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Antibacterial Nanosystems for Cancer Therapy

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Bacteria and cancer cells share unique symbiotic relationship in the process of cancer development and treatment. It has been shown that certain bacteria can mediate cancer and thrive inside cancerous tissues. Moreover, during cancer treatment, microbial infections have been shown to impair the therapeutic efficacy and lead to serious complications. In the past decades, application of antibiotics has achieved great success in fighting against numerous bacteria, but the administration route, low localization effects and related drug resistance limit the further utilization of antibiotics. Recently, advances in nanotechnology have made a significant impact in the medical field, which enhance drug solubility and can target lesion site, and some nanomaterials can even be applied as the therapeutic agent itself. In this review, we introduce anti-bacterial nanosystems for cancer therapy in the aspect of spontaneous and triggered anti-bacterial action, and our notions as well as proposed research directions for the further development of this field are discussed.

Introduction

Cancer leads to around 9.6 millions of deaths each year and has become the leading cause of death worldwide.[1] Researchers are committed to investigating the cause, development, related treatment as well as postoperative intervention of cancer. Among all cancer-related factors, bacteria, which seemed at first to be independent of cancer, have attracted significant attention since increasing amount of evidence indicate that bacteria can contribute to cancer development and interfere with therapy via mediating its carcinogenesis and related infection.[2]

Bacteria can exacerbate tumor development through inflammatory responses and secretion of bacterial enzymes, toxins and oncogenic peptides.[3] Bacteria-induced cancers include gastric cancer (GC), intestinal cancer and pancreatic cancer. For examples, *Helicobacter pylori* (*H. pylori*) usually parasitize on the surface of the epithelium of the gastric antrum and play a decisive role in the development of GC.[4-5] *H. pylori* can induce chronic inflammation, impaired gastric acidification, and changes in cell proliferation and apoptosis, thereby promoting the development of GC.[6] For intestinal cancer, the colon contains more than 500 kinds of bacteria and the disorder of intestinal microbiota can cause various diseases as well as malignancies.[7] It is confirmed that gut microbiota contribute to cancer via inflammatory and immunological interactions.[8] For example, *Bacteroides fragilis* is known for human inflammatory diarrhea, which can also secrete toxin to activate colon cancer.[9] *Escherichia coli* can enhance the tumor-promoting macrophages and facilitate the tumorigenesis.[10] In the development of pancreatic cancer, bacteria such as *Porphyromonas gingivalis*, *Mycoplasma* and some gut bacteria, possess the tumorigenic activity by inducing inflammation, secreting toxins, disrupting the metabolic pathways, inhibiting apoptosis and mutating genes.[11-12] In addition to the above bacteria-related cancers, *Chlamydia trachomatis* enhances the risk of cervical cancer,[13] *Neisseria gonorrhoeae* is associated with bladder cancer [10]and *Mycobacterium tuberculosis* may induce lung cancer.[14] Herein, the significant role of bacteria in the occurrence and development of cancer has been well established.

In addition, cancer patients are prone to developing bacterial infections after therapy since bacteria can thrive in cancerous tissues due to the bacterial-friendly microenvironment and highly immunocompromised function of patients.[15] According to a report, 42% solid tumors patients had Gram-positive infection and 27% had Gram-negative infection, whereas in hematological malignancies patients, the statistics were 47% and 30% respectively.[16] For most solid tumors, surgical resection is commonly used, which leaves wound or grafts with high risk of infection and results in inflammation, delayed wound healing and other related complications.[17] For skin cancers, the cancerous tissue must be removed, yet it is a major challenge to achieve wound healing and anti-infection after surgery. Once infection occurs, the fragile tissue will bleed, excessively exudate, and induce pain as well as fever, all of which are extremely unfavorable for cancer patients. In cases of bone tumor resection, the cancerous bone is usually replaced by orthopedic implant. However the potential infection may lead to inadequate soft tissue coverage, wound complications and implant failure.[18]

In addition to surgery, other methods can be used in cancer treatments or adjuvant therapy. Radiotherapy is useful in some situations where surgery is implausible. In case of cancer cells detached from lesion or liquid cancer, chemotherapy is a suitable choice. These treatments can severely damage the immune system, often leading to secondary bacterial infection, and the localized bacteria may escape to the systemic circulation with high risk of fatal diseases like sepsis.[19-20] Growing evidence indicate that bacteria can also influence the effect of chemotherapeutic drug, which may inactivate the drug before it kills cancer cells.[21-22] During the pancreatic cancer treatment, the presence of bacteria in tumors may decrease the internalization of drugs, leading to drug resistance. Hence, in terms of cancer development and treatment, it is necessary to address both the bacteria-related tumor and cancer treatment-induced infection.

In general, bacteria associated diseases are treated using antimicrobial drugs or antibiotics. For example, to treat *H. pylori* infection, a widely recommended regimen is the triple therapy which includes a proton pump inhibitor and two antimicrobial drugs (clarithromycin, metronidazole or amoxicillin).[23] However, traditional oral and intravenous administrations face varying transport barriers in different organs, tissues, and subcellular compartments, which often prevent effective antibiotic activity. Besides, the uncontrolled and indiscriminate diffusion of antibiotics within the tissues makes lesion site targeting infeasible, while the fast drug clearance further reduces the effective drug retention, not to mention the destruction of some antibiotics in stomach acid when ingested. All these obstacles lead to an insufficient antimicrobial concentration and a failure of reaching deep-rooted bacteria.[24] Additionally, most antibiotics are hydrophilic and cannot spontaneously pass the plasma membrane of infected cells, thus the intracellular infections therapy may be invalidated.[25] Moreover, the usage of drugs can lead to multidrug resistance since the prolonged misuse of antibiotics may allow the bacterial genes to adapt and mutate.[26] As a result, these antibiotics will eventually be ineffective and lead to side effects. Hence researchers try to design various delivery systems and seek new approaches for cancer therapy.

