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Molecular mechanisms of photodynamic therapy

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1. ABSTRACT

Despite its more than 100-year history in experimental and clinical use, photodynamic therapy (PDT) is only starting to be appreciated for its full potential. PDT combines a photosensitizer (PS) and light in the presence of oxygen to treat cancer and other disorders. This manuscript reviews molecular mechanisms that have been evaluated over the past years for the effects of PDT at the cellular level as well as in therapeutic settings *in vivo*. The availability of multiple PS with different structures and functional properties makes PDT an extremely versatile and, conversely, a challenging approach to cancer therapy. The advancing understanding of molecular pathways helps to design improved regimens. As most cancers are being treated with combination therapies, PDT is being integrated into rationally designed combined regimens that exploit molecular responses to PDT for improved efficacy.

2. INTRODUCTION

Photodynamic therapy (PDT) is an oxygen-dependent photosensitization modality, in which a photosensitizer (PS) and electromagnetic radiation in the visible range (light) are combined at the site of desired action. Most often PDT is targeted for cancer treatment (1), but numerous other applications have been explored. PDT is a versatile treatment with multiple PS at hand, which exhibit different molecular properties and photobiological effects. The wavelengths of light for PS activation are chosen according to the absorption properties of the PS and the desired tissue penetration depth (2).

The photochemical reactions in PDT are depicted in a simplified scheme in figure 1. The PS in the ground state absorbs light and is activated to the single excited state, a short-lived existence that either returns to the ground state by non-radiative decay or by emitting

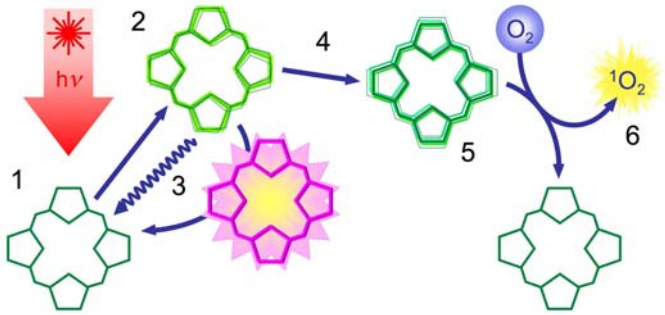

Figure 1. Simplified scheme of photosensitization in PDT. The PS in the ground state (1) absorbs light (hν) and enters the first singlet excited state (2). This short-lived species gives off energy in form of fluorescence or vibrational energy (3) when the PS returns to the ground state. The singlet excited state can also undergo intersystem crossing (4) to the triplet excited state (5). The triplet state is longer-lived and can transfer its energy to molecular oxygen, creating singlet oxygen (6).

fluorescence. Alternatively, by intersystem crossing, the triplet excited state is formed that is much longer-lived and thus has the opportunity to interact with other molecules. The energy transfer to molecular oxygen results in the formation of singlet oxygen, the most important reactive species in PDT (3, 4).

In a clinical setting, the PS is injected and distributes throughout the body, accumulating with some preference in the tumor (figure 2). In a subsequent waiting period the PS is retained in the tumor, while the rest of the body clears it more rapidly. At this time PS fluorescence may be used to evaluate the tumor extent and its PS content for optimized dosimetry (5, 6). The irradiation is done preferably with red light to allow deep tissue penetration. The tumor is destroyed and the tissue heals with some scarring. Because of its dual selectivity, which stems from both the preferential accumulation and retention of the PS in the tumor and targeted light delivery, damage to normal tissue surrounding the tumor is minimized. PDT under clinical conditions is not genotoxic, and repeated use does not result in cumulative toxicity. Furthermore, neither light nor PS interferes with the metabolism or the pharmacokinetic and pharmacological properties of other anti-neoplastic drugs. Consequently, PDT is well suited for use in combination with other treatment modalities, an approach that is getting increasing support from preclinical research (7, 8).

Between the initial photochemical reaction of the PS and the therapeutic response of the tumor lies a sequence of molecular effects and cellular reactions that determine immediate tissue response and long-term outcome. These events affect gene expression, neovasculature, death pathways, and tumor immunity. In this manuscript we will discuss multiple molecular responses that have been elucidated in cells after exposure to PDT. We will concentrate on mammalian cells, although PDT has been explored beyond this range, with applications in the treatment of bacterial, fungal, and parasitic diseases. One has to caution that due to the vast variety of photosensitizing protocols, certain molecular mechanisms may only occur in specific combinations of target cell, PS, light dose, and may not apply, or even show opposite effects, in a different biological setting.

3. MOLECULAR MECHANISMS

3.1. Molecular targeting

The molecular mechanisms of photosensitization can be separated into two sections, those that affect PDT before the light exposure, and those that occur in response to the photosensitized reaction. The former mostly relate to the distribution of PS in cells and tumors. The structure of many PS is based on the tetrapyrrol ring (e.g., protoporphyrin IX, Photofrin, chlorins) or related to it (purpurins, phthalocyanines, pheophorbides). Other agents that have been used as PS include quinine-type structures (hypericin), xanthene-based compounds (rhodamines) and phenothiazines (9). Lipophilicity of certain PS is a driving force for their cell uptake and distribution to the plasma membrane and membranes of intracellular organelles. Primary structure, side chain substitutions, complexed metal ions and charge decide molecular properties including polarity, solubility, pharmacokinetics, and subcellular distribution. They also determine absorption spectrum, as well as triplet state and singlet oxygen yields upon irradiation (10, 11). In addition to their inherent localization properties PS can be redirected to localize to specific structures by combination of PS with targeting moieties, such as monoclonal antibodies or receptor ligands. Conjugates in comparison to the unconjugated PS are more selective and may confer additional biological activity, e.g., through antibody binding itself (12, 13). A detailed review of targeting mechanisms and strategies for PDT has been recently published (14).

