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Cell reactions and immune responses to photodynamic therapy in oncology

Procesy komórkowe oraz odpowiedzi immunologiczne na terapię fotodynamiczną w onkologii

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Summary

Photodynamic therapy (PDT) is a noninvasive, highly selective method for the treatment of diseases characterized by uncontrolled cell proliferation. It was clinically approved more than 30 years ago. PDT involves the selective uptake of a photosensitizer (PS) by neoplastic tissue, which is able to produce reactive oxygen species (ROS) upon irradiation with visible or near-infrared (NIR) light. ROS induce destruction of target cells and damage of tumor-associated vasculature and activate an antitumor immune response, leading to tumor regression. The execution of this process is attained by different mechanisms, including host immune responses and activation of cell death pathways: apoptosis and necrosis.

Keywords: photodynamic cancer therapy • immune response • cell death • apoptosis • necrosis

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Introduction

Photodynamic therapy (PDT) is a minimally invasive modality used in the treatment of a variety of cancers and benign diseases (table 1). It was originally used in the management of a small number of selected tumors [25] and has expanded to areas of application as diverse as dermatology [4,54] and cosmetics [84,85], immunology [17], ophthalmology [63,80], cardiology [89,92], urology [8] and dentistry [45,61]. Furthermore, PDT has been successfully used against antibiotic-resistant bacteria [3,81], for the treatment of viral [16,87] and fungal infections [11,73,74], for the inactivation of pathogens in blood products [88], for water sterilization [7,58] and for disinfection [10,59]. The photodynamic process is also used for drug delivery and the release of endocytosed molecules in the cytosol [5,6].

Photosensitizers and photodynamic reaction

The destruction of target cells in PDT is achieved by activation of a light-absorbing photosensitizer (PS) with visible or near-infrared light (figure 1).

The activated PS is excited to its singlet state, and, after intersystem crossing to the triplet state, PS transfers its energy to molecular oxygen and generates reactive singlet oxygen (type II reaction), or reacts directly with biomolecules (type I reaction), forming reactive oxygen species (ROS): superoxide anion, hydroxyl radical, hydrogen peroxide. ROS mediate oxidative damage of intracellular structures, causing cell death via apoptosis or necrosis [12,68], vascular shutdown, induction of an antitumour immune response, and the consequent destruction of the tumor [2]. Because the PS is effective only in the presence of light, generalized toxicity in PDT is avoided by illuminating only the specific area. Unfortunately the ROS also switch on a stress response of cancer cells that helps them to deal with the PDT-induced oxidative stress (repair and survival pathway).

The majority of currently used PSs (table 2) are cyclic tetrapyrrolic molecules – porphyrins and their analogs, chlorins, phthalocyanines, etc. – and their characteristics have been thoroughly reviewed [71]. The first clinically approved PS was Photofrin, a hematoporphyrin derivative, widely used in clinical PDT [90]. Shortcomings of Photofrin [70] stimulated research of compounds which can meet the requirements for an ideal PS [77]. Researchers succeeded in several aspects: synthesis of stable PSs absorbing red and NIR light (650–800 nm), which allow for better tissue penetration [18,19,93]; better pharmacokinetics for faster elimination from the body and reduction of side effects; and selectivity – increasing the target/healthy tissue ratio [2,60,78,82].

In further improvement of PSs, priority was given to the targeting of the PS to particular cellular organelles, increasing PS uptake and shifting absorbance to longer light wavelengths. Key elements in PDT are illumination and optical properties of tissues that determine the depth and efficacy of the treatment. Light absorption by endogenous chromophores, such as hemoglobin and melanin, limit light penetration at wavelengths <650 nm, whereas light penetration is reduced due to absorption by water at wavelengths over 1,300 nm. The first study involved the natural pigments bacteriochlorins and bacteriopurpurins, with strong absorption of NIR light (720–850 nm) [39], but revealed that they are photounstable and permit limited chemical modifications [38,66]. Recently developed new synthetic bacteriochlorins are more stable and demonstrate improved pharmacokinetics and high PDT efficacy [18,19,20,38,93].

