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Review

Photodynamic therapy of cerebral glioma – A review Part I – A biological basis

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Abstract

Photodynamic therapy (PDT) has been investigated extensively in the laboratory for decades, and for over 25 years in the clinical environment, establishing it as a useful adjuvant to standard treatments for many cancers. A combination of both photochemical and photobiological processes occur that lead to the eventual selective destruction of the tumour cells. It is a potentially valuable adjuvant therapy that can be used in conjunction with other conventional therapies for the treatment of cerebral glioma. PDT has undergone extensive laboratory studies and clinical trials with a variety of photosensitizers (PS) and tumour models of cerebral glioma. Many environmental and genetically based factors influence the outcome of the PDT response. The biological basis of PDT is discussed with reference to laboratory and preclinical studies.

Keywords: Brain tumours; Glioma; Photodynamic therapy; Haematoporphyrin

1. Introduction

Photodynamic therapy (PDT) is a binary treatment modality that involves the selective uptake of a photosensitizer (PS) by tumour cells followed by irradiation of the tumour with light of the appropriate wavelength to excite and activate the PS, resulting in selective tumour destruction.

The efficiency of PDT is dependent on the interaction of the PS and the activating light to cause selective damage to the tumour tissue being treated.

The wavelength range of the activating laser light is normally between 600–900 nm with many of the early clinical studies utilizing the 630 nm wavelength of the first generation porphyrin-based PS. The effective penetration depth of the treatment is dependent on the wavelength of light used to activate the PS in question. The longer the wavelength, the deeper the penetration depth of the laser light but the optical properties of the tissue to be treated will have an impact on the fluence (light dose) administered within a given time. Absorption and scattering of the light in the tissue will determine the depth of treatment along with the concentration of the PS in the tissue and surrounding stroma.

An additional critical component in this relationship is the availability of oxygen which is important in the production of a short-lived excited singlet state of oxygen, which is generated as a result of the PDT process. This form of oxygen is highly cytotoxic with a short radius of action and lifetime, and therefore produces a localized effect on the tumour cells. The relationships of the many components of the PDT process are complex and alterations to any of these factors can influence the biological response.

2. History of PDT

Photosensitizing drugs in conjunction with light have been used in a variety of medically based procedures such as rickets, psoriasis, vitiligo and skin cancer in Indian,

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Greek, Chinese and Egyptian cultures for thousands of years.[1] In 1903, Jesionek and von Tappeiner utilised the phototherapeutic properties of eosin to treat lupus of the skin and skin cancers[2] and in 1904 von Tappeiner and Jodlbauer discovered that oxygen was essential for the photosensitization process and named this process photodynamic therapy.[3] In the 1920s, the French physician Policard noted that tumour tissue was inherently more fluorescent when animal tumours were exposed to a Woods lamp, indicating a selective localization of endogenous porphyrins to tumour tissue.[4] This led to studies by Figge et al.[5,6] and Rasmussen-Taxdal et al.[7] in the 1940s and 1950s, who attempted to accurately detect tumour tissue by fluorescence in patients and tumour-bearing animals after the administration of natural porphyrins. In 1961, Lipson and Schwartz reported that haematoporphyrin derivative (HpD) could be used to detect tumours and destroy tumour tissue[8,9] and in 1966, HpD was first used to treat a patient with a recurrent breast cancer.[10] Experimental studies in the 1970s showed that singlet oxygen was the cytotoxic product of the photodynamic process,[11] which motivated Dougherty to utilize HpD because of its high singlet oxygen quantum yield and absorption maxima in the red region of the light spectrum and he subsequently treated 25 patients for a variety of systemic tumours.[12] Perria et al.[13] were the first to utilize PDT as a treatment for human glioma and during the 1980s a number of neurosurgeons began treating glioma patients with PDT.[14–19]