Most PS are administered systemically (figure 2); they are not suitable for topical delivery because the large molecules prevent effective skin penetration. The utilization of aminolevulinic acid (ALA)-induced protoporphyrin IX (PpIX) requires a different approach. Here a small prodrug, ALA, can easily penetrate into the cells, where it is converted to PpIX by the intracellular enzymes of the heme pathway, which is then exploited for PDT (15, 16). This enzymatic process represents an added level of complexity to PDT, but also expands the possibilities for improving selectivity and overall efficacy. For example, the pretreatment of cells with pharmacological agents has resulted in enhanced PpIX

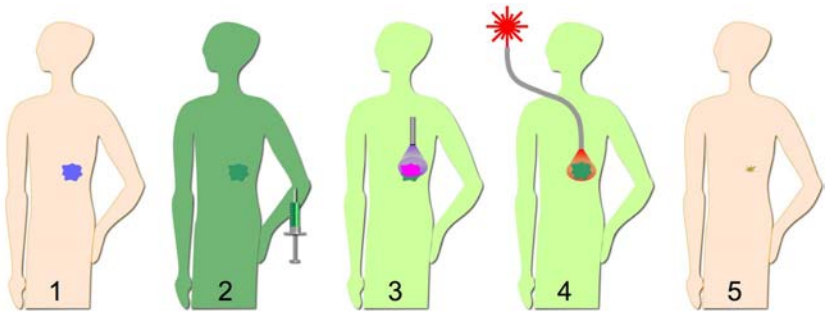

Figure 2. PDT in an optimal clinical setting. A patient with a solid malignant tumor (1) receives an intravenous injection with a PS (2) that gets distributed throughout the body and localizes with preference to the tumor. During a waiting period the PS is cleared from most of the body while being retained in the tumor. At this time, fluorescence diagnosis may be used for e.g. PS quantification (3). After the light exposure (4) the tumor regresses over time with minimal scarring (5).

production upon ALA exposure in a number of different cells (17, 18). Some of the molecular mechanisms involved have been elucidated (17-19). In an alternative approach, several derivatives of ALA, such as its methyl and hexyl esters have been introduced for therapeutic and diagnostic purposes. These conjugations alter physicochemical parameters of the parent compound (ALA) and aim for improved prodrug penetration and higher selectivity for malignant cells and therefore for enhanced therapeutic efficiency and selectivity (20-22).

3.2. Molecular effects of photosensitization

3.2.1. Immediate effects

3.2.1.1. Photochemical reactions

Singlet oxygen is the predominant cytotoxic agent created by the photochemical reaction in most photosensitizing protocols (figure 1). The lifetime of singlet oxygen in aqueous solution is not longer than 4 μs, resulting in a diffusion range of roughly 125 nm (23). This means that singlet oxygen may move this distance in any direction before it returns to its ground state, potentially reacting with biomolecules on its path. In a physiological environment, the reactivity of singlet oxygen with biomolecules results in both, its reduced lifetime and shortened diffusion distance. Consequently, the singlet oxygen lifetime in cells was estimated to be as low as 10-40 ns with a corresponding diffusion range of 10-20 nm (24). These data explain that cellular damage will be expected at subcellular sites where the PS molecules localize. For example, those PS primarily localizing to mitochondria, such as ALA-PpIX, Pc4, and certain cationic dyes will cause initial mitochondrial damage leading to apoptosis (25, 26).

3.2.1.2. Lipid peroxidation and protein crosslinks

Reactive oxygen species, such as singlet oxygen can react to form lipid peroxides in oxygen rich cell membranes (27). Lipid oxidation products may act as signaling moieties similar to enzymatically formed ceramide and arachidonate (28). In addition, protein adducts and protein crosslinks may be formed in the photosensitization process (29, 30). Several specific protein targets that are modified by PDT have been identified, including epidermal growth factor receptor (EGFR), the anti-apoptotic protein Bcl-2, and the signal transducer and activator of transcription-3 (STAT-3) (31, 32). For STAT-3 a correlation of PDT-induced crosslink levels with treatment outcome in animal models and human cancer has been described (33).

3.2.2. Early molecular responses

3.2.2.1. Early response genes and transcriptional activation

Exposure to PDT results in prolonged activation of the early response genes c-fos and c-jun, which form heterodimers that regulate gene expression (activator protein, AP-1). AP-1 activation is critical in proliferation, differentiation, and inflammation. Multiple responsive genes include those coding for inflammatory mediators, such as interleukin 6 (IL-6). Photosensitization with both Photofrin (PF) and ALA-induced PpIX have been shown to drive c-fos and c-jun expression (34-36).

The nuclear factor (NF)- kappaB and its inhibitor IkappaB are representatives each of several family members that interact for transcriptional regulation of hundreds of genes, including those involved in inflammation, immune response, proliferation, and apoptosis. Multiple stimuli including oxidative stress have been shown to activate NF-kappaB (37), and ROS created by porphyrin photosensitization enhances NF-kappaB binding (38). A recent review by Piette's group evaluates details of these mechanisms and the different activating pathways involved in response to PDT (39). NF-kappaB is involved in the regulation of proinflammatory responses (IL-1beta, IL-6, IL-8, G-CSF, ICAM, VCAM, E-selectin) and apoptotic pathways (40), but also modulates expression of genes that are involved in tumor survival and regrowth, such as COX-2 and MMP-9 (41, 42).

