Photothermal Therapy and Photodynamic Therapy

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Multidrug-resistant (MDR) bacteria are rapidly emerging, coupled with the failure of current antibiotic therapy; thus, new alternatives for effectively treating infections caused by MDR bacteria are required. Hyperthermia-mediated photothermal therapy (PTT) and reactive oxygen species (ROS)-mediated photodynamic therapy (PDT) have attracted extensive attention as antibacterial therapies owing to advantages such as low invasiveness, low toxicity, and low likelihood of causing bacterial resistance.

Keywords: photodynamic therapy ; photothermal therapy ; synergistic effect

1. Introduction

The prevalence of multidrug-resistant (MDR) bacteria and their infections in humans has frightened the global health system. Identifying them is a critical issue that must be addressed to ensure that people live in safe and healthy environments [1]. The overall number of deaths from bacterial infections is expected to increase to 10 million per year by 2050, illustrating the severity of MDR bacterial infections [2]. Currently, it is feasible that a bacterial infection might not respond to current antibiotic therapies. The overuse or misuse of conventional antibiotics is to blame for this unbelievable situation [3]. Notably, bacteria develop resistance to antibiotics at a considerably higher rate than that at which new antibiotics are discovered.

Bacteria have evolved various protection mechanisms against antibiotics over time [4][5]. These include the development of the drug efflux pump in bacteria for allowing drugs to be expelled outside of cells, evolved abilities to break down antibiotics using enzymes produced by bacteria, modifications of bacterial metabolic pathways to protect them from antibiotics, formations of biofilms, and structured colonization of bacterial cells with a self-produced extracellular polymeric substance matrix. Antibiotics cannot function through this protective biofilm matrix and are captured in the matrix [6]. Furthermore, bacteria enclosed in the biofilm matrix can efficiently communicate and transfer antibiotic-resistance genes among all bacteria, making it more difficult to kill using antibiotics from outside the biofilms. Unsurprisingly, approximately 80% of chronic and recurrent infections in the human body are associated with the formation of dense bacterial biofilms [6]. Therefore, an urgent need exists for thorough and methodical research on techniques for preventing MDR bacteria from rapidly multiplying after infecting humans, in addition to techniques for eliminating bacteria.

Research has explored various alternatives to conventional antibiotics to manage this constantly hazardous and demanding scenario with varying degrees of effectiveness. However, these alternatives are not perfect solutions for overcoming the limitations of antibiotic therapies. For instance, naturally occurring antimicrobial compounds have been investigated; however, they are expensive to use [7]. Antimicrobial peptides (AMPs) have been characterized and suggested as promising alternatives owing to their potent antibacterial activity and species selectivity; however, they are unstable and very vulnerable to proteolysis, limiting their potential for use [8]. To overcome these limitations, molecules designed to mimic the properties of antimicrobial peptides have resulted in synthetic mimics of antimicrobial peptides [9]. These are polymeric mimics of AMPs, peptidomimetic oligomers, or small molecules. Most are prepared with the aim of overcoming the issues of protease lability, toxicity, and high costs in manufacturing AMPs. However, optimizing these materials to achieve controlled bioactivity remains challenging. Quaternary ammonium compounds have been used because of their antibacterial activity; however, their bacterial resistance after long-term use needs to be resolved [10]. Metal-based nanoparticles have recently been extensively developed in view of their well-received antibacterial activity, but their toxicity to mammalian cells is yet to be fully resolved [11].

Following the above trends, phototherapy has emerged as a promising strategy against bacteria owing to its excellent antibacterial activity, non-invasive nature, and fewer chances of bacteria generating bacterial resistance [12]. Hyperthermia-mediated photothermal therapy (PTT) and reactive oxygen species (ROS)-mediated photodynamic therapy (PDT) are the two most widely utilized phototherapies against bacterial infections. The basic mechanism of PTT depends on the light-to-heat conversion ability of photothermal agents (PTAs) after irradiation with desirable light sources. PTAs