Nanomaterials have inherent advantages in the field of cancer medicine. First of all, nanoscale particles can passively target tumor sites by the enhanced permeation and retention (EPR) effect. Additionally, through surface modification, nanomaterials can be functionalized to actively target tumor tissues or cancer cells as well as accumulate at tumor site, for example, using cancer targeting peptides (e.g. arginine-glycine-aspartic acid (RGD)) to identify specific receptors (e.g. αvβ3 integrin receptor),[27] modifying the nanomaterial surfaces with some cationic elements (e.g. arginine) [28] to improve the tumor penetrating ability, or enhancing tumor retention by changing the shape or size of nanomaterials. Secondly, the unique hydrophobic and hydrophilic structure of nanomaterials can load different drugs in a relatively high dose and enhance the drug solubility, as well as protect drugs from degradation. Thirdly, some nanosystems can work as a therapeutic agent

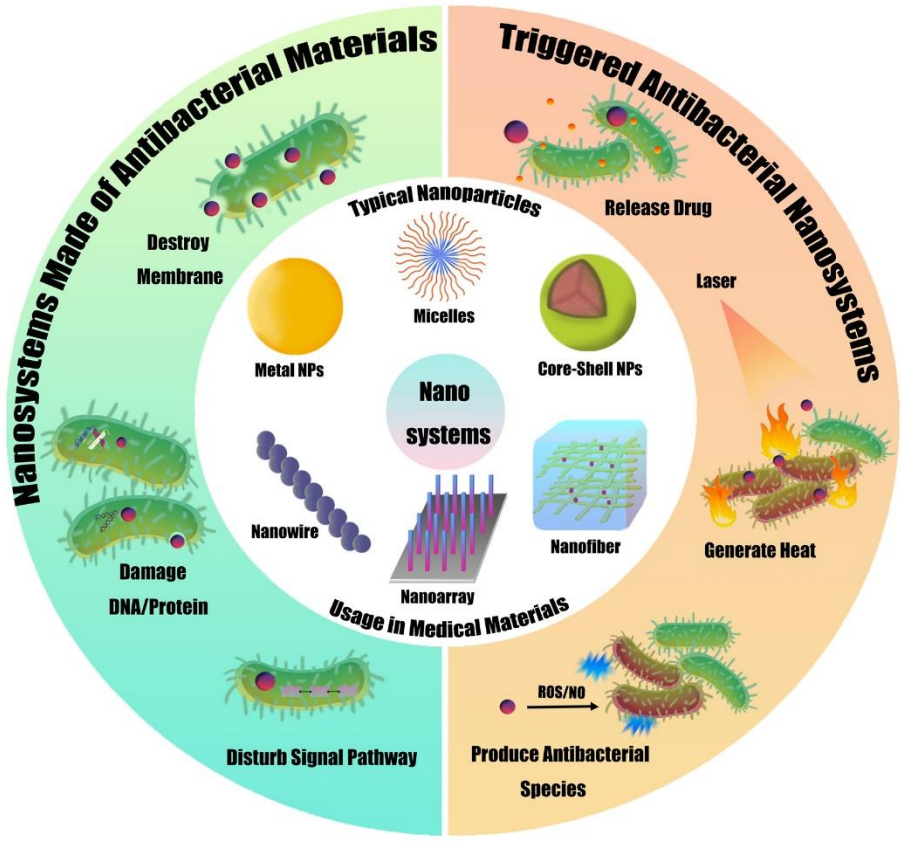

Figure 1. Illustration of nanosystems made of antibacterial materials and their antibaterial mechanism

by adjusting the compositions and materials, namely self transfer systems, metallic particles, and upconversion nanosystems. Furthermore, due to the diversity of the physical properties of components or loaded-drugs, nanomaterials can also be used for imaging and diagnosis. Traditional strategies use nanoparticles (NPs) to inhibit bacteria, while NPs face the limitation of biodistribution, so integrating nanosystems with medical materials is the future trend of antibacterial nanosystems in cancer treatment. Such hybrid designs preserve the engineering flexibility and controllability of nanosystems, and endow these materials with different abilities to form a multifunctional therapeutic platform. In this review, we introduce how these nanosystems effectively inhibit bacteria during cancer treatment in aspects of spontaneous and triggered antibacterial behaviours. Figure 1 showed the antibacterial mechanism of these nanosystems. The nanosystems made of antibacterial materials can destroy bacterial membrane, damage some important biomolecules and disturb signal pathway owning to their intrinsic compositions. And the triggered antibacterial nanosystems can release or produce antibacterial agents to kill bacteria under external stimulation.

Nanosystems Made of Antibacterial Materials

Some nanosystems, such as cationic NPs and gold (Au) nanoclusters,[29-30] can work as antibacterial components due to their inherent properties, special compositions or surface modifications, and these nanosystems will spontaneously kill bacteria under physical condition.

Cationic Compositions

Cationic materials can target cell membranes by electrostatic interactions and possess antibacterial activity by destroying microbial cell membrane, which suggests that cationic materials can potentially circumvent the multidrug resistance.

Antimicrobial Peptides

Antimicrobial peptides (AMPs) are composed of cationic blocks which can kill invading microorganisms through non-receptor mediated membrane disruptions.[31] In particular, amphiphilic AMPs can self-assemble into nanostructures. Owing to the abundance of functional groups, AMPs can also be modified with other nanomaterials and form a functionalized system.

For example, Wang et al. developed an active targeting vesicle against liver cancer cells.[32] Poly (caprolactone) (PCL) formed the hydrophobic component, while the antibacterial AMP poly [Phe_{12}-*stat*-Lys_9-*stat*-$(Lys\text{-}FA)_6$] and the cancer-targeting folic acid (FA) composed the hydrophilic corona. The Lys possessed positive charges in aqueous solution, which gave the system a chance to penetrate the membrane. The vesicles were effective against both Gram-positive and Gram-negative bacteria with a better efficiency than the pure polypeptide due to the increased positive charge density after micelle formation. Furthermore, the nanosystems could target cancer cells and release the loaded doxorubicin (DOX). The degraded polymers then were excreted from the body in a relatively safe manner through metabolism.

