Forging Forward in Photodynamic Therapy

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In 1978, a *Cancer Research* article by Dougherty and colleagues reported the first large-scale clinical trial of photodynamic therapy (PDT) for treatment of 113 cutaneous or subcutaneous lesions associated with ten different kinds of malignancies. In classic applications, PDT depends on excitation of a tissue-localized photosensitizer with wavelengths of visible light to damage malignant or otherwise diseased tissues. Thus, in this landmark article, photosensitizer (hematoporphyrin derivative) dose, drug–light interval, and fractionation scheme were evaluated for their therapeutic efficacy and normal tissue damage. From their observations came early evidence of the mechanisms of PDT's antitumor action, and in the decades since this work, our knowledge of these mechanisms has grown to build an understanding of the multifaceted nature of PDT. These facets are comprised of multiple cell death pathways, together with antivascular and immune stimulatory actions that constitute a PDT reaction. Mechanism-informed PDT protocols support the contribution of PDT to multimodality treatment approaches. Moreover, guided by an understanding of its mechanisms, PDT can be applied to clinical needs in fields beyond oncology. Undoubtedly, there still remains more to learn; new modes of cell death continue to be elucidated with relevance to PDT, and factors that drive PDT innate and adaptive immune responses are not yet fully understood. As research continues to forge a path forward for PDT in the clinic, direction is provided by anchoring new applications in mechanistically grounded protocol design, as was first exemplified in the landmark work conducted by Dougherty and colleagues.

See related article by Dougherty and colleagues, Cancer Res 1978;38:2628–35

Introduction

Photodynamic therapy (PDT) is used in the treatment of solid tumors because it creates tissue-damaging cytotoxic species upon light-mediated activation of a photosensitizer. Dougherty and colleagues published the first clinical report of the therapeutic potential of PDT in a sizable group of cancer patients in *Cancer Research* in 1978 (1). The report included findings that PDT response was generated in tumors of all ten different malignancies that were studied. In fact, among 113 cutaneous and subcutaneous lesions on 25 patients, only 2 were nonresponsive, while 13 had a partial response, and 98 exhibited a complete response. PDT effectiveness across different types of malignancies and even diseases is now understood to result from the multiple, varied mechanisms through which it exerts a cytotoxic effect. In the time since this landmark publication, much has been learned of these mechanisms (**Fig. 1**), including observations of vascular effects in normal and then in tumor tissue, the identification of singlet oxygen as a direct cytotoxic mediator of tumor damage, and findings that PDT alters immune response—initially detected as immunosuppressive but leading to later observations of PDT-generated antitumor immunity. As mechanistic knowledge has grown, so has the rational development of treatment regimens, achievable through the purposeful selection of a PDT approach to best suit a particular application. Even in the early landmark study by Dougherty and colleagues, parameters including drug dose, drug-to-light interval, and fractionated delivery were evaluated for their effects on tumor and normal tissue damage. Necrosis and inflammation after PDT could be altered by choice of these parameters, providing initial evidence of the versatility and tunability of this treatment and its mechanisms of action.

From the microscopic to the microenvironment

Elucidation of cell death pathways that mediate cytotoxicity of PDT has been of long standing importance in the field, and, over years of investigation, necrosis, apoptosis, autophagy, and paraptosis have all been found to play a role. The balance of these cell death mechanisms is driven largely by the subcellular localization inherent to a specific photosensitizer and its incubation conditions, together with light dose. High drug/light doses and plasma membrane localization can trigger "accidental" death by necrosis, whereas localization to intracellular organelles (especially endoplasmic reticulum or mitochondria) and lower drug/light doses can favor apoptosis. Signal transduction in pathways associated with stress response (e.g., IRE1, HRI, ATF6, UPR, ISR, PERK, etc.) and cell death (e.g., BCL2, MAPK, etc.), alongside activation of transcription factors (e.g., Nrf2, NF-κB), will determine cell response to PDT. For example, pro-death autophagy can be revealed by inhibition of apoptosis after PDT, and a role for PDT-induced paraptosis is uncovered when interfering with necrosome formation (2).