Another transcription factor, hypoxia-induced factor (HIF)-1α, has received much attention in PDT. Photosensitization depends largely on molecular oxygen that gets consumed during the photosensitization process resulting in localized hypoxia, which induces HIF-1α expression (43). A recent investigation demonstrated that PDT using PF induces HIF-1α expression even under normoxic conditions (44). In a study using human esophageal cell lines, high HIF-1α levels were induced by pretreatment with $CoCl_2$, which resulted in reduced

sensitivity to ALA-PDT. Concomitant suppression of HIF-1α expression using siRNA technology partially restored the photosensitivity (45). HIF-1α plays a role in the upregulation of vascular endothelial growth factor (VEGF) expression after PDT. Potential consequences of the increased expression of VEGF and other target genes of HIF-1α include reduced PDT response, tumor growth, invasion, and metastasis.

3.2.2.2. Stress proteins

The generation of oxidative stress by PDT has been shown to induce stress protein expression at the mRNA and protein level (46, 47). Increased stress protein levels in cells exposed to PF PDT confer tolerance to heat and adriamycin, thus confirming functional relevance (48, 49). The efficacy of this effect *in vitro* depends on the PS, but several PDT modalities tested *in vivo* resulted in HSP-70 induction (49). Although PDT-induced HSP-70 protects from hyperthermia, constitutive overexpression of HSP-70 and heat resistance do not reduce the sensitivity to PDT (50). Gomer's group also reported that the promoter of one PDT-induced chaperone gene related to ER stress, glucose-regulated protein (GRP) 78 is so consistently induced by PDT that it may be utilized as a molecular switch for transcriptional activation (51). Overexpression of GRP-78 depends on photosensitization conditions and by itself does not necessarily protect from the cytotoxicity of PDT. In contrast, constitutive overexpression or induction by calcium ionophore of GRP-78 increased sensitivity to mitochondrial targeted PDT (52). It is clear, however, that stress proteins are an important part of the cellular response to PDT-induced stress (53).

Heme oxygenase (HO)-1 is a member of another family of proteins that are upregulated by oxidative stress. HO-1 plays a central role in defense against environmental stress including ROS, but also responds to a host of other stimuli, including ultraviolet A radiation and hypoxia. HO-1 confers protection from a variety of noxious stimuli (54). While tin PpIX inhibits HO-1, hematoporphyrin derivative (HpD) and zinc phthalocyanine induce its mRNA expression in the absence of light (55). Cancer cells became resistant to PF-PDT after increasing HO-1 levels (56). Cells exposed to exogenous ALA synthesize more heme and consequently show increased HO-1 expression, which protects them from photosensitization. This protective effect is abrogated by HO-1 suppression or inhibition (57). PDT using ALA and hypericin has been shown to induce HO-1 in human cancer cells thus protecting them from apoptotic cell death (57, 58). It was suggested that the p38 MAPK signaling pathway plays an important role in HO-1 upregulation.

3.2.2.3. Signal transduction

Exogenous signals are transmitted to downstream effector molecules through interaction and modification of cellular proteins including surface receptors, phosphatases, kinases, and transcription factors (59). Stimuli such as ROS-induced molecular modifications are amplified by signaling cascades thereby regulating cellular processes including proliferation, transformation, differentiation, activation, and apoptosis. At the plasma membrane ceramide generated by sphingomyelinases has also evolved as a second messenger (60). Several studies demonstrated ceramide production in both apoptotic and protective pathways after PDT (61, 62). Lysosome-based acid sphingomyelinases have been implicated in apoptosis after PDT using Pc4 (63). Ceramide is involved in signaling through phospholipases PLA2 and PLC and protein kinase C. These signals have been associated with apoptosis as well as survival depending on PS and cell line (64, 65).

The mitogen activated protein kinase (MAPK) pathway has several analogous signaling cascades, including classical EGFR signaling. Because of its involvement in proliferation, survival, tissue invasion, and metastasis, EGFR has been targeted by PDT using PS conjugates, and such an approach may even help to overcome multi-drug resistance when used in a combined regimen (12, 13). Upon ligand binding, autophosphorylation of the receptor elicits downstream activation and signaling by several other proteins that associate with the phosphorylated tyrosines through their own phosphotyrosine-binding SH2 domains. These and analogous downstream signaling proteins initiate parallel signal transduction cascades, along the MAPK, extracellular signal-regulated kinase (ERK) and jun-N-terminal kinase/stress activated kinase (JNK/SAPK) pathways, leading to DNA synthesis and cell proliferation. PDT-resistant cells sustained activation of a subfamily of the MAPK pathways, ERK 1/2, after PF PDT longer than PDT-sensitive cells. Also, blocking ERK1/2 activation partially restored PDT sensitivity, indicating a protective mechanism of this specific signal (66).

The SAPK/JNK and the p38-MAPK pathways are activated by exogenous stress including oxidative damage, and PDT with a variety of PS has been shown to activate these kinases (67, 68). The pathways may promote or inhibit apoptosis and in certain settings may counteract each other. One other survival signal elicited by oxidative stress is phosphorylation of protein kinase B (Akt) apparently through activation of the phosphinositol-3-OH kinase, because its inhibitors prevented Akt phosphorylation (69). In growth factor-induced activation of Akt, however, singlet oxygen reduced this signal likely due to ceramide-mediated dephosphorylation of Akt (70). In the setting of PDT, activation of Akt is involved in a survival response in treated cells and tissues (71, 72). As reported for breast cancer cells, Akt is phosphorylated in the presence of PF even in the absence of light, giving this pathway added interest for its involvement in the rescue response after PDT (71).