Similarly, in a study of Kim et al., AMP was introduced into a theranostic nanosystem.[33] Peptide consisting of arginine and N-alkyl/aryl pyrazole amino acid derivatives was designed. Then the AMPs were attached to tumor-targeting cyclic arginine-glycine-aspartic acid (cRGD) and a cancer diagnosis gadolinium (Gd^{3+})-chelated tripeptide. Upon self-assembly, the nanoagents could form various nanostructures such as spheres, vesicles, cylinders, and sheets. They found that spherical micelles possessed better antibacterial activity against *Escherichia coli* (*E. coli*) and *Staphylococcus aureus* (*S. aureus*) than two-dimensional planar network nanostructures because the ability of three-dimensional spherical nanostructure could penetrate and disrupt cell membranes. In this system, AMPs not only exhibited antibacterial activity, but also worked as a linker to connect two functional parts. The addition of cRGD could target tumor cells by recognizing αvβ3 and αvβ5 integrin receptors and the chelated Gd^{3+} to the hydrophobic end of peptide amphiphiles could provide higher relaxation in magnetic resonance imaging. Hence the peptide-based nanoagents had shown good cancer targeting as well as theranostic efficacy with antimicrobial activity.

Recently, Zhu et al. designed a nanocluster to sequentially kill bacteria and cancer cells (Figure 2A).[34] Conjugated polymer nanoparticles (CPNs) with photothermal conversion ability were prepared. Then the AMP tachyplesin-I was modified on CPNs and the bioimaging agents Au ions were added in this system to form the fluorescent nanoclusters (AuNCs). The interactions between CNP@AMP-AuNCs and human colon cancer cell line (HT-29) could be visualized by confocal fluorescence microscope. Next, the HT-29 cells and *E. coli* were cultivated together to evaluate the CNP@AMP-AuNCs' inhibiting effect of cancer cells and bacteria. The CNP@AMP-AuNCs efficiently inhibited *E. coli* after 1 h of incubation, while maintaining the viability of HT-29 cells. After near-infrared (NIR) light irradiation for 5 min, the HT-29 cells were killed due to hyperthermia (Figure 2B). This system could be applied for cell tracking, bacterial inhibiting, and cancer cell killing and provided an all-in-one strategy for the stepwise killing of cancer cells and bacterial infection.

Cationic Nanoparticles

Cationic nanoparticles possess bacteria killing ability owing to the positive charge elements. Typical cationic polymer is polyethyleneimine (PEI), in which the rich amino-groups grant it positive charge. These cationic nanoparticles inhibit bacteria by damaging the cell membrane.

In a study by Davoodi et al., a double-walled microparticle-embedded hydrogel was fabricated for localized drug delivery.[35] Chemotherapy drugs cisplatin (Cis-DDP) and paclitaxel (PTX) were loaded into the core and shell respectively and the microparticles were subsequently embedded into alginate-branched PEI (Alg-ald:PEI) hydrogel. The hydrogel retained the particles in the surgical cavity and regulated the release profile, while the cationic PEI could provide anti-bacterial ability. The antibacterial results showed that the hydrogels enhanced the bacterial inhibition ability with increasing PEI concentration. Compared with bare alginate, the hydrogel showed 100 times higher antibacterial efficiency at 1 *wt.*% PEI. When the concentration of PEI reached 2.5 *wt.*%, no colony was found on agar plates after 18 h incubation. In addition, the hydrogel could significantly reduce the bacteria activity (1000 times) even at extremely high bacteria concentration (10^8 colony-forming unit (CFU) mL^{-1}). With the incubation of drug-loaded hydrogel and breast cancer cells (MDA-MB-231), the release of PTX and Cis-DDP caused substantial cell death. Overall, the hydrogel could retain particles in the tumor resected site after debulking surgery and prevent surgical infection.

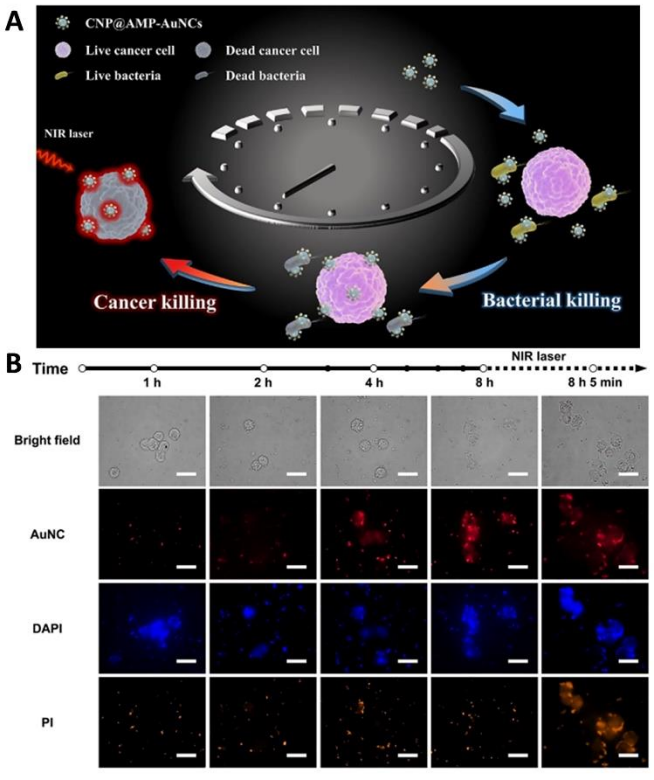

Figure 2. (A). Schematic illustration of CNP@AMP-AuNCs stepwise killing of bacteria and cancer cells. (B). Fluorescent images of *E. coli* and HT-29 cells after treated with CNP@AMP-AuNCs. DAPI (blue) and PI (red) represent survival and dead conditions. Scale bar: 10 μm. (Image was reprinted from: S. Zhu, X. Wang, S. Li, L. Liu, L. Li, *ACS Appl. Mater. Inter*., 2020, 12, 11063-11071 with permission)