Direct PDT cytotoxicity occurs in all light-exposed cells that accumulate photosensitizer, irrespective of tumor or normal tissue cell type. Indeed, PDT effects on cells of the blood and blood vessels define its antivascular effects. Entire fields of PDT research have been built around studying the cells and physiology of the tumor microenvironment as determinants of PDT response. Often central to these investigations is PDT dependence on tissue levels of molecular oxygen via type II photochemistry. Thus, PDT has been combined with approaches to combat preexisting or treatment-induced transient hypoxia during illumination, which can impede its cytotoxicity. Oxygen carriers and oxygen breathing have been studied for their ability to enhance PDT efficacy, including novel nanoparticle formulations for oxygen delivery (3). Type I photosensitizers can also reduce oxygen dependency. Oxygen conserving illumination protocols (e.g., low fluence rates or hyperfractionated light delivery) may improve PDT therapeutic efficacy or even facilitate real-time dosimetry based on treatment-induced changes in tumor blood flow (4).

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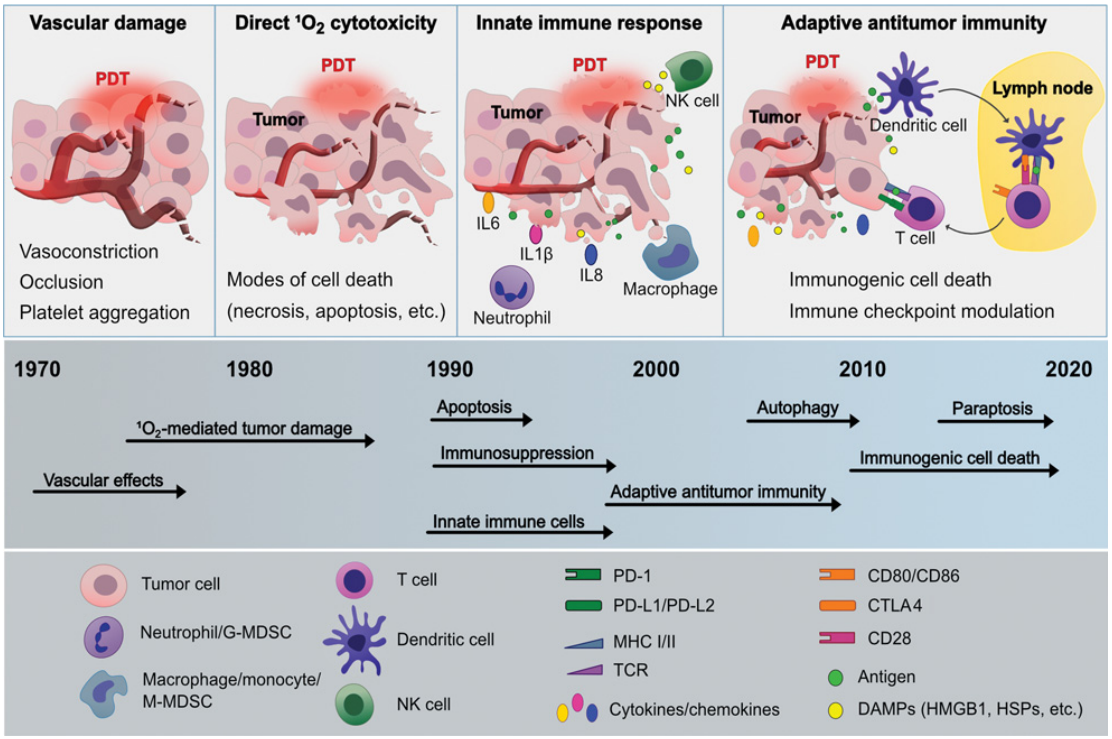

Figure 1.

