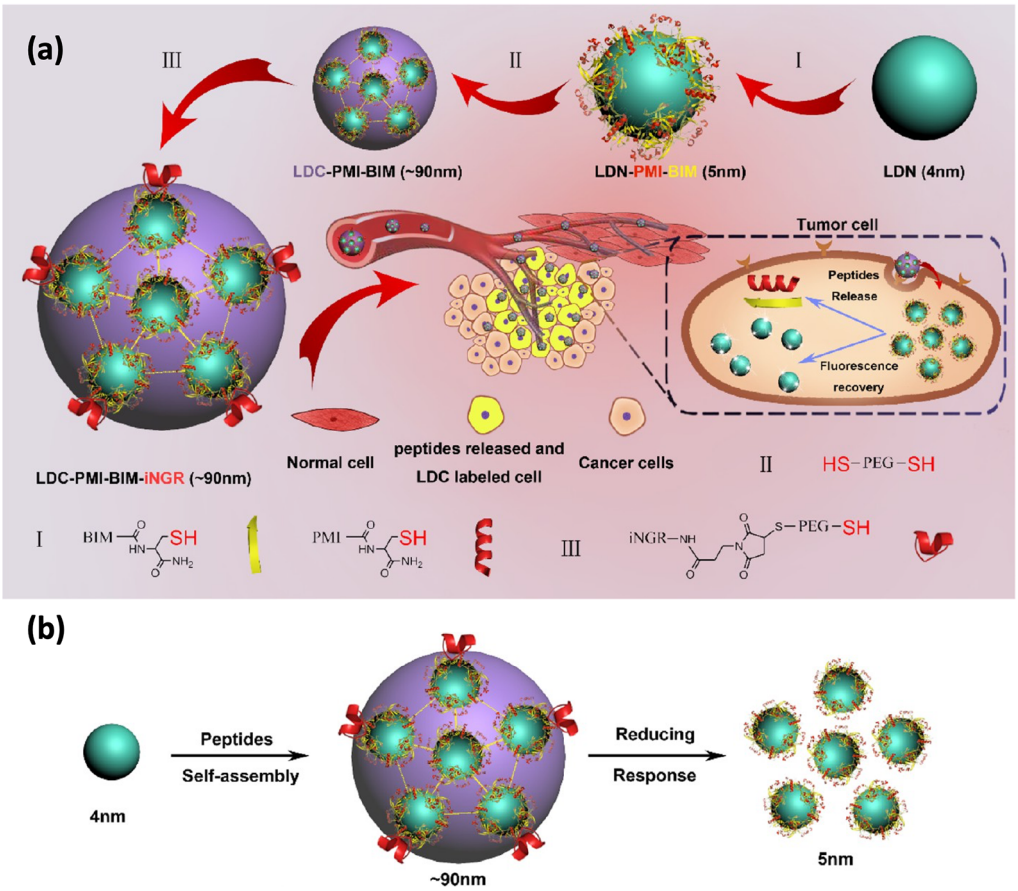

Figure 4. Schematic diagram of peptide-based nanoclusters and their anticancer activity: (a) Graphical illustration for the construction of lanthanide-doped nanoclusters (LDC) and their cancer cell killing activity. (b) Schematic diagram of the production of small nanoparticles by the disintegration of large size nanocluster in the reducing intracellular environment. Reproduced with the permission of ref 60. Copyright 2018 American Chemical Society.

cancer cells with lower toxicity to normal tissues.[54] The $(KLAKLAK)_2$ (KLAK) amphiphilic peptide is a well-known antitumor peptide widely used in cancer therapy in vitro and in vivo that suppresses the growth of aggressive tumors by damaging the membrane of mitochondria.[55] Wang et al. prepared a library of KLAK- based nanomaterials for cancer therapy by in situ polymerization and optimized the nanomaterials with different ratios and components.[56] The beclin1 peptide is another tumor suppressor peptide; however, the in vivo application of this peptide is limited because of its low stability. The stability of this peptide was improved by a supramolecular approach, conjugating poly(β-amino ester)s with the beclin1 peptide (P-Bec1), which significantly enhanced its in vivo stability, extending its circulation time and EPR effect. The (P-Bec1) nanoparticles were tested in MCF-7 breast cancer cells and showed enhanced cytotoxicity and in vivo therapeutic effects.[57]