In another example, Jin et al. established a cationic polymer decorated natural layered silicate (NLS) for GC treatment.[36] NLS such as montmorillonite (MMT) and attapulgite (At) are composed of exchangeable cations with crystalline hydrated octahedral layered magnesium aluminium silicate, which can absorb gastrointestinal disorders related bacterial toxins. Modifying cationic-polymer offers NLS the advantage of carrying genes and intercalating drugs to produce therapeutic effects. In this study, anticancer drug 5-Fluorouracil (5-FU) was integrated into the interlayer. Then PEI was integrated on the surface of the NLS, followed by the encapsulation of therapeutic tumor necrosis factor (TNF)-related apoptosis-inducing ligand (pTrail) to form the multifunctional compound. Anti-proliferative experiment indicated that the NLS system with 5-FU and pTrail gene could induce tumor cells apoptosis. Moreover, the *H. pylori* were efficiently adsorbed and immobilized onto the surface of the NLS with an enhanced adsorbing effect compared with non-PEI group. The results revealed an extensive 70-80% of *H. pylori* death, which was contributed to the interacted effect between PEI and NLS. The modified NLS was a multifunctional compound which could inhibit bacteria-associated GC.

For maxillofacial tumors, soft liners are required to cover the implantation at surgical wound, yet bacteria can colonize and even penetrate those materials. In this regard, AtarFroyman et al. incorporated poly-cationic nanoparticles in denture lining.[37] The synthesized crosslinked quaternary ammonium PEI (QPEI) nanoparticles had strong antibacterial activity even at low concentrations. Incorporated QPEI nanoparticles in denture lining could provide antibacterial effect. *In vitro*, the bacteria decreased by 5-6 logs on the contact surface of soft liner. Besides, these soft liner materials were implanted into three post-surgery maxillofacial patients, and the reduced bacterial viability was observed when using liner incorporating QPEI nanoparticles. The system showed broad-spectrum bactericidal properties both *in vitro* and in *vivo* in particular for orofacial cancer patients.

Metallic Nanoparticles

Metal ions such as copper ions (Cu^{+}/Cu^{2+}), silver ions (Ag^{+}), gadolinium ions (Gd^{3+}), manganese ions (Mn^{2+}) and zinc ions (Zn^{2+}) are widely applied in disease diagnosis and treatment.[38-39] As special elements to kill microbe, metal ions raise attention in antibacterial treatment since they can inhibit bacteria wall synthesis, disrupt cell membrane and impair the functions of nucleic acid and protein. Metal ions can be incorporated into various systems.

In a recent study, Li et al. developed a multi-functional biodegradable nanowire.[40] This nanowire was comprised of poly (citrates-siloxane) and copper sulfide (CuS), namely PCS-CSNW. The former ingredient possessed biodegradable ability while the latter performed antibacterial effect. The hydrophobic-hydrophobic interaction between the CSNW and polymer chain facilitated the formation of nanocomposites. With the biodegradation of nanowire and the release of Cu^{2+} from CSNWs, the nanowire exhibited broad-spectrum antibacterial activity with antimicrobial performance up to 99% both *in vitro* and *in vivo*. Meanwhile, PCS elastomers had good photoluminescent properties under excitation and CuS showed good optical-electrical performance. Hence PCS-CSNW could also achieve both *in vivo* thermal imaging and bio-tracking as well as killing cancer cells by the photothermal performance.

In another study of Joseph et al., they fused chemotherapy with antibacterial efficacy in a smart nano-chemobiotics (NCB) platform which could be used for *in vivo* bio-distribution by surface enhanced Raman scattering (SERS).[41] Silver nanoparticles (AgNPs) were excellent antimicrobial agents and could work as nano-biophotonics. Based on this, they combined AgNPs with PST001, a kind of polysaccharide derived from plants with cancer cell specific cytotoxicity to achieve anticancer/antibacterial therapeutic efficacy and investigated bio-distribution by SERS fingerprinting. Due to the release of silver ion and the formation of free radicals, AgNPs@PST could damage bacterial membrane functions. The minimum bactericidal concentration values and minimum inhibitory concentration of AgNPs@PST against *E. coli* were 15.625 μg/mL and 3.90 μg/mL. Additionally, AgNPs@PST caused tumor volume reduction with less systemic toxicity. As a Raman substrate, AgNPs@PST showed excellent SERS spectral amplification in the tissues. Hence, this strategy was a multi-therapeutic nanoprobe with realtime *in vivo* monitoring for bacterial infections and cancer.

In a report by Wu et al., they incorporated Ag into a multifunctional system.[42] They used ZrO_2@SiO_2 as nanocarrier, where Zr possessed CT imaging function and SiO_2 allowed for the gathering of silver. Encapsulated with microwave sensitizer 1-butyl-3-methylimidazolium hexafluorophosphate (IL), the nanorattles (consisted of one or more movable cores enclosed by a shell with tailored properties) had microwave susceptibility effect. Then Ag was added, which worked as antimicrobial agent and accompanied with Zr in CT imaging. Lastly, polyethylene glycol (PEG) was coated onto the nanorattles to achieve the long-circulating behaviour. The minimal bacterial inhibition concentrations of PEG-IL/ZrO_2-Ag@SiO_2 NRs on *E. coli* and *methicillin-resistant staphylococcus aureus* (*MRSA*) were 3.125 and 6.25 μg mL^{-1} respectively. The PEG-IL/ZrO_2-Ag@SiO_2 NRs was also found to reduce infections *in vivo* with the decreased bacterial colonies. This nanosystem had potential application in real-time monitoring, where the CT imaging signals were concentration-dependent. Additionally, this system had good tumor treatment outcomes (with inhibition rate at 96.4%) due to the microwave thermal therapy and significant anti-bacterial properties.