PDT actions. Mechanisms of action of PDT have been investigated since the first studies of PDT as a cancer treatment. Early observations of PDT-treated tissues included evidence of vascular effects, subsequently identified as vasoconstriction, occlusion, platelet aggregation, which functionally lead to reductions in tissue perfusion and hyperpermeability. Direct cytotoxicity mediated by $^1O_2$ (or other PDT-generated reactive species) was first shown to contribute to tumor necrosis and apoptosis, which are now joined by more recently identified cell death pathways such as autophagy and paraptosis. Innate immune response in the form of inflammation was noted early as a characteristic effect of PDT and later accompanied by identification of cytokine and chemokine release, together with local accumulation of innate immune cells such as neutrophils, granulocytic myeloid–derived suppressor cells (G-MDSC), tissue macrophages, blood monocytes, monocytic myeloid–derived suppressor cells (M-MDSC), and natural killer (NK) cells. Observations of adaptive antitumor immunity followed, grounded in the response of $CD4^+$ and $CD8^+$ T cells, aided by antigen presentation in the context of major histocompatibility complex (MHC I/II) by dendritic cells in tumor-draining lymph nodes. With an understanding of immunogenic cell death, recognition was given to the immunologic contributions of PDT-generated tumor-associated antigens and damage-associated molecular patterns (DAMP) released by treated cells. Appreciation also now exists for the role of immune checkpoint modulation in the generation of adaptive immunity in response to PDT; PD-1 on T cells can interact with PD-L1/PD-L2 expressed on tumors or myeloid cells, inhibiting T-cell targeting, and similarly, CTLA4 (inhibitory) and CD28 (stimulatory) on T cells compete for binding with ligands CD80/CD86 on antigen-presenting cells. Figure components were adapted from Cramer and colleagues (11).

PDT can be targeted to cells of interest (tumor cells, endothelial cells, etc.) with monoclonal antibodies (i.e., photoimmunoconjugates), peptides, carbohydrates, nanoparticles, or numerous other approaches. Furthest along in this realm is EGFR-targeted IRDye700Dx, a phthalocyanine-based photosensitizer linked to cetuximab (EGFR targeting monoclonal antibody) that is in clinical trials for PDT of head and neck cancer. Nanomedicine also offers other microenvironmental-centric platforms for PDT. This includes options for combating tissue hypoxia, codelivery of chemo- or immunotherapies, light-based theranostics, and even improvements in selectivity through photosensitizer activation in the tumor microenvironment (e.g., molecular beacons; ref. 5).

Combining forces for greater efficacy

The varied mechanisms of PDT action provide a unique opportunity for multimodality treatments combining PDT with other cancer therapies, including chemotherapy, radiotherapy, molecular-targeted drugs, or immunotherapy (5). As an example, combinations of PDT with chemotherapy can be designed to take advantage of specific PDT mechanisms: PDT-induced hyperpermeability can increase chemotherapy accumulation in tumors; inhibition of multidrug resistance proteins (e.g., ABCG2) by PDT can reduce chemotherapy efflux from cells; PDT-mediated disruption of tumor stroma can improve chemotherapeutic effectiveness; induction of hypoxia by PDT can be exploited by hypoxic cell sensitizers; and the effect of PDT on cellular resistance pathways can sensitize cells to apoptosis. In other approaches, sublethal doses of PDT can promote controlled release of endocytosed drugs in cells (photochemical internalization), or subtherapeutic dosing of molecular therapies (e.g., tyrosine kinase inhibitors) can augment mechanisms of PDT damage (e.g., antivascular actions). Mechanism-based combinations have even led to protocols that combine PDT with itself. Such protocols may use tumor-controlling PDT in combination with an immunostimulatory regimen (6). They may also be designed at the subcellular level to exploit the synergistic activation of cell death pathways by PDT in different organelles, feasible via choice of photosensitizers that differentially localize in a cell or use of nanoparticles that facilitates

photosensitizer delivery to multiple organelles (e.g., both the mitochondria and the lysosomes) (7).