3.2.2.4. Complement activation

Cormane described complement deposition (C3) in light-exposed skin of porphyria patients, and later, reduction of CH50 and cleavage of several complement components were recorded dependent on porphyrin concentration and light dose (73, 74). Complement activation apparently plays a role in photosensitization efficacy, as in animal models complement blockage led to reduced tumor cure after PDT (75). Pharmacological

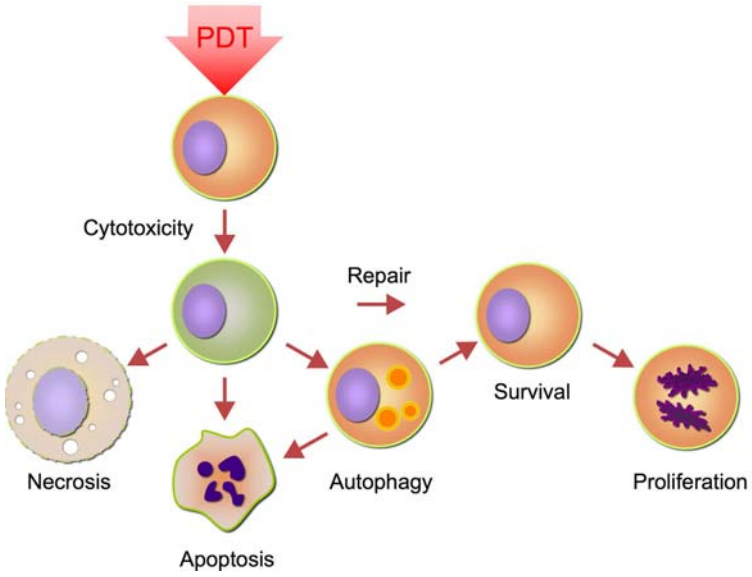

Figure 3. Cell death pathways. Exposure to PDT leads to cellular damage that may result in cell death via different pathways. In clinical PDT a combination of all cell death programs may be encountered.

complement activation resulted in improved PDT outcome using a number of different PS (76-79). The enhanced antitumor activity was associated with an infiltration with CD8+ lymphocytes. Complement activation mediates neutrophil infiltration of tumors after PDT and circulating blood neutrophilia after photosensitization of tumors or normal back skin in mice (78, 79). Complement may be involved in the activation of multiple inflammatory mediators, including TNFalpha, interleukin (IL)-1beta, IL-6, IL-10, G-CSF, thromboxane, prostaglandins, leukotrienes, histamine, and clotting factors (80). Complement gene activation has been demonstrated in tumor-associated macrophages after PDT of experimental tumors. This is likely mediated by tumor cell-derived signals, such as HSP70 that binds to toll-like receptors and activates NF-kappaB-mediated transcription (81). A recent report evaluated the expression of acute phase proteins in response to PDT (82). Some of these are complement components (C3 and mannose-binding lectin A), others are members of the pentraxin family, such as C-reactive protein (CRP) and serum amyloid P component (SAP). The expression of these genes and their products was quantified in tumor-bearing mice. Significant increases in the liver were recorded over 24 hours after PDT. Large and persistent increases of SAP in the tumor were attributed to tumor-infiltrating macrophages (82). Many of these proteins are involved in both, modulation of the inflammatory response and orchestrating the removal of the remnants of photosensitized tumors (83).

3.2.2.5. Cytokines

Several porphyrin PS have been shown to induce secretion of IL-2, IL-3, TNFalpha, and interferon gamma by blood mononuclear cells in the absence of light (84). These findings challenge the concept that in PDT, two inherently inactive components are combined at the site of desired action; however, the significance of these dark effects is not known.

PDT induces cytokines, such as TNFalpha, a versatile cytokine involved in inflammatory disorders and in cell death signaling. Enhanced expression of TNFalpha has been demonstrated together with IL-1beta and IL-6 after PDT with PF (34, 80). Similar findings were reported for a pyropheophorbide (85). In this latter investigation, the murine analogues of IL-8 and Gro-α enhanced the effects of IL-1beta, IL-6, and TNFalpha on the induction of the adhesion molecule expression, which mediates leukocyte recruitment to the photosensitized tumor. IL-6 may play an additional role in tumor control by enhancing PDT effects through trans signaling affecting cell cycle modulation (86). Administration or induction of TNFalpha significantly enhanced the effects of photosensitization of experimental tumors, confirming its role in executing PDT (87). Leukocytes play an important role not only in the tumoricidal process, but also in the induction of immune responses as described below (75). With excessive inflammatory mediator activation, experimental animals have exhibited a shock-like lethal effect after systemic PF administration and localized light exposure to subcutaneous tumors. Attesting to the inflammatory nature of this response, it may be suppressed by antihistamines, aspirin, and indomethacin (88). In experimental treatments of human bladder cancer, increased excretion of IL-1, IL-2, and TNFalpha was reported hours to days after PDT, indicating clinical relevance of the findings in animal models (89).

3.2.3. Cell death after PDT

In PDT that is targeted for cancer treatment, lethal cytotoxicity is a desired consequence of photosensitization. This aim may be reached through several pathways, including apoptotic, autophagic, and necrotic cell death (figure 3). Which specific pathway

dominates in each therapeutic setting, depends on the PDT parameters, including the PS, its concentration, its subcellular localization, and the light dose (90, 91).