Cell responses

The PS is preferentially taken up and retained by tumor cells, and its subcellular localization determines the sites of primary damage and influences the way of cell death [43]. Generally speaking, mitochondrially localized PSs induce programmed cell death (apoptosis), whereas lysosomally localized ones can cause either a necrotic or an apoptotic response [42,64]. A dose-dependent apoptosis to necrosis shift has been found for most PSs [27,75].

Depending on morphology, enzymatic activity and immunologic responses, the cell death mode is designated as either programmed or non-programmed [50]. Apoptosis is the standard programmed cell death characterized by nuclear and membrane degradation [26]. It is triggered by specific signals that lead to the activation of cascade pathways and result in degradation of nucleic and polypeptide materials and a suicidal outcome. Apoptosis involves a family of caspases – cysteine aspartyl proteases – that stimulate other effector agents to disassemble cellular contents.

Table 1. Clinical applications of PDT in medicine

	Clinical applications of PDT
Cardiology	arteriosclerosis endothelial cell hypertrophy
Dentistry	endodontic treatment periodontitis
Dermatology	psoriasis keratoses
Immunology	immune responses modulation specific drug delivery
Infectious diseases	viral, fungal and bacterial infections
oncology	malignancies precancerous lesions (detection and therapy)
Ophthalmology	choroidal neovascularization
Transfusion medicine	inactivation of pathogens in blood products
Urology	prostate cancer superficial bladder carcinoma