Growing knowledge of the immunologic effects of PDT provides particular opportunity for combinational strategies with immunotherapy. Mechanisms of immune effects by PDT have evolved from initial observations of inflammation, as in the landmark study (1), to detection of immunosuppressive elements, involvement of innate immune cells, triggering of antitumor immunity, and most recently, the generation of immunologic cell death. Combinations of PDT with immune modulators that stimulate immunity or impede immune suppression have been studied preclinically. Ongoing research builds on the strength of PDT in generating immunogenicity. PDT tumor vaccines have been developed, and research is rapidly growing on best approaches to combine PDT with immune checkpoint blockade (8).

Clinical Paths

The publication by Dougherty and colleagues set the stage for subsequent trials in support of clinical PDT adaptation. Since the 1990s, oncologic applications have been approved by the FDA and other worldwide health agencies for the photosensitizers Photofrin (porfimer sodium), Foscan (temoporfin, mTHPC), Levulan/Ameluz (aminolevulinic acid hydrochloride), Metvix/Metvixia (methyl aminolevulinate), Laserphyrin (talaporfin, NPe6), and Tookad (padeliporfin); these drugs are joined by country-specific formulations of sometimes similar photosensitizers under other names. PDT has received clinical approvals for several indications, including high-grade dysplasia in Barrett's esophagus, esophageal cancer, endobronchial cancer, bladder cancer, early stage lung cancer, actinic keratosis, basal cell carcinoma, head and neck cancer, and prostate cancer. Clinical trials evaluating PDT are ongoing for many other cancers (mesothelioma, lung, brain, breast, or pancreatic cancers, etc.). Moreover, photosensitizers used for PDT have recently been approved for fluorescence-guided resection, offering additional opportunities for new combinational approaches incorporating PDT (9).

Expansion of PDT into nononcologic applications has been aided by a growing understanding of PDT mechanisms. One major success has been in ophthalmology, with the 2000 FDA approval of Visudyne (verteporfin)-mediated PDT for its antivascular effects in treatment of wet age-related macular degeneration. In dermatology, PDT is used off-label to treat acne, rosacea, photoaging, sebaceous hyperplasia, and certain types of warts. In cardiology, the plaque-localizing tendency of some photosensitizers has triggered study on control of atherosclerosis. The antimicrobial effects of PDT have been applied for wound healing; as a nasal photodisinfectant (e.g., Steriwave, approved in Canada and the European Union); and in dentistry to combat periodontitis, dental caries, and other periodontal disease. In the timeliest of applications, the antiviral capabilities of PDT are under investigation for reduction of SARS-CoV-2 viral load, as the causative coronavirus of COVID-19.

Conclusions

In summary, the ongoing development of PDT is supported by the still expanding knowledge of its mechanistic underpinnings. Advances in technical aspects of treatment, for example, the dosimetry of light delivery, remain important to fully achieve the desired mechanistic benefit from a selected treatment regimen, and may involve consideration of the multifaceted effects of PDT on tumor, vascular, and immune responses. Toward this goal, PDT boasts of remarkable technical versatility, as it can be delivered via a broad range of light sources (lamps, lasers, light-emitting diodes, daylight, etc.) using illumination directed to a surface or penetrating into tissues via interstitial fibers. In considering treatment indications, the self-limiting depth of PDT with visible light can be exploited as an advantage in specific contexts, and new possibilities for photosensitizer excitation by internal illumination generated through bioluminescence, upconverting nanoparticles, radiation scintillators or Cerenkov radiation can be harnessed in other conditions (10). Ultimately, there remains much to be learned and much to be gained from mechanism-informed design of PDT applications to meet the needs of clinical medicine, a path that was initiated by Dougherty and colleagues in their landmark publication.

Authors' Disclosures

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