damage and kill bacteria through various processes (for example, membrane disruption and intracellular component disintegration of bacteria) [13]. Owing to their non-invasive nature, the chances of bacteria becoming resistant to this process are very unlikely relative to those with antibiotic therapies. Moreover, the usual light source utilized in this strategy is near-infrared (NIR) light between 700 and 1400 nm, which shows good tissue penetration ability owing to its longer wavelength. Accordingly, it can influence deep tissues for photothermal antibacterial treatment [14]. Additionally, a biofilm structure can be damaged by hyperthermia, facilitating the penetration of antibacterial agents through the biofilm matrix and efficiently killing bacteria [15]. This localized hyperthermia-mediated strategy for broad-spectrum antibacterial activity has potential clinical applications. However, it also has certain limitations, such as requiring high temperatures (≥60 °C), long-term laser exposures, and a high PTA dosage, which may cause inevitable thermal damage to normal tissues [16].

PDT is another non-invasive therapy. It utilizes a light source to activate photoresponsive materials to generate ROS. The ROS inflict oxidative damage on intracellular components of bacteria and eventually kill them [17]. Similar to PTT, the chance of bacteria becoming resistant to PDT is very unlikely, owing to its light source mechanism. Over the years, the biocompatibilities of the photoresponsive materials for PDT have been optimized with various types of functionalization for more productive and effective antibacterial activity, thereby providing greater potential for clinical applications [12]. However, limitations such as the weak penetration ability of the short-wavelength light for PDT [18] and the lifetime of ROS [19] need to be addressed before the strategy can be fully utilized in clinics.

In this regard, a combination of PTT and PDT seems promising, as both strategies can complement each other's limitations [20]. The PTT and PDT synergistic therapy combination not only maintains the beneficial properties of each strategy but also compensates for the deficiencies of each strategy. The high-temperature requirement of PTT and the weak penetration ability of PDT can be easily overcome if PTT and PDT are synergistically utilized.

2. Photothermal Therapy (PTT) and Photodynamic Therapy (PDT)

2.1. Photothermal Therapy (PTT)

PTT is a therapeutic method in which light energy is converted into heat energy after PTAs are irradiated by external light sources, such as NIR [20]. This converted heat energy can effectively kill bacteria through a variety of thermal effects, such as cell membrane rupture, cell fluid evaporation, protein/enzyme degeneration, and cell hollowing. Previously, anti-cancer applications were the most used fields for PTT [21]. However, researchers have also utilized PTT in various ways for antibacterial activity and wound healing [13][20]. PTT is a non-invasive technique with low side effects and high specificity. Owing to these beneficial attributes, PTT has emerged as a promising strategy for combatting MDR pathogenic infections.

2.1.1. Mechanism of PTT

The working mechanism of PTT involves the conversion of light energy into heat energy for use in the surrounding environment by photothermal materials. Owing to the distinct photophysical characteristics of various materials, it is evident that photothermal conversion mechanisms are different for different materials. In this section, the photothermal conversion mechanisms of all the photothermal materials are broadly described.

PTTs using noble metal (for example, Ag and Au)-based nanomaterials are well-known [22], and their excellent photothermal properties can be attributed to the localized surface plasmon resonance (LSPR) effect of the nanomaterials [23]. Free electrons from the noble metallic nanoparticle surface are excited after the nanoparticles absorb the energy of photons at the appropriate wavelengths. The conduction band electrons then start to vibrate collectively at the same frequency. The LSPR effect is the term applied to this phenomenon [24]. LSPR can decay both radiatively and non-radiatively. The plasmonic enhancement of the electric field in the near-field regime is mainly governed by the radiative decay process, whereas the formation of hot electrons is directed by the non-radiative decay process via intra- or inter-band transitions. As light absorption (for example, NIR light) can be increased by modifying a particle size or structure, the LSPR effect is significantly correlated with several characteristics, including particle morphology, size, and composition [25]. The plasma coupling effect is another approach for enhancing the LSPR effect. Although noble metal (Ag and Au)-based nanomaterials are mostly used for the plasmonic effect, some materials, such as Al, Cu, Co, Ni, and CuS, have also been investigated for the same purpose [23].

Another photothermal conversion mechanism comprises the generation and relaxation of electron (e^-)–hole (h^+) pairs; these often occur in semiconductors [26]. In this process, the semiconductor absorbs photons to produce active e^-–h^+ pairs after being irradiated with light energy (the energy should be equal to or greater than the band gap energy of the semiconductor). After light irradiation, electrons are generated in the conduction band (CB), followed by electronic vacancies or holes in the valence band (VB). At this point, either the radiative (photons) or non-radiative (phonons)

process is used for the subsequent relaxation from the higher excited states to the lower-energy states. This non-radiative process releases heat, resulting in a thermal (vibrational) energy increment of the lattice, which can be measured as an increase in their temperature.

Lattice vibrations are another photothermal conversion mechanism by which carbon and polymer-based materials exhibit excellent photothermal properties [26]. In this mechanism, less tightly held electrons in π bonds from the π orbital can be easily excited to the π* orbital with lower energy input. Notably, the light-irradiated excitation of electrons (π→π*) induces a strong absorption in the NIR region. The excited electrons released the absorbed energy as heat during their return to the ground state, resulting in an increase in the temperature.

2.1.2. Advantages of PTT

PTT has emerged as a potential solution for treating MDR pathogens and a viable alternative to antibiotics [13][20][27] owing to the following advantages: (1) broad-spectrum antibacterial effects for both Gram-negative (G−) bacteria and Gram-positive (G+) bacteria irrespective of the membrane structure, owing to the penetration ability of the light sources (for example NIR) utilized in PTT; (2) a good tissue penetration ability without causing tissue damage based on the commonly utilized NIR light source (700–1400 nm), which enhances the chances for successful bacterial treatments (even in deep tissues); (3) localized hyperthermia for the antibacterial activity to reduce the risk of damaging normal cells; (4) facilitation of antibacterial agent penetration inside the biofilm via hyperthermia; and (5) a non-invasive and non-contact mechanism which minimizes the opportunity for bacteria to obtain resistance against the therapy. From the above features, it is easy to understand why PTT-mediated therapy for combatting MDR pathogens is gathering significant attention.

2.1.3. Limitations of PTT

Despite the considerable interest in PTT, significant obstacles remain before PTT can be fully employed for practical applications. First, PTT usually requires high temperatures (≥60 °C) to kill bacteria [20]. Such prolonged hyperthermia kills bacterial cells and thermally harms the normal tissues around bacterial infection sites [16]. Therefore, a more strategic design is necessary to optimize the conditions, for example, with shorter treatment times at lower temperatures (~50 °C). Additionally, normal tissues may be critically affected by the necessity for a high excitation light power and high PTA dosage; these aspects require quick attention to ensure safer and more efficient PTT.

2.2. Photodynamic Therapy (PDT)

PDT combines photoresponsive materials such as photocatalysts and photosensitizers (PSs) and a light source to kill bacterial cells [17]. Currently, PDT has mainly been applied to cancers as a clinical therapeutic approach to treating non-invasive tumors. It is regarded as a major step in anti-cancer applications, including surgery, chemotherapy, and radiotherapy [28]. Additionally, PDT has been applied to other hard-to-treat diseases such as rheumatoid arthritis, actinic keratosis, and bacterial infections. Researchers have used PDT for antibacterial activity owing to its low toxicity, the negligible chance of drug resistance with mild adverse reactions, and excellent antibacterial potential.

2.2.1. Mechanism of PDT

The primary mechanism of PDT relies on the generation of ROS, including hydroxyl radicals (·OH), singlet oxygens ($^1O_2$), or superoxide radicals ($\cdot O^{2-}$) after photoresponsive materials are exposed to laser irradiation [29]. It is widely acknowledged that “toxic” cellular waste (i.e., ROS) can permanently damage macromolecules such as nucleic acids, lipids, and proteins after entering bacterial cells. The ROS generated by the PDT can directly or indirectly interfere with the physiological activities of the cells, ultimately leading to cell death [30]. In a different procedure, ROS can attach to bacterial cell walls and membranes, leading to cell death.