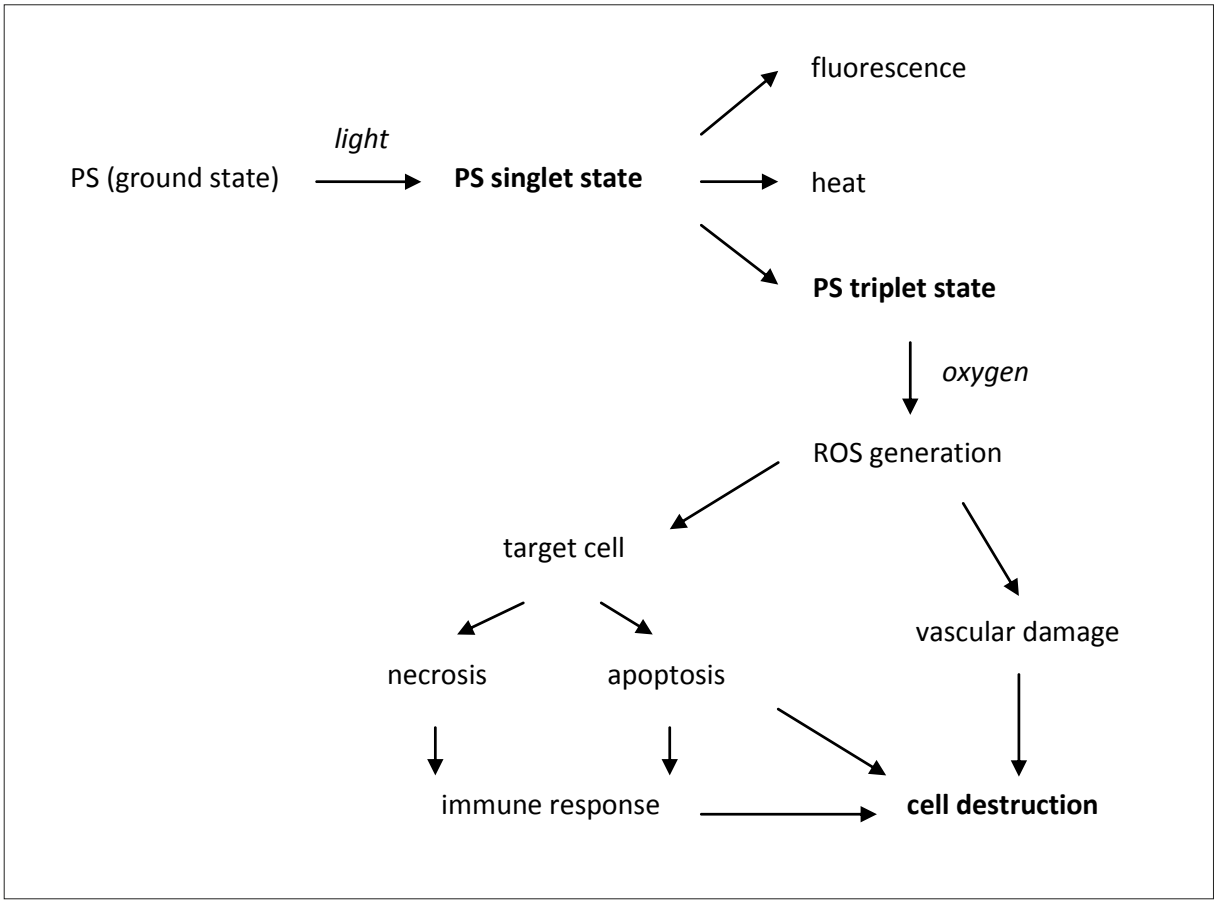

Fig. 1. PDT-mediated cellular effects.

Table 2. Clinically available PS

Group	Substance	Commercial name	Manufacturer
Chlorine	2-(1-Hexyloxyethyl)-2-devinyl pyropheophorbide-a (HPPH)	Photochlor	*Roswell Park Cancer Institute*
	talaporfin	Apoptosin, Laserphyrin, Litx, LS11, Photolon	Light Sciences
	temoporfin	Foscan	Biolitec Pharma
Padoporfin	bacteriochlorophyll	Tookad	The Weisman Institute of Science
Phthalocianines	phthalocyanine	Pc4	Case Western Reserve University
	phthalocyanine	Photosens	Russian General Physics Instute
Porphyrin	aminolevulinic acid	Levulan	DUSA Pharmaceuticals
	hematoporphyrin derivative	Photofrin	Axcan Pharma
	hematoporphyrin derivative	Photogem	Moscow Research Oncological Institute, TimTec
	hexaminolevulinate	Hexvix	Photocure ASA
	methyl aminolevulinate	Metvix	Galderma
	verteporfin	Visudyne	Novartis Pharmaceuticals
Texaphyrin	lutexaphyrin	Antrin, Lu-Tex	Pharmacylics

Affected cells round off and wind up communication with adjacent cells, their plasma membranes fragment and phosphatidylserines translocate to the outer layers. Other changes follow: cross-linkage and polymerization of proteins, chromatin condensation, nuclear fragmentation by cation-dependent endonuclease and, finally, fragmentation into apoptotic bodies and removal. Mitochondrial membranes' increased permeability and the release of apoptogenic substances, such as cytochrome C, characterize the intrinsic pathway of apoptosis. The extrinsic pathway involves the activation of cell membrane death receptors, such as tumor necrosis factor receptor 1 (TNFR1) or Fas/CD95 [26,41,44].

Generally, PSs with a predilection for mitochondrial accumulation and causing Bcl-2 protein destruction are inducers of apoptosis [67]. For example, silicon phthalocyanine (PC-4) was proven to promote apoptosis of malignant CD4+ CD7– T-lymphocytes by destruction of Bcl-2 [53]. Similarly, in breast cancer cells a metallo-PC--mediated PDT led to apoptosis, with the predominance of apoptotic cells after PDT, nuclear fragmentation and increased expression of Bcl-2, DNA fragmentation factor alpha (*DFFA1*) and caspase 2 (*CASP2*) genes [62]. Another way for apoptotic cell death induction is the transfer of calcium ions (Ca^{2+}) from endoplasmic reticulum to mitochondria, causing calcium overload in mitochondria. That leads to morphological changes and apoptosis in a nonnuclear and Ca^{2+}-dependent manner [33]. Additionally, PDT has the ability to induce cell damage in the presence of an increased level of intracellular Ca^{2+}, which appears to be p53 dependent [32].