However, normal metallic particles face the risk of the undesirable release and inevitable leakage of toxic metal ions which may cause serious side effects; therefore metal ions need to be controllably and precisely released. In a study, Zhang et al. used the NIR irritation to control the release of Ag ions.[43] AgNPs was modified on porphyrin porous coordination network (PCN), and the nanoplatform was camouflaged with neutral cell membrane (NM), hence this system was named as PAM. Due to the ability to target inflammation site, NM could lead the whole system to selectively accumulate at tumor or infectious site. After NIR light irradiation, the induction of oxidative stress produced by PCN

could enhance the release of Ag^+ from AgNPs to kill tumor cells and bacteria locally. The antibacterial test (using *S. aureus*) showed that the PAM had the fewest bacterial colonies than other groups *in vitro* and could effectively inhibit bacterial growth in infected-animal models due to the combination effect of Ag^+ and singlet oxygen ($^1O_2$). Besides, the PAM injected mice exhibited strong fluorescein isothiocyanate (FITC) fluorescence at infected and tumor site indicating that PAM had good tumor/infection tissue targeting ability. After antitumor treatment for 14 days, the PAM+light group showed strongest tumor suppression effect. This nanohybrid was beneficial for the design of a safe and controllable treatment of bacteria associated cancer.

Other Antibacterial Material Systems

Some inorganic materials and carbohydrates are active antibacterial therapeutic agents and have been applied in the construction of nanosystems. These materials can inhibit bacteria by mediating signal pathway or interfering immunity.

According to Cheng et al., after surgical resection of osteosarcoma, surgical-site infection and bone tumor recurrence might occur in patients, which may need a long-term administration of antibiotics or complex secondary surgery interventions. To solve these problems, the authors constructed an antibacterial and anticancer implant material.[44] They coated titanium dioxide (TiO_2) nanoarray with selenium (Se) nanoparticles, where TiO_2 nanoarray worked as a topographic induction carrier and Se nanoparticles as anticancer and antibacterial agent. Se achieved antibacterial effect by producing superoxide radicals, which could interact with membranes and DNA.[45] The authors found that 6.43 wt% Se in the nanoarray had promising antibacterial abilities against *S. aureus* and *E. coli* with deteriorated morphology and decreased bacterial colonies. After seeding MG63 cells (osteosarcoma cells) on the nanoarray for 3 days, the growth and migration of MG63 cells were inhibited. It is expected that the nanoarray had potential applications in orthopedic implants and postoperative treatment of osteosarcoma.

Recently, Huang et al. fabricated a supramolecular assembly system to inhibit *methicillin-resistant staphylococcus epidermidis (MRSE)* infection by imitating the innate immune process of neutrophil extracellular traps (NETs).[46] Since the immune system can be activated to produce plenty of reactive oxygen species (ROS) under bacterial infections, they designed ROS-responded supramolecular which could self-assemble *in situ* under ROS stimulation to interrupt bacterial infections. A quinazolinone derivative with an aryl boronate immolative linker (BQA-GGFF) was synthesized, and this system underwent oxidation to form a stable hydrogel. The network could efficiently trap *MRSE* and prevented aggressive dissemination. When cultured with *MRSE*, the bacteria were tightly trapped onto the nanofibers within the hydrogel and decreased bacterial growth *in vitro* could be observed due to the transcriptomes alterations. The supramolecular nets showed a three times stronger efficacy compared to vancomycin *in vivo*. This *in situ* self-assembly system was independent from the nanoparticles-related toxicity and reliance on antibiotic, which was promising to improve cancer treatment.

Besides, Wang et al. utilized butyrate, an agent with antibacterial and anticancer abilities, for bacteria-associated cancer therapy.[47] They inserted butyrate into the interlayer of nitinol (Ni–Ti) layered double hydroxide (LDHs). Making use of the hydrogen peroxide (H_2O_2) at tumor site, the prepared films reverted H_2O_2 to hydroxyl ions (OH^-). The butyrate ions would be substituted by the produced OH^-, leading to butyrate release. The butyrate-inserted LDHs showed a nearly 100% bacterial inhibition ability to *E. coli* and *S. aureus*. In the following *in vivo* experiments, bacterial colonies appeared in Ni-Ti and LDHs groups, while there were no bacterial colonies in LDH/butyrate. The *in vivo* anticancer abilities of the prepared samples showed that LDH/butyrate had the strongest inhibition effect and had no cancer metastasis. This butyrate eluting film possessed potential to be applied on the surface of medical implants in contact with tumor tissues for inhibition of bacterial growth and metastasis.

Triggered Antibacterial Nanosystems

In this part, the nanosystems themselves had no ability to kill bacteria, and the antibacterial effect can be achieved by releasing drugs or generating heat/antibacterial species upon stimulation, e.g. reactive oxygen species (ROS) or nitric oxide (NO).

Nanosystems for Drug Delivery

The antibacterial effect of drug delivery systems is achieved by encapsulating antibacterial drug (e.g. penicillin, cephalosporins, aminoglycosides, glycopeptides, and quinolones)[48] inside the nanosystems. These drugs inhibit bacteria via interfering with essential survival processes, e.g., by blocking the synthesis of RNA, DNA and vital proteins.[49] The antibiotics can be loaded into nanosystems through cavity encapsulation, surface modification, and mixture with nanoparticle-comprised material.