3. Photosensitizers

PDT is reliant on the concept of selective localization of the PS to the tumour that can subsequently be activated by the absorption of light of the appropriate wavelength unique to the absorption spectral fingerprint of the compound, which then leads to the generation of active species such as singlet oxygen and free radicals that are toxic to the cells in which they are produced. The targeting of the PS is achieved by the increased uptake in neoplastic tissue, making the treatment somewhat selective. HpD, which is a first generation PS, has been almost solely used for clinical studies in the treatment of glioma. It is a complex mixture of porphyrins whose chemical structure is based on the tetrapyrrole ring. The composition of this compound varies depending on the method of synthesis and storage.[20–22] Lipson et al.[23] first described the synthesis of HpD utilizing the reaction of acetic and sulfuric acids on haematoporphyrin which was then subsequently neutralised with sodium hydroxide to produce HpD (Fig. 1). Kessel et al.[24] used an alternative method beginning with purified haematoporphyrin diacetate that resulted in a greater proportion of oligomeric porphyrins in the final product.[25] HpD has an optimum absorption at around 400 nm but this wavelength penetrates tissue very poorly and therefore a weaker Q-band in the 628–632 nm region is used clinically for excitation in the PDT process, which has been shown to have a better penetration depth.[26,27] Many endogenous molecules, such as haemoglobin, strongly absorb light at wavelengths below 600 nm that would attenuate most of the incoming photons, reducing the amount of activating light penetrating the target neoplastic tissue, hence the use of absorption peaks above 600 nm.[28]

Many of the first generation of PS such as haematoporphyrin and its derivatives were based on the porphyrin ring platform and after a variety of chemical modifications and purifications, many different porphyrin products have been used clinically. These include HpD, Photofrin®, Photosan and Photocan[29] which vary in their composition of porphyrin monomers, dimers and oligomers[30] and subsequently their PDT efficacy. Investigations into alternative compounds have continued since the devel-

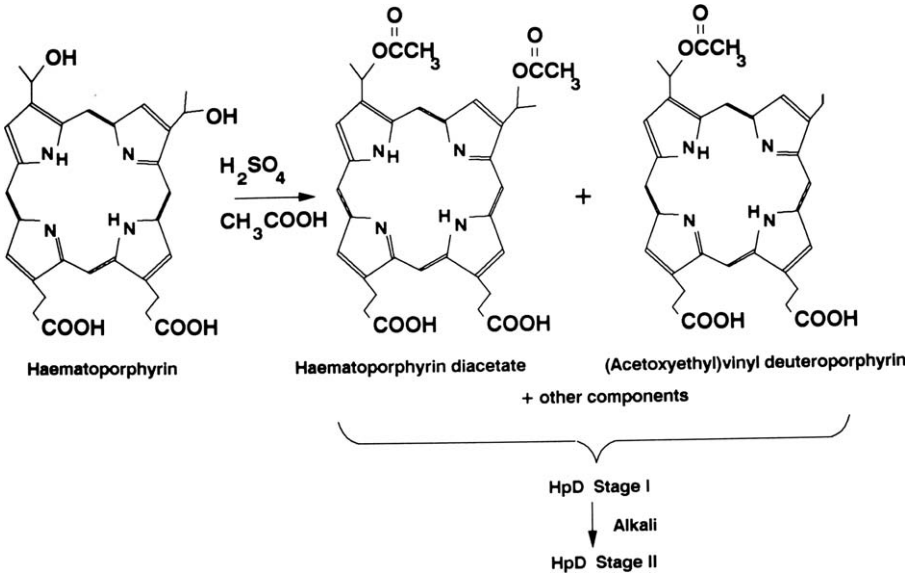

Fig. 1. The synthesis of HpD from Haematoporphyrin.

opment of these early PS in the 1970s and 1980s in order to improve both the selectivity of the PS and increase the PDT response. Important characteristics of an ideal PS are that it possess peak activation at 650–900 nm (increased tissue penetration but below the 900 nm threshold where the production of activated singlet oxygen is markedly reduced), is a single component compound, is systemically non-toxic and is water-soluble. It should have increased tumour tissue selectivity, reduced skin phototