Photodynamic Therapy against Cancer

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Contributor: Sandile Phinda Songca

Photodynamic therapy (PDT) is based on the initial absorption of light by the photosensitizer (PS) and the subsequent direct and oxygen-mediated reactions with the cell membrane and cytoplasmic cell components.

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1. Introduction

Several compounds known as photosensitizers absorb light energy and transfer it to oxygen in the triplet ground state to produce reactive oxygen in the singlet excited state. Following this, a series of other reactive oxygen species are produced in biological media. Upon excitation with light energy, most of these compounds can also react directly with the biological cell membrane and cytoplasmic components, including monosaccharides, nucleic and amino acid components of DNA, RNA, glycan, and protein molecules. Photodynamic therapy (PDT) is based on the initial absorption of light by the photosensitizer (PS) and the subsequent direct and oxygen-mediated reactions with the cell membrane and cytoplasmic cell components. These reactions initiate cell death by apoptosis or their cell destruction by necrosis. Thus, PDT requires the accumulation of the PS through targeted delivery to the disease site and cells, which either does not occur in normal healthy cells or does so to a relatively lower degree compared to the disease site and cells.

2. Anticancer Photodynamic Therapy

When applied to cancer, PDT can act through a combination of cancer cell death and inhibiting the growth of tumors due to cancer cell growth inhibition. It relies on the preferential accumulation of the PS in cancer tissue, where it photosensitizes the generation of reactive oxygen species which kill cancer cells in the microenvironment of the disease. The origin of the clinical approach is attributed to the direct administration and some level of preferential accumulation of hematoporphyrin and hematoporphyrin derivative following systemic circulation [1]. Current focus is now paid to targeted nanomaterial-mediated PS administration. However, some researchers still administer the free PSs directly without nanomaterials. The integration of coumarin into amphoteric nanocapsules is an example of the administration of the PS encapsulated in organic nanomaterials with the aim of optimal systemic navigation due to the amphiphilicity of the nanomaterial and disease accumulation due to hydrophobicity of the PS [2].

Comparison of the in vitro efficacy of novel zinc (II) phthalocyanine-quinoline conjugate with Photofrin, on the other hand, illustrates the direct approach without incorporating the PS in any form of nanomaterial [3]. In this study, the zinc (II) phthalocyanine-quinoline conjugate and the Photofrin were administered to the cell lines as solutions in N, N-dimethylacetamide containing 3.8% polyoxyethylene-35-castor oil, and phosphate-buffered saline, respectively. The advantages of using nanoparticles as carrier and delivery agents for the PS, compared to using the free PSs, which include the improvement of solubility, biodistribution, uptake, retention, targeted cancer cell delivery, the reduction of self-degradation, and applications in combination therapies involving PDT, have been elucidated with numerous examples of metal nanoparticles encapsulated in various shells containing the PS [4]. In this regard, silver and gold nanoparticles are among the most widely studied [5]. While metal oxide nanoparticles are widely studied as carriers and delivery nanosystems of the organic dye type of PSs for targeted anticancer PDT [6], iron oxide nanoparticles have been highly prized for magnetic hyperthermia, magnetic tumor targeting and magnetic resonance imaging-assisted anticancer PDT [7][8][9][10]

Cancer cell-targeted, controlled, and stimulus-responsive release of the PS is seen as the ultimate gold prize of nanomaterial-mediated PDT, through which deep metastatic cancer cells can be isolated for destruction before they form tumors [11][12]. Much research has therefore focused on metastatic cancer cell targeting for PDT. Photoimmunotherapy, for example, is a technology that combines PDT and immunotherapy, in which the PS is conjugated to a monoclonal antibody or biologically recognizable fragment thereof to target antigens actively and specifically for high-precision targeted drug delivery and induction of anticancer immune response [13]. Additionally, a peptide that is easily cleaved by the cysteine protease Cathepsin B was used as a linker for anchoring the PS Verteporfin onto the surface of gold nanoparticles so that upon cancer cell internalization of the nanoconjugate the PS is released after cleavage of the peptide linker [14].

3. Antimicrobial Photodynamic Therapy

From its origins as an anticancer therapeutic technology, PDT has evolved. It is now widely used against a variety of ailments, the top among which is antimicrobial PDT as applied against bacterial, fungal, and viral infections, as well as applications in the sanitization of the environment and pest control [15]. Antimicrobial PDT against many viral infections, such as the recent COVID-19 viral pandemic [16], bacterial [17] and fungal [18] infections, and environmental sanitation [19], have been widely investigated. Examples of applications of antibacterial PDT include periodontal disease [20][21], superficial wounds [22], and burns [23]. It is considered to hold great promise for the developing world, where bacterial infections cause a large number of deaths, in a global context where the widespread use of antibiotics is fuelling the rapid emergence of bacterial resistance [24].