The ROS generation mechanism for PSs differs from that for photocatalysts [31]. There are two main molecular-level mechanisms in the photosensitization route [32] for controlling PDT-mediated antibacterial activity. One of the mechanisms normally occurs in bacterial cell membranes. In this mechanism, molecules from the PS temporarily migrate from the ground state to the singlet state (^{1}PS) and subsequently reach the time-extended triplet state (^{3}PS) by inter-system scurrying. In this scenario, the ^{3}PS produces ROS, such as ·OH and $\cdot O^{2-}$, through electron transfer after reacting with biomolecules in the surrounding environment. Subsequently, the ROS disrupt the bacterial cell membranes and increases their ion permeability for killing bacteria. In the second mechanism, the ^{3}PS can directly react with oxygen molecules to undergo an energy transfer for the formation of $^1O_2$ with a very short lifetime (and only able to react within a micrometer range of its generation site). This singlet oxygen can cause oxidative damage to intracellular bacterial compounds and eventually kill them. The PS molecules return to their ground states for the next cycle of reactions after the reactions are complete.

SPR also has the potential to enhance PDT-mediated antibacterial activity [33]. Photoinduced noble metals (Ag and Au) and metallic compounds (CuS) can produce SPR, which activates electrons that can be transferred to the CBs of the photocatalysts. As a second mechanism, the irradiation near the plasmon resonance frequency of noble metals can substantially enhance the local electric field, accelerating the separation of e^{-}-h^{+} pairs. In this regard, PSs and noble metals can be applied together for better antibacterial activity [34].

Up-conversion nanoparticles (UCNPs) represent another approach to resolving the poor penetration ability of PDT. UCNPs can convert the excitation of long-wavelength light into short-wavelength light for PDT based on visible light-responsive photocatalysts [35].

2.2.2. Advantages of PDT

Researchers are eager to seek alternatives to antibiotics owing to the ever-increasing number of MDR pathogens. In this regard, PDT has emerged as a viable option for treating MDR pathogens, owing to the following advantages: (1) broad-spectrum activity with ROS production, which disrupts many metabolic pathways of bacteria and their cellular structures rather than focusing on a single process or structure; (2) light-irradiation-induced antibacterial activity with photoresponsive ROS-generating materials; correspondingly, the chances of bacteria becoming resistant to the photoresponsive materials are very minimal; (3) preferential control of the binding to bacteria at the infected site of the body, light time, and location [36]; (4) low cytotoxicity to normal cells when treating bacterial infections in living organisms; (5) combinations with other therapies, such as radiotherapy, chemotherapy, and PTT; and (6) remote chances of any self-adaptability transferring to the next generation of bacterial cells in a very short time. Hence, the chances of bacteria becoming resistant are greatly reduced.

2.2.3. Limitations of PDT

Despite the above-mentioned advantages of PDT, certain limitations must be addressed before it can be fully utilized to treat bacterial infections in living organisms. ROS-mediated PDT depends on photoresponsive materials and a light source for the irradiation of biological tissues. However, owing to the thickness of human tissue, the poor penetration ability or shallow depth of short-wavelength light or both has hindered the application of PDT to human tissues for antibacterial infections [37]. A longer-wavelength light source could provide greater tissue penetration. However, the ROS production for PDT is directly correlated with the energy of the light; therefore, light sources with longer wavelengths and low energies limit the production of ROS. Thus, UV light with a short wavelength and high energy can produce more ROS and is highly effective in killing microorganisms [38]. However, UV irradiation can also damage normal cells and tissues. Hence, the selection of an appropriate light source must be addressed to improve PDT applications.

Additionally, the development of PDT for clinical use is constrained by the limited release distance and lifespan of the ROS, as well as the low stability, toxicity, and ineffective bacterial targeting of certain photoresponsive materials [17]. Notably, PDT is less effective for G− bacteria than for G+ bacteria owing to the different membrane structures and limited penetration ability of ROS; this also requires further research. Therefore, the limitations of PDT need to be fully addressed before it can be further applied in practical applications.

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