3.2.3.1. Apoptosis

Apoptosis is a well-studied mode of cell death that has a pivotal role in development, cellular homeostasis, and cancer. A compromise of the apoptotic machinery may have severe consequences and redundant pathways exist for preservation of this critical cellular function. Conversely, and in view of its great significance, apoptosis is an important target mechanism in cancer therapies including PDT (91, 92). PDT can be very efficient and is likely the most rapid modality for inducing apoptosis, depending on the photosensitizing protocol (93, 94).

Apoptosis can be activated by an extrinsic pathway, involving receptor signaling, and by an intrinsic pathway with a central role for mitochondria (figure 4). Both pathways converge at the critical step of caspase activation. Caspases are a family of cysteine-dependent aspartate-specific proteases that are the executioners of apoptosis. Hydrolyzing a multitude of substrates, including each other, caspases are responsible for most morphological and biochemical markers of apoptotic cell death (90, 92).

3.2.3.1.1. Extrinisic pathway

Upon binding of their respective ligands the cell surface death receptors TNF receptor 1, TRAIL receptor, or Fas activate the extrinsic pathway of apoptosis. An oligomeric adapter complex binds initiator procaspases-8/10 resulting in their activation by proteolytic cleavage. Activated caspases-8/10 cleave effector procaspases-3/7, which execute the apoptotic program. Caspase-8/10 action on the Bcl-2 family member Bid may activate the intrinsic pathway simultaneously (95, 96).

The extrinsic pathway is not dominant in PDT-induced apoptosis. A number of experimental protocols have demonstrated activation of the death receptor-mediated pathway with increased expression of death signals and death receptor levels after PDT (96, 97). It has also been shown that exogenous activation of death receptors by their ligands enhances PDT effects on cells and tumors (87, 98).

3.2.3.1.2. Intrinsic pathway

The dominant activation switch in PDT-induced apoptosis is through the intrinsic pathway. The mitochondria play a central role. Early events include a loss of the mitochondrial transmembrane potential ($\Delta\Psi_m$) and the release of cytochrome c (Cyc) from the intermembrane space into the intracellular space (94). Cytoplasmic Cyc associates with the apoptotic protease activating factor 1 (Apaf-1) and forms the heptameric apoptosome that integrates procaspase-9, leading to its cleavage and resultant activation. Caspase-9 hydrolyzes and activates caspases-3/7, reaching the same terminal path as the extrinsic pathway (99, 100). Because of the destructive powers of caspases the activating steps are under tight control of a network of counteragents. The Bcl-2 family of proteins contains about 20 members that either promote or counteract apoptosis. Anti-apoptotic Bcl-2 itself resides in mitochondrial and ER membranes and is named after a cancer where cells accumulate because they fail to undergo apoptosis. Bcl-2 has demonstrated protective properties against PDT-induced apoptosis (101, 102); however, absolute Bcl-2 levels appear to be less important than the ratio of Bcl-2 to Bax, indicating that the balance of family members is critical in apoptosis control (103). PDT can degrade Bcl-2 thus promoting apoptosis (31, 104). A pharmacological antagonist of Bcl-2 has also been shown to enhance PDT efficiency synergistically (105, 106). In addition to Cyc, other mitochondrial proteins are released that help enhance the apoptotic response. Smac/DIABLO (Second mitochondria-derived activator of caspase/direct inhibitor of apoptosis-binding protein with low pI) is such a protein and its release depends on cell type and photosensitizing protocol (107, 108). Smac/DIABLO interferes with the inhibition exerted by a family of proteins called inhibitor of apoptosis (IAP), such as survivin, on procaspase-9, thus making it available for activation in the apoptosome. Survivin is overexpressed in many cancers and associated with unfavorable prognosis. PDT has been shown to affect survivin and its targeting is associated with enhanced photosensitization (71). Apoptosis-inducing factor (AIF) is a mitochondrial protein that gets released during the initiation of apotosis and translocates to the cell nucleus. There it degrades DNA independently of caspases (109, 110). The addition of pan-caspases inhibitor VAD.fmk was found to prevent oligonucleosomal DNA fragmentation but failed to inhibit PDT- mediated apoptosis (107).

The hierarchy of events is controversial and may be different depending on the PS localization and the treatment protocol. The dissipation of the mitochondrial transmembrane potential ($\Delta\Psi_m$) appears to be a central and early mechanism. This step is sensitive to increased cytoplasmic calcium ion (Ca^{++}) level, which is a consequence of endoplasmic reticulum (ER) photosensitization. Many PS do not localize to one type of cell organelles exclusively, but are present in cellular membranes of all kinds. In such setting, direct photosensitization of mitochondrial targets likely synergizes with indirect damage by Ca^{++} levels that increase due to ER compromise (90).

3.2.3.2. Autophagy

Autophagocytosis or autophagy is a tightly controlled process in which cell components, including whole organelles, are sequestered in membrane-bound vesicles that fuse with lysosomes for degradation and reutilization of their components. This process plays a role in developmental processes, human disease, and cellular response to nutrient deprivation (111). Autophagy has also recently been demonstrated in response to PDT and may represent an attempt by the cell to remove organelles damaged by photosensitized ROS generation. Because apoptosis is so prominent and occurs rapidly after PDT, autophagy was obscured until emergence of these recent reports. Initially this mechanism was described and characterized in photosensitized cells devoid of Bax and