MDM2 is an E3 ubiquitin ligase that can target p53 for polyubiquitination and proteasomal degradation.[58] For restoring p53 tumor suppression activity, the disruption of interactions between the MDM2 and p53 axis is a promising strategy. PMI, a potent inhibitor of MDM2-p53 interactions, can efficiently activate p53 and the downstream BH3-only family proteins (such as Bim, PUMA, and NOXA) to promote apoptosis by sequestering antiapoptotic Bcl-2 family proteins. However, because of its low proteolytic stability and poor cell-membrane penetration, the tumor-inhibiting activity of PMI is severely limited.[59] Yan et al. suggested combining the BIM peptide, which forms the BH3 domain of the pro-apoptotic Bim protein, with PMI in a nanoplatform-based peptide delivery system to achieve potent antitumor activity. The peptide−lanthanide clustered nanosystems (LDC-PMI-BIM-iNGR) were synthesized through thiol−poly(ethylene glycol)−thiol (SH-PEG-SH) polymer-induced molecular assembly of three peptides (PMI, BIM, and a cyclic peptide iNGR targeted to cancer cells) with biocompatible lanthanide-doped fluorescent nanoparticles (LDN). LDC-PMI-BIM-iNGR were tested in vitro and in vivo and showed lower systemic toxicity and off-target effects than doxorubicin, a commonly used chemotherapeutic agent, achieving a safe and reliable antitumor efficacy (Figure 4).[60]

Several other self-assembled peptide-based nanomaterials for therapeutic applications have been well summarized by Qi et al.[55] and Wu et al.[54]

MDR is one of the major problems for traditional chemotherapeutic systems and one of its mechanisms is the overexpression of drug efflux pumps, such as P-glycoprotein (P-gp), which expel different agents out of the tumor cells. Several P-gp inhibitors have been developed. Tuguntaev et al. synthesized vitamin E derivatives by combining P-gp inhibitors to overcome MDR. The authors developed a nanomicellar drug-delivery system with a thin-film hydration technique as a carrier for doxorubicin in which D-α-tocopheryl polyethylene glycol 1000 succinate was used as a P-gp inhibitor. The system

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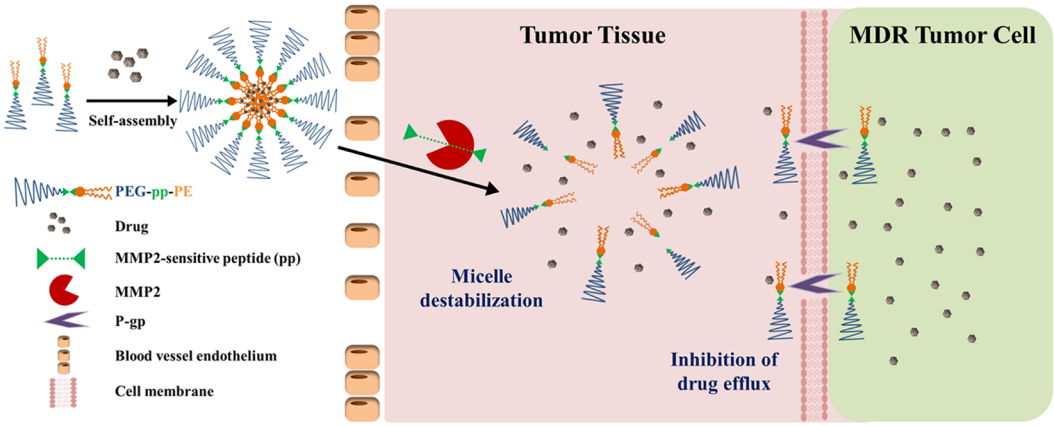

Figure 5. P-gp inhibition by PEG-pp-PE micelles. Reproduced with permission from ref 62. Copyright 2016 American Chemical Society.

showed excellent cytotoxicity for in vitro and in vivo experiments.[61] In another report, Dai et al. prepared self-assembling polyethylene glycol-phosphoethanolamine-based copolymers (PEG-pp-PE) as a targeted delivery system and as an inhibitor of P-gp (Figure 5).[62] Kou et al. summarized several other examples of P-gp inhibitory nanomaterials and their applications as drug-delivery systems.[63]

The synthesis of these organic nanomaterials always depends on considering their action to inhibit cancer tumors, e.g., peptide-based nanoclusters are used to enhance their in vivo stability and penetration abilities inside tumors. Similarly, P-gp inhibitors are conjugated to increase their in vivo stability and enhance their cytotoxicity. However, the overall synthesis of the materials should follow the same standards as defined in the literature for any drug-delivery systems such as size, shape, and surface properties, with safe elimination of byproducts.