The formation of biofilms drives the development of resistance with some bacterial and fungal infections through a multistage process involving planktonic microbial quorum sensing [25], surface adhesion, colony formation and maturation, and biofilm formation, with microbial detachment from biofilms leading to attachment elsewhere, starting the process all over again as the biofilm grows [26][27]. Throughout its life cycle, the bacterial cells remain suspended in, and otherwise embedded in the biofilm, which is made up of an extracellular polymeric substance matrix consisting of polysaccharides, proteins, peptides, nucleic acids, and lipids, making it difficult to reach the

suspended bacterial cells [28][29][30]. Antibacterial PDT has been shown to overcome the biofilm-mediated bacterial resistance strategy by breaking down the extracellular polymeric substance matrix, thereby providing access to the bacterial cells that are embedded in it [31][32].

Nanoconjugates incorporating the PS in their structure and composition constitute the most widely reported antibacterial PDT strategy compared to the application of free PSs [33]. The structure of these nanoconjugates is designed to ensure labile incorporation of the PS into the conjugate so that it retains the capability to generate reactive oxygen species [34]. Several nanoparticles act as antibacterial PDT PSs capable of biofilm degradation and bacterial cell destruction on their own. The most widely reported include nanoparticles of porphyrins [35] and phthalocyanines [36], metallic silver [37] and metallic gold [38], and copper sulphide [39], as well as oxides of nanographene [35], zinc [40], and iron [41]. For example, the three different morphologies of copper sulfide nanostructures, including microspheres, nanosheets, and nanoparticles, were found to exhibit different antibacterial PDT activities against *E. coli*, and this was largely attributed to their different concomitant photothermal conversion coefficients upon irradiation with normal sunlight [42]. Most of the magnetic metal chalcogenide nanomaterials exhibit concomitant photothermal and magnetothermal conversion capability and are therefore used as agents for combination therapies involving PTT, MGH, and PDT. For example, iron oxide nanoparticles are used in MGH, PTT, and PDT combinations [41]. Furthermore, studies have shown that nanographene oxide and copper sulfide nanoparticles are efficacious PTT and PDT agents [35][39]. Bacterial infection stimulus-responsive release of the PS derived from cleverly designed nanoconjugates for antibacterial PDT exploits any of the characteristics of the biofilm microenvironment, such as lower pH, insufficient oxygenation, and the altered concentration of enzymes and hydrogen peroxide compared to normal tissue microenvironments [43][44]. **Table 1** lists the some of the current applications of PDT.

Table 1. Some of the applications of photodynamic therapy.

Applications and Description	References	
1	Anticancer	[1][2][3][4][5][6][7][8][9][10][11][12][13][14]
2	Antimicrobial	[15][16][17][18][19][20][21][22][23][24][25][26][27][28][29][30][31][32] [33][34][35][36][37][38][39][40][41][42][43][44]
3	Viral Herpes	[45][46]
4	SARS-CoV-2	[16][47]
5	Bacterial Acne	[48][49]
6	Wet age-related macular degeneration	[50][51]
7	Atherosclerosis	[52][53]
8	Psoriasis	[54][55]

Applications and Description	References	
9	Environmental sanitization	[15][56][57]
10	Pest control	[15][58][59]
11	Dermatology	[60][61]

4. Other Applications of Photodynamic Therapy

As the pathogenic cause of acne, bacterial and fungal growth that occurs when the hair follicles become plugged with oil and dead skin cells in the skin, especially on the face, may be treated with antibacterial PDT [48]. Wet age-related macular degeneration occurs when abnormal blood vessels grow in the back of the eye and damage the macula [62]. PDT destroys the macula blood vessels, after which new growth gives rise to normal blood vessels [63]. An accumulation of plaque in the inner lining causes atherosclerosis as a thickening or hardening of the arteries [64]. Fast-growing skin cells cause an itchy scalp and flakes on the skin known as psoriasis [65]. The recent emergence of viral pandemics, such as the recent pandemic caused by COVD-19, has triggered an avalanche of interest in antiviral PDT [66]. PDT has been shown to destroy viruses, bacteria, and fungi [67]. For this reason, the technology has been tested for sanitization of the environment, such as work surfaces, where the reactive oxygen species produced can kill microorganisms. It has also been tested as a pesticide against insect larvae [58]. From the foregoing discussion, it is easy to see why the applications of PDT have gone beyond cancer and bacterial infections to include the treatment of acne [48][49], wet age-related macular degeneration [50][51], atherosclerosis [52][53], psoriasis [54][55], and antiviral treatments [61][68], including herpes [45][46] and the COVID-19 [47] virus. Investigations have been conducted for environmental sanitization [56] and pest control [58][59] and why it is among the most commonly used therapeutic techniques in dermatology [60][69].

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