Necrosis is defined as accidental and non-programmed cell death, characterized by an inflammatory response and the absence of signals associated with apoptosis. A necrotic response can be stimulated by stress factors such as infectious pathogens, toxins and trauma [50,55]. It was found that signal transduction and catabolic reactions of the necrotic pathway are initiated by toll-like receptors (TLR) and the death domain [14]. Seven types of necrotic pathways have been recognized, but the sequence of events is common for all, including oncosis (swelling of the nucleus and mitochondria and cytoplasm vacuolization), membrane permeability, lysosomal perforation, movement of calcium ions across the endoplasmic reticulum and calpain (a family of calcium--dependent, non-lysosomal cysteine proteases) activation, followed by degradation of cell components and induction of the inflammatory response [15].

PCs leading to cell membrane disintegration and local depletion of oxygen and nutrients would stimulate cell death mainly by necrosis [67]. Liposomal aluminum chloro-phthalocyanine (AlClPC) mediated PDT led to 90% necrotic cell death and disruption of blood vessels, in both *in vitro* and *in vivo* studies using an oral cancer cell line [56,57]. Another evident increase of necrotic--related cell death was observed in the case of application of phthalocyanine tetra-sulfonated zinc [76].

The relative uptake and subcellular localization are dependent on particular chemical features of PC. Neutral PCs show more diffuse localization and tend to be primarily localized in the Golgi apparatus in the perinuclear area, whereas ionic PCs are initially collected in lysosomes. The cationic (ahead of the neutral) PCs seem to be more effective than the anionic ones. Following irradiation, PCs undergo relocalization, which is charge dependent, and this demonstrated that the secondary localization site is more important in predicting the outcome of any PC-mediated PDT [91].

Worth mentioning, a promising strategy for more effective PDT is the use of two combined PSs. Simultaneous administration of two chemically different PSs – zinc(II)-phthalocyanine (ZnPc) and the cationic porphyrin *meso*-tetrakis(4-*N*-methylpyridyl)porphine (TMPyP) – in three cell lines (HeLa, HaCaT and MCF-7) provided synergistic cure rates compared to standard PDT. Moreover, depending on the light dose, changes from predominant apoptosis (without cell detachment) to predominant necrosis were detected [1].

Immune responses

The immune system plays a leading role in the therapeutic outcome of PDT. Recent studies in mice revealed the importance of effector immune cells for the therapeutic response [28,46,69].

Non-specific immune response in PDT

PDT-induced oxidative damage affects mainly the membranes and cytoplasm of tumor cells, tumor vasculature, and other stromal elements. The local host response develops as acute inflammation [46], triggered by release of cytoplasmic components, vasoactive agents and activation of the complement cascade. This acute inflammation is expressed by the secretion of cytokines, leukocyte chemoattractants, growth factors, and other regulators, leading to infiltration of the tissue with neutrophils, macrophages, mastocytes, and natural killer (NK) cells [24].

Among cytokines (interleukins [IL-1β, IL-6, IL-10], tumor necrosis factor [TNF], granulocyte-colony stimulating factor [G-CSF]) and chemokines (murine chemokines [KC], macrophage-inflammatory protein-2 [MIP-2]) induced by the photodynamic reaction, IL-1β seems to be the most important [35]. Neutralization of IL-1β reduces the efficacy of PDT, whereas no significant effects are observed with anti-IL-6 and anti-TNF-alpha antibodies [83]. Furthermore, PDT combined with recombinant cytokines (G-CSF, GM-CSF, and TNF) is more effective [23,34,51]. Also anti-inflammatory cytokines such as IL-10 and transforming growth factor beta (TGF-β) improve PDT outcomes [46].