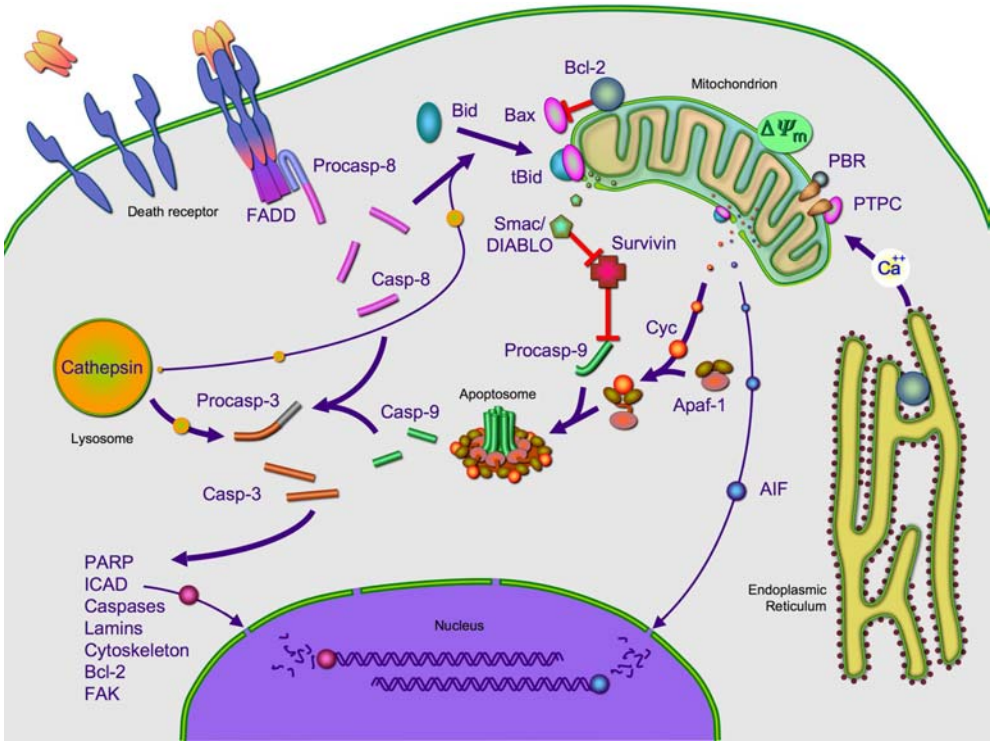

Figure 4. Steps and components of apoptosis that have been associated with PDT. For simplicity, analogous molecules are represented by a typical family member rather than by their exhaustive listings. For example, the Bcl-2 family of proteins encompasses a large number of proteins that either promote or counteract apoptosis at the mitochondrial level; however, only Bcl-2, Bax, and Bid are shown here. AIP: apoptosis inhibiting factor, Bid and Bax: Bcl-2 family members, Casp: caspase, FADD: Fas-associated protein with death domain, FAK: focal adhesion kinase-1, ICAD: inhibitor of caspase-3-activated DNase, PARP: poly-ADP ribose polymerase, Procasp: procaspase, PBR: peripheral benzodiazepine receptor, PTPC: permeability transition pore complex; all other acronyms see in the Abbreviations section.

Bak (112-114). Additional reports confirmed that autophagic cell death becomes more prevalent and more easily detectable in settings of impaired apoptotic machinery or with low PDT doses (114, 115). It will have to be determined, if autophagy is a regular occurrence in PDT and how apoptotic and autophagic mechanisms interact. The autophagic process potentially has implications for the development of tumor immunity after PDT, as lysosomal processing may expose antigens.

3.2.3.3. Necrosis

There is a distinction between tissue necrosis and molecular pathways resulting in necrotic cell death. In most experimental and clinical applications *in vivo*, vascular shutdown resulting in tissue necrosis dominates the clinical tumor response (116, 117)**.** At the cellular level, necrosis is defined by organelle swelling and cytoplasmic membrane rupture (118). Some investigators believe that there is a distinctive molecular pathway resulting in necrosis with key candidate regulators including the TNF signaling related protein, receptor interacting protein (RIP-1), and cyclophilin D (119). Poly-ADP ribose polymerase (PARP), calpains, and cathepsins are also required for necrotic cell death; however, a firm association with PDT-mediated necrosis has not been established (90). The most important differential effect of necrosis *versus* autophagy and apoptosis is that necrosis causes tissue inflammation **(**120). Conceptually, acute inflammation is a favorable process as it may enhance formation of an anti-tumor immune response (75).

3.2.4. Defensive responses

Several molecular responses induced by PDT have been reported that favor tumor survival and re-growth. They create a microenvironment where surviving tumor cells are enabled to proliferate, invade and metastasize. The understanding of these responses enables counter measures to enhance PDT efficiency (7).

3.2.4.1. Vascular endothelial growth factor

Roberts investigated PS uptake by murine tumors and described increased phthalocyanine concentration in tumors with higher VEGF content (121). VEGF is overexpressed in malignant tumors in response to hypoxia promoting neovascularization. VEGF is also involved in metastasis. A connection was made between PDT, the induction of HIF-1α by photosensitized oxygen consumption, and resulting VEGF expression (122), although other signaling pathways may be involved, such as p38 MAPK (123). In a xenograft model of human Kaposi sarcoma in nude mice, PDT-induced VEGF was derived from both (human) cancer cells and (murine) host

cells (122). Antiangiogenic agents have been investigated in their efficacy when used in combination with PDT. Different antiangiogenic principles have been applied, such as binding of circulating VEGF (e.g., bevacizumab), inhibition of VEGF-dependent signaling (e.g., ZD6474), and inhibition of endothelial cell migration and proliferation (TNP-470). When antiangiogenic treatment was applied to reduce VEGF levels in experimental tumors this resulted in improved cure rates after PDT (43). Kosharskyy demonstrated that the temporal sequence in the combination might be crucial, with TNP-470 treatment being most efficient in a prostate cancer model, when given after PDT (124).