S. aureus are intracellular bacteria in cancer cells and macrophages, which can lead to recurrent systemic infections. Vancomycin has been widely used in the treatment of *MRSA*, yet it can induce serious adverse effects and toxic symptoms. Encapsulating it within nanocarriers can prolong activity and reduce systemic toxicity. For example, Bose et al. designed drug-loaded apoptotic bodies to treat intracellular infections.[50] After culturing cancer cells *in vitro*, they induced apoptosis to collect apoptotic vesicles, and then prepared antibiotic-loaded reconstructed apoptotic bodies (ReApoBds) with encapsulation efficiency (vancomycin) around 60%. The results demonstrated that the system was able to kill intracellular *S. aureus* more effective than free drugs, with a two-log order higher colony-forming unit decrease *in vitro*. ReApoBds can specifically target cancer cells and macrophages *in vivo*. This kind of nano-decoys had the potential in targeted delivery, imaging and cancer immunotherapy.

Aminoglycosides can kill Gram-negative bacteria and some Gram-positive bacteria by inhibiting the protein synthesis in the cytoplasmic matrix. In addition, since aminoglycosides and their derivatives have the high binding affinity to RNA, they have been utilized for delivering genes. Yet the antibacterial activity of aminoglycosides can be eliminated during the modification with lipid. To overcome this limitation, Huang et al. synthesized a degradable hyperbranched polymer. The aminoglycosides and 2-hydroxyethyldisulfide were conjugated via Michael-addition polymerization to form SS-HP,[20] where the disulfide bonds provided biodegradable ability and the hydroxyl-rich sections could significantly reduce the risk of hemolysis. Then p53 gene was loaded to the vectors to suppress cancer cells. In the presence of glutathione (GSH) at tumor site, the disulfide bonds would be cleaved to promote the biodegradation of SS-HP, which was beneficial to gene transfection and drug release. Overall, SS-HP exhibited high antibacterial activity against *E. coli* and *S. aureus* with 0.5 mg/mL minimum

inhibitory concentration, besides the samples effectively inhibited the growth of tumors *in vivo*. The proposed multifunctional system possessed the combined virtues of gene transfection capability, biocompatibility, and antibacterial activity.

In addition to nanoparticles, nanofibers can also be used to load and release antibacterial drugs.[51] Xi et al. designed a multifunctional elastomeric nanofibrous scaffold.[52] The nanofibers were fabricated by electrospinning poly (L-Lactic Acid) (PLLA)-poly (citrate-siloxane) (PCS) and assembling polydopamine (PDA)/curcumin (named PPCP matrix) (Figure 3A). PDA was designed for photothermal therapy while curcumin was chemotherapeutics agent, and its antibacterial/antioxidative activity would promote wound healing/skin regeneration. After irradiation for 3 times, the cell viability of A375 (melanoma cells) treated with PPCP decreased to 12.8 ± 1.4%. And the killing efficiency of PPCP to *E. coli* and *S. aureus* was 93.3 ± 1.2% and 97.7 ± 0.7%, respectively. (Figure 3B) *In vivo* antitumor effect results showed the PPC+Laser group decreased the average tumor volume on day 14 due to the chemo-photothermal therapy. Bacteria from wound tissue were cultured, and no

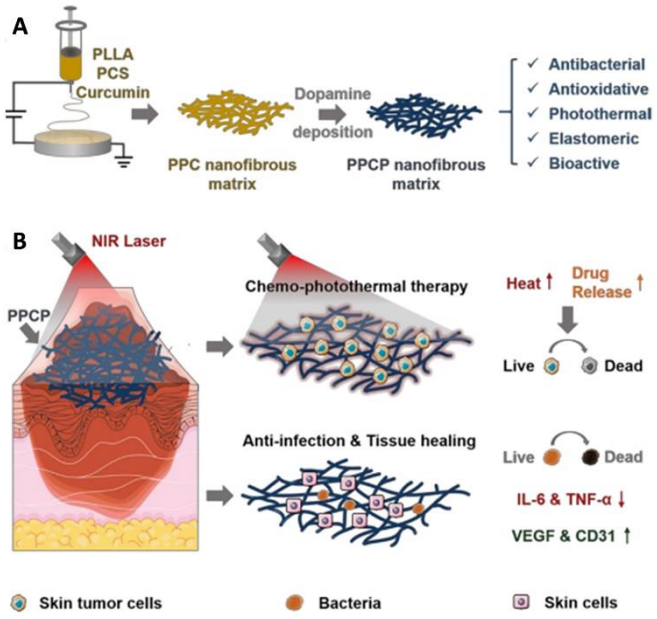

Figure 3. (A) Synthesis of PPCP nanofibrous scaffolds. (B) Chemo-photothermal treatment of skin cancer and infection. (Image was reprinted from: Y. Xi, J. Ge, M. Wang, M. Chen, B. Lei, *ACS Nano*, 2020, 14, 2904-2916 with permission)

bacteria in PPCP group were observed on day 10. Besides, compared with the other groups, the PPCP group had better epithelial coverage of more than 99% of the repaired wound. This strategy had great potential in the field of skin cancer and wound healing as well as skin tissue regeneration.

However, even though drug-loading nanosystems can enhance the delivery efficiency, the multidrug resistance is still a huge obstacle. Hence, more therapeutic approaches are developed.

Photothermal Therapy

Photothermal therapy (PTT) utilizes NIR or microwave absorbing materials to ablate tumor by generating hyperthermia.[53-54] They have attracted great interest for its non-invasiveness, low toxicity, and high therapeutic specificity.[55] Different from traditional chemotherapy, PTT agent can effectively illuminate disease regions via photothermal imaging.[56] Meanwhile, the photothermal agents can interact with bacteria and use thermal ablation to kill bacteria.[57-58] Herein, PTT has attracted widespread attention in the antibacterial treatment during cancer therapy.