3. OTHER SELF-THERAPEUTIC NANOMATERIALS

In recent years, other reports have been published about the anticancer abilities of nanomaterials and their byproducts. Recently, Li et al. published a report about the biodegradation of graphene-based nanomaterials in blood plasma and their in vitro and in vivo antitumor abilities. After incubating graphene (G) and graphene oxide (GO) in blood plasma at 37 °C for several days, the resulting nanomaterials were tested for their antitumor abilities in in vitro and in vivo experiments.[64] The results showed that the pristine graphene-based materials caused secondary structure damage to proteins and disturbances of cellular metabolic pathways while the bio transformed materials (degraded) were biocompatible and influenced specific organ therapies. The materials were further used as traditional drug-delivery systems by the loading of doxorubicin. The bio-transformed materials exhibited high efficiencies of drug delivery and more pronounced targeting and tumor-killing abilities. In another report, Law et al. used a panel of cobalt tris (bipyridine) systems having an anticancer effect with collateral sensitivity toward multidrug resistance (MDR) cancers. The authors synthesized cobalt complexes (1−6) by a simple hydrothermal method from cobaltous chloride and ammonium hexafluorophosphate as precursors.[65] To confirm the anticancer abilities of the cobalt complexes in MDR cells, the authors utilized a panel of different MDR cells with different origins. The results showed that the cobalt complexes were able to specifically induce collateral sensitivity in Taxol-resistant and p53-deficient cancer cells.

A very interesting report has also been published by Jiang et al. using sodium chloride nanoparticles (SCNPs) synthesized from sodium oleate, molybdenum chloride, and oleylamine as a surfactant.[66] Mammalian cells maintain low ratios of intracellular to extracellular sodium and chloride and high ratios of potassium and these asymmetric ionic gradients are involved in the regulation and control of cell function.[67] Reducing and increasing extracellular sodium and chloride concentrations can cause cytoskeleton destruction, cell cycle arrest, and cell lysis. In light of all this information, the authors hypothesized that NaCl nanoparticles could be used as a Trojan horse strategy to deliver ions to cells and cause a disruption of ion homeostasis.[68] The NaCl nanoparticles enter the cell through endocytosis, bypassing the physiological ion-transport system, and release Na^+ and Cl^- ions inside cancer cells because of their high solubility, causing a surge of osmolarity and rapid cell lysis.[66]

All of these reports could support the efforts of scientists to develop self-therapeutic nanomaterials with future applications in cancer therapy.

4. CHALLENGES AND FUTURE PERSPECTIVES

There is an urgent need for researchers to develop self-therapeutic nanomaterials and successfully transition them from the bench to clinics. Since these are single-step therapeutic systems, there is no need to load any extra therapeutic compounds, such as the therapeutic systems in which nanomaterials are used only as drug carriers.

Although self-therapeutic nanomaterials still contain many drawbacks of the classical nanomaterials utilized for drug-delivery systems such as bioincompatibility and poor tumor-targeting ability,[69,70] their reduced complexity could assist in faster translation to the clinic. Combining the intrinsic therapeutic features of nanomaterials[71] without any external stimuli or other agents in one nanosystem could exhibit superior anticancer efficacy and reduce side effects, providing new strategies to fight cancer.

We also need to take into account that nanomaterials could possess quantum mechanical effects. According to the theory of quantum biology, cancer driver DNA mutations develop from the tunneling of protons that change the configuration of hydrogen bonding and allow hydrogen atoms to interact abnormally with DNA molecules.[72] Self-therapeutic nanomaterials could release the energy quanta (due to their wave-particle dual nature) or produce larger vibrations that cause

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changes in their frequencies at tumor sites and kill cancer cells. These larger vibrations or higher frequencies in the energy states of nanoparticles can produce heat in peritumoral regions or directly inside cancer cells and be effective in tumor metastasis treatment.

Together with the catalytic and deoxygenating effects described in this review, which could create unfavorable conditions such as hypoxia, high redox stress and inflammation, self-therapeutic nanomaterials could be a leading system in clinics in the near future if all of the associated problems could be minimized and act as "all in one" "magic bullet" that specifically targets the tumor and destroys it completely in a safe manner without any pain or other side effects. However, it remains to be seen if self-therapeutic nanomaterials are more potent than other therapeutic systems and able to inhibit cancer cells; otherwise it will be hard to breakdown the clinical barriers.

5. CONCLUSIONS

In this review, we summarized the main available reports of self-therapeutic nanomaterials, focusing on the mechanism of action of the nanomaterials in regard to the inhibition of tumor cells. Inorganic nanomaterials that are used to kill cancer cells due to specific cancer inhibition mechanisms such as enzyme inhibition, oxygen capture approaches from tumor sites, and the production of free radicals in the tumor microenvironment were described. It was also highlighted that the self-therapeutic properties of organic nanomaterials such as self-assembled peptide-based nanomaterials and P-gp (MDR1 protein) inhibitors are useful for providing new opportunities to overcome MDR in the current therapeutic systems. Although there are several challenges related to this technology, its multiple interesting properties suggest that these therapeutic systems are very promising in regard to cancer therapy in the near future.

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