3.2.4.2. Cyclooxygenase-2

Cyclooxygenases (COX) are involved in prostanoid synthesis, and the inducible isoform, COX-2, is linked to carcinogenesis and tumor progression in multiple organs. COX-2 inhibition has been used successfully in chemoprevention and in combination cancer therapies (125). COX-2 expression was increased after PDT with several different PS. Functional relevance of elevated enzyme levels was established using selective inhibitors of COX-2, which did not cause increased cutaneous photosensitivity but resulted in improved tumor response (126-128). The transcriptional activation of COX-2 by PF PDT of mouse fibrosarcoma cells was shown to utilize the p38 MAPK signaling pathway (129), while NF-kappaB was implicated in COX-2 activation after pyropheophorbide PDT of human cancer cells (42).

3.2.4.3. Matrix metalloproteinases

Matrix metalloproteinases (MMPs) are a group of zinc-dependent endopeptidases that degrade extracellular matrix components. They play an important role in tumor development and invasion and are involved in cancer cell survival and tumor progression (130). Inhibitors of MMPs have been shown to prolong survival, e.g., in animal models of prostate cancer (131). Uroporphyrin photosensitization has been shown to up-regulate MMP 1 and MMP 3 **(**84), and PDT of fibroblasts using ALA-PpIX or a novel porphyrin compound, ATX-S10 (Na), induced expression of these same enzymes (132, 133). In a mouse mammary tumor model, MMP 9 was upregulated together with its positive regulator, extracellular MMP inducer (EMMPRIN), while a tissue inhibitor of MMP (TIMP 1) was downregulated after PDT with PF (134). MMP-2 expression was not altered in this setting. The clinically applied MMP inhibitor prinomastat enhanced the response to PDT and increased long-term survival in tumor-bearing mice. Interestingly, cutaneous photosensitivity was not affected (134).

3.2.4.4. Immunological responses

PDT was long considered a tool of local tumor control, where ROS result in direct cytotoxicity to the tumor cells, induce vascular occlusion, and cause a local inflammatory response. Later, multiple signs of systemic inflammation were discovered in response to PDT. These are apparently mediated by complement activation and release of cytokines (for references see 3.2.2.4.). There are two separate aspects of PDT-induced systemic immunomodulation: one induced by exposures of large areas of skin, similar to UV phototherapy protocols, and the other induced by the localized reaction to photosensitization of tumors.

Both acquired and innate skin immune functions can be modified by PDT (135). PDT reduced the severity of experimentally induced immune diseases at sub-threshold doses for cutaneous inflammation or erythema (136). PDT using verteporfin or phthalocyanine suppresses the CHS response to topically applied hapten, likely through IL-10-mediated mechanisms. The CHS response was also suppressed when hapten was applied to a non-exposed site, suggesting systemic mechanisms (137-139). Monocytes, dendritic cells, and Langerhans cells as well as activated lymphocytes bearing the IL-2 receptor and HLA-DR are selectively sensitized by 5-ALA, HpD, and verteporfin (140-143). Non-activated cells remain relatively unchanged. An up-regulation of IL-6 mRNA levels occurred in murine tumors treated with PDT and was accompanied by a significant increase in IL-10 expression in the skin (144). It has been suggested that IL-6 has a pivotal role in the localized inflammatory effect produced by PDT, while IL-10 may be involved in systemic immunosuppression (144).

When treatment parameters were used that target tumors, PDT was seen to act as a biological response modifier enhancing the antitumor response (145). This concept is supported by the clinical observation that incomplete local control of skin cancers by a single PDT exposure may result in delayed cure (unpublished data, B.O. and PG.C-P.). A recent report demonstrated a systemic immune response against cutaneous angiosarcoma after PDT using chlorin e6. Here, distant tumors responded to localized PDT and showed a dense CD8+ lymphocytic infiltrate (146).

Experimental tumor models have confirmed that cellular immunity plays an important role in tumor control after PDT. Release of histamine, prostaglandin D2, and platelet activating factor by mast cells, expression of adhesion molecules by endothelial cells (85, 147), and release of the tumor necrosis factor by macrophages can contribute significantly to PDT effects (97). The involvement of the immune system in PDT-mediated tumor clearance is supported by the finding that PDT was less effective in the cure of tumors in severe, combined immunodeficient (SCID) mice or T cell-deficient nude mice than in immune competent mice (148, 149). Reconstitution of immunodeficient mice by adoptive transfer of splenocytes from immunocompetent animals did not improve PDT response. However, if adoptive transfer was from mice cured of tumors by PDT five weeks earlier, PDT was much more efficient. This process was tumor-specific, strongly associated with PDT, and mediated by cytotoxic T lymphocytes (150). PDT has demonstrated its ability to induce specific tumor immunity that protects treated animals from tumor challenge (120, 151, 152). Gollnick's group showed that CD8+ T cells mediate the eradication of distant tumor cells. Interestingly, this CD8+ effect is independent of CD4+ T cells but requires natural