In a study, Xue et al. prepared a biodegradable PDA functionalized bioactive glass nanoparticles (BGNs) platform (BGN@PDA) for chemo-photothermal therapy (Figure 4).[59] Although BGNs had good ability to inhibit bone tumors and promote tissue repair, they could easily aggregate due to the poor stability, which would reduce the transfer efficiency. The mussel-inspired surface assembly with PDA could

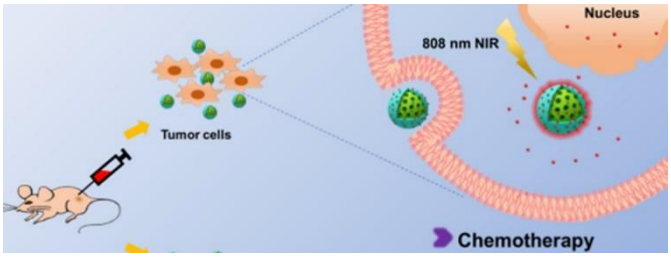

Figure 4. Schematic illustration of BGN@PDA-DOX synergic effect on cancer photothermo-chemotherapy, bone regeneration, and photothermal imaging. (Image was reprinted from: Y. Xue, W. Niu, M. Wang, M. Chen, Y. Guo, B. Lei, ACS Nano, 2020, 14, 442-453. with permission)

enhance the stability of BGNs, and form a NIR-excited photothermal nano-platform for ablating tumor. More than 99.99% of *S. aureus* and *E. coli* were killed in BGN@PDA group after 6 h. After loaded with anticancer drug DOX, cervical cancer cells and colon cancer cells were significantly killed by synergistic chemo-photothermal therapy *in vivo*. Moreover, during the implantation process, BGN@PDA could promote the healing process and new bone formation *in vivo* by reducing the inflammation at the wound site. Therefore, BGN@PDA-DOX could be developed for local cancer therapy and related infection as well as bone regeneration.

Recently, Younis et al. prepared a plasmonic metal/semiconductor nanohybrid to achieve simultaneous antibacterial/anticancer PPT.[60] They choose plasmonic gold nanorods (AuNRs) for their tunable NIR absorption. The AuNRs were assembled on graphene oxide (GO) nanosheets, forming the plasmonic AuNRs/GO nanohybrid, where GO had excellent thermal and electrical conductivity. With the synergistic effect of Au and GO, the photothermal conversion efficiency (PCE) of nanohybrid was remarkably higher than the single groups under low laser power density (300 mW), indicating the enhanced synergistic phototherapeutic performance. After irradiation for 5 min, the viability of both *E. coli* and *S. aureus* was remarkably reduced to 14.94% and 4.049%, respectively. Meanwhile, AuNRs/GO decreased Hela cancer cell viability from 97.24% to 4.17%. The strategies provided an enhanced therapy under low power single laser excitation for cancer and infection.

In a new study of Su et al., they proposed a combined therapy strategy of photothermal and sonodynamic system on titanium (Ti)-sulfur (S)-doping (Ti-S-TiO_2-x) system.[61] Ti could be easily oxidized into TiO_2 and TiO_2 nanoparticles worked as a sonosensitizer to produce ROS to kill bacteria. Meanwhile, TiO_2 nanoparticles exhibited high photothermal conversion efficiency with good antibacterial efficiency. Besides, the S treatment could significantly enhance the NIR light absorption. The Ti group could not kill *S. aureus* with a single treatment, but after 15 min NIR light and ultrasound treatments, Ti-S-TiO_2-x showed 99.995% antibacterial efficiency against *S. aureus in vitro* and the *in vivo* antibacterial efficiency reached 99.26% under the synergistic effect of heat and ROS. Importantly, the Ti-S-TiO_2-x implant showed an unchanged structure and remained a good antibacterial performance even after soaked in water for 6 months. This strategy was promising for cancer therapy as an implant material.

Antibacterial Species Production

ROS and NO have been widely used as antibacterial agents. Antimicrobial photodynamic therapy (PDT) utilizes light,[62-63] photosensitizer and molecular oxygen to generate ROS such as hydroxyl radicals (•OH) and superoxide radicals (O_2•).[64] ROS can mediate bacterial death via irreversible damage to membrane, proteins and nucleic acid.[65] In addition, these antibacterial species offer tremendous promise to combat drug resistance.[66] While as an endogenous gasotransmitter, NO can induce nitrification and oxidative stresses on cells or bacteria as well as react with DNA and inhibit the repair of nucleic acid, thus killing cancer cells and bacteria.[67]

For example, Liu et al. developed a triggered •OH releasing system.[68] Hydrogen peroxide (H_2O_2) can react with essential biomolecules, but the slow processing and high concentration limit its application. Researchers found the conversion of H_2O_2 to •OH could avoid these limitations. It has been reported that ascorbic acid (AA) worked as pro-oxidant as a prodrug of H_2O_2, and molybdenum disulfide (MoS_2) served as a catalyst since its peroxidase-like activity which can transform low-concentration H_2O_2 to •OH. The authors prepared mesoporous ruthenium (Ru) NPs to load the prodrug AA, and used hyaluronic acid (HA) to encapsulate it, where RuNPs could be used for PPT and HA was used as capping agent to combat infection. This system was then modified with the MoS_2 nanoparticles on the surface to endow this system with an enzyme-responsive ability (AA@Ru@HA-MoS_2). Moreover, MoS_2 nanoparticles could be coated with an antibacterial agent ciprofloxacin (CIP), which could enhance the bacteria killing efficiency. With the secretion of Hyal, HA would be degraded to released AA, and then •OH would be generated *in situ* in presence of catalyst MoS_2. In addition, taking advantages of PTT of RuNPs and CIP, this nanosystem possessed combined-antibacterial therapeutic effect. Meanwhile, the MoS_2 nanoparticles had the potential to load anti-cancer drugs; hence this system could be used in many medical fields.