The first cells invading PDT-treated tumor sites are neutrophils. Depletion of neutrophils in mouse and rat

models impairs the efficacy of antitumor PDT [22,47]. Macrophages infiltrating the tumor bed also play a role in the PDT-induced response. Inactivation of macrophages with silica particles decreases cure rates in mice, while macrophage-activating GM-CSF or vitamin D3-binding protein improves PDT antitumor effects [49,51]. Another major element of the non-specific immune response is NK cells. The response to a suboptimal PDT dose is significantly reduced by NK cell depletion [37].

Innate immune cells encounter released tumor antigens (including oxidatively modified ones) and molecules known as damage-associated molecular patterns (DAMPs) or cell death-associated molecular patterns (CDAMPs) [24]. DAMPs and CDAMPs serve as warning signals and promote inflammatory responses to cell stress, injury, or death. DAMPs bind to pattern recognition receptors (PRRs) of infiltrating leukocytes and stimulate antigen-presenting cells (APCs). DAMPs released from PDT-treated tumor cells are considered to be key players in the immunogenicity of tumor cells. The best known PDT-induced DAMPs are the heat-shock protein family (HSP), adenosine triphosphate (ATP), high mobility group box-1 (HMGB-1), and calreticulin (CRT) [29,31].

Specific immune response in PDT

It has been noted that the adaptive immune response is influenced by PDT-mediated inflammation [9]. The intermediaries between innate and adaptive immune systems are dendritic cells (DCs), the most potent APCs [79]. DC maturation is triggered by PDT-elicited local and systemic inflammation caused by PDT-related oxidative stress and tumor cell apoptotic and necrotic death [30,36,40,52]. Activated and functionally mature DCs that have captured tumor-derived proteins and encounter DAMPs migrate to the secondary lymphoid tissues, where they prime T cells with tumor-associated antigens (TAA) associated with major histocompatibility complex class I and II molecules (MHC).

An effective specific immune response depends on proper selection, proliferation, and differentiation of antigen-specific T lymphocytes into activated effector T cells [72], which infiltrate the tumor site [65]. Several studies accentuate the role of cytotoxic CD8+ T cells in PDT outcome and clinical efficacy [13]. Long-term tumor control after PDT treatment is possible only in immunocompetent mice. However, adoptive transfer of T lymphocytes from naive mice that underwent successful PDT restored antitumor PDT efficacy in immunodeficient ones [37,48]. Moreover, PDT of multifocal angiosarcoma resulted in spontaneous regression of untreated distant tumors [86]. T-cell depletion studies revealed that the CD8+ T-cell population is essential for a successful PDT response, whereas the CD4+ T cell population plays only a supportive role [37]. MHC class I molecules lacking tumors are resistant to a specific immune response since recognition of an antigen complexed with MHC I is necessary for CD8+ T cell activation [21].

Conclusion

Cell death processes lead to elimination of undesirable cells from the organism. The execution of these processes is accomplished by cell senescence, apoptosis and necrosis. The generation of ROS and induction of oxidative responses are essential for these eradicating mechanisms. PDT is an efficient treatment modality selectively inducing oxidative damage in cancer cells. PDT remains an attractive and promising therapeutic strategy in the light of steadily growing knowledge of the interaction between the immune system and tumor cells. It is believed that the unique properties of PDT combined with adjuvant immunotherapy may offer not only simple destruction of the primary tumor but also stimulation of the host immune system to recognize, track down, and ultimately destroy tumor cells that have metastasized to distant regions of the body. Further research is needed, especially in the fields of PS selectivity and tumor cell survival pathways and their inhibitors. Higher PDT efficacy will lead to better disease management and prolonged patient survival.

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