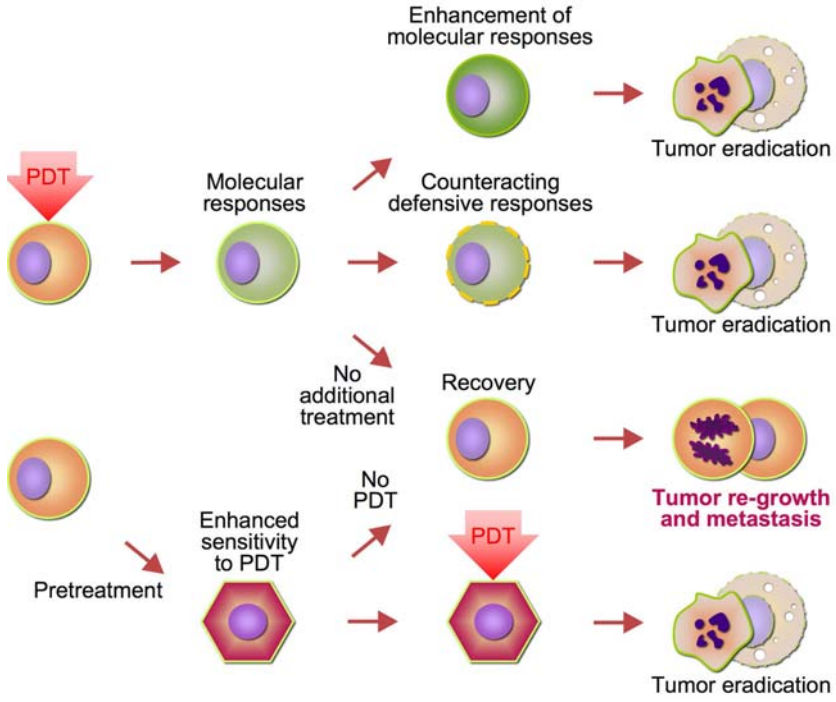

Figure 5. Rationally designed combination therapies in PDT of cancer. The understanding of molecular responses to PDT allows enhancing those effects that promote tumor eradication and suppressing or counteracting those that are tumor protective. In a different approach pretreatment of the tumor makes it more susceptible to certain PDT regimens. (Adapted from (8))

killer cells (152). In addition, it was demonstrated that tumor-infiltrating neutrophils play a role in proliferation and, possibly, survival of the lymphocytes that mediate this response (153). Korbelik's group described increased animal survival after localized GMCSF delivery to PDT-treated tumors (154). Consequently, boosting tumor immunity appears to be inherent to PDT and may be exploited for enhanced therapeutic regimens. Combined PDT with localized BCG vaccination increased cure rates of EMT6 tumors independently of which of several PS was used (155). The injection of naïve dendritic cells into PDT treated tumors resulted in improved local control and regression of distant metastases (156). As vaccination strategies are being developed for clinical applications (157), Gollnick explored PDT as a means to create efficient tumor vaccines and found that lethal photosensitization is the most efficient way to create whole tumor vaccines (147). This type of vaccination is sustained by chemokines, cytokines, and chaperoned immunogenic proteins that are released by injured and dying cells. It can induce dendritic cell maturation and their acitivation to produce IL-12 that has a critical importance in the development of the cellular immune response (85). The molecular and cellular mechanisms involved in creating tumor vaccines have been recently reviewed in detail (120).

4. PERSPECTIVE

The understanding of complex cellular-molecular responses goes beyond academic interest. It will take much additional effort to pinpoint all molecular responses of PDT-treated cells and tumors that can be exploited to improve PDT efficacy (figure 5). Several research groups have been investigating this approach by rationally designing combination therapies (7, 8). A number of strategies have been proposed, including pretreatment of tumors to make them more responsive to subsequent PDT. This specific strategy works in ALA-PDT by increasing the tumor cell capacity to synthesize PpIX from exogenous ALA. Regimens, in which PDT is combined with anti angiogenic drugs, counteract the defense mechanism of increased VEGF expression after photosensitization and improve response to treatment. This approach has proven useful in several experimental settings and may be beneficial in human disease, where anti-angiogenic agents are currently in use. Based on animal models, similar combination regimens are feasible for clinical PDT combined with inhibitors of COX-2 and MMPs. With the expansion of the understanding of tumor immunity after PDT improved cancer vaccination strategies are feasible aims as well.

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Abbreviations: Akt: protein kinase B, ALA: aminolevulinic acid, AP-1: activator protein 1, Apaf-1: apoptotic protease activating factor 1, Bcl-2: B cell leukemia-2 protein, COX: cyclooxygenase, CRP: C-reactive protein, Cyc: cytochrome c , $\Delta\Psi_m$: mitochondrial transmembrane potential, EGFR: epidermal growth factor receptor, ER: endoplasmic reticulum, ERK: extracellular signal regulated kinase, Fas: Fas receptor/CD95, G(M)-CSF: granulocyte (macrophage) colony stimulating factor, GRP: glucose regulated protein, HIF: hypoxia-induced factor, HO: hemoxygenase, HpD: hematoporphyrin derivative, HSP: heat shock protein, IAP: inhibitor of apoptosis , IL: interleukin, JNK/SAPK: jun N-terminal kinase/stress activated protein kinase, MAPK: mitogen activated protein kinase, MMP: matrix metalloproteinase, Pc4: a silicon phthalocyanine photosensitizer, PDT: photodynamic therapy, PF: photofrin, porfimer sodium, PK: protein kinase, PpIX: protoporphyrin IX, PS: photosensitizer, ROS: reactive oxygen species, Smac/DIABLO: Second mitochondria-derived activator of caspase/direct inhibitor of apoptosis-binding protein with low pI, STAT: signal transducer and activator of transcription, TNFalpha: tumor necrosis factor alpha, TRAIL: TNFalpha-related apoptosis-inducing ligand, VEGF: vascular endothelial growth factor

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