Similarly, by using enzyme effect, Zhang et.al developed a light-free ROS generating nanosystem.[69] Magnetic nanoparticles (MNPs) are proved to exhibit the enzyme-mimic effect, which were similar to horseradish peroxidase (HRP), and the surface Fe^{2+}/Fe^{3+} can catalyse the decomposition of H_2O_2 to generate ROS via Fenton or Haber-Weiss reactions. ROS provoked an oxidative stress to kill bacteria or cancer cells in the physiological condition. Herein, the enzyme-mimic MNPs could be used in anti-bacteria treatment and cancer therapy. Besides, MNPs could work as potential magnetic resonance imaging contrast agents in cancer diagnostics. In this study, they found that the enzyme activity was inversely proportional to the size of MNPs. The inhibition ratio (*E. coli*) of 6 nm MNPs reached nearly 100%. Then the MNPs could significantly kill more than 80% HeLa cells *in vitro* and effectively suppress tumor growth *in vivo*. These enzyme-mimic MNPs could be used for cancer theranostic and epidermal infection.

In an example of NO delivery, since NO is a diatomic free radical and unstable with a very short half-life,[70] to deliver NO by a controlled manner, Yu et.al designed a light-controlled NO delivery nanoplatform.[71] Super-paramagnetic iron oxide Fe_3O_4 nanoparticles were coated with PDA, and then the NO donor photolabile ruthenium nitrosyls (Ru-NOs) and FA were modified on Fe_3O_4@PDA. The Fe_3O_4 core made the system super-paramagnetic, and the PDA coating offered PPT. This nanoplatform selectively accumulated in tumor tissue under magnetic field guidance, and targeted tumor cells by the interaction between folate receptor and FA. Since Ru-NOs could controllably release NO under irradiation, this nanosystem achieved NO release under an 808 nm NIR light irradiation and triggered PTT, thereby enhancing treatment efficacy. The NO concentrations varied from 140 nM to 370 nM when mass fraction of Fe_3O_4@PDA@Ru-NO ranged from 0.8% to 2.0% under irradiation. Furthermore, they integrated Fe_3O_4@PDA@Ru-NO into chitosan (CS) and poly (vinyl alcohol) (PVA) *in-situ* gelating CS-PVA/NO hydrogels. The CS-PVA/NO hydrogels achieved controlled NO delivery under mild (<150 mW cm^{-2}) NIR irradiation and showed efficient antibacterial effect for both *E. coli* and *S. aureus*. Therefore, this concept could be used in the treatment of cancer, infection and wound healing.

Future Perspectives

The antimicrobial treatment has made great progress in cancer therapy, especially with the rapid advance of nanomedicine. Major efforts have been devoted to the development of nanosystems to increase the drug delivery efficacy, and adopt new therapeutic agents or new

treatment approaches to minimize drug resistance, as well as achieving local antimicrobial therapy. The new strategies, however, always come along with new challenges.

In terms of nanocarriers, size and surface charge is very important since they can influence the recognition, adsorption and elimination of nanoparticles which subsequently affects their biodistribution. In the circulatory system, nanoparticles with smaller scale can be rapidly cleared and leaked back into bloodstream even when they have reached at the tumor site, while large nanoparticles have good retention ability but cannot achieve penetration into cells. Some studies with nanoparticles for antibacterial treatment failed to comprehensively consider the therapeutic effect, appropriate sizes as well as evaluate their behaviour *in vivo*: too large or too small in sizes may induce unsatisfied outcomes.[72] For the surface charge, anionic nanoparticles have a prolonged circulation, while positively charged nanoparticles are more likely to be cleared or phagocytised. However, cationic nanosystems are very popular in bacterial inhibition because their membrane destroying ability. Although these cationic nanosystems have good performance *in vitro*, the rapid clearance may lead to insufficient drug concentration and potential waste. Some organs, such as lung, have tendency to gather cationic nanoparticles, which may cause side effect if these organs are not the target site. Moreover, positively charged materials have a risk of hemolysis, leading to another safety concern. Thereby, it is essential to control the electric potential of nanosystems in a reasonable range, or design smart nanosystems which can conceal themselves in circulation and restore electrical properties at the lesion site. Besides, the safety concerns of nanoparticles should be taken into account. For example, metallic nanoparticles are difficult to metabolize and degrade, causing potential toxicity to normal tissues.

For PTT, due to the thermal resistance mediated by heat shock protein, long-term or multiple PTT may result in ineffective treatment.[73] In this case, the nonspecific heating and the inevitable heat diffusion can induce inflammation and threaten the surrounding normal cells or tissues.[74] Herein, future PTT should take thermal resistance into account. In terms of PDT, Gram-positive bacteria offer photosensitizers a chance to penetrate walls owing to the porous structure but Gram-negative bacteria can resist photosensitizers due to the outer membranes.[75] This barrier may restrict the use of PDT, so scientists can design new photosensitizers for broad-spectrum bacterial inhibition in future studies. Besides, there should be a balance between adequate immune response and excessive inflammatory responses caused by ROS, since excess ROS can cause irreversible damage to neighbouring healthy cells and tissues.[76]

Lastly, incorporation of antibacterial and anticancer therapy with respect to the disease development process remains challenging. Most of nanosystems simply integrate all the functional agents together, and are administrated into the animal models even when there is no induced infection at tumor site. This method is good for some cancers inherited with bacteria and tumor postoperation caring, but it has potential toxicity for other cases since the antibacterial agents may damage the normal cells. The future research can be based on spatiotemporal order effect to achieve responsive and reasonable therapy, such as performing antibacterial ability in response to infection condition or designing procedural therapy.

Overall, the achievements of antibacterial nanosystems in cancer therapy are inspiring, but there is a long way to achieve effective and safe use of these strategies. We hope this review can be helpful to researchers for designing new nanosystems in this field.

Conflicts of Interest

The authors declare no conflict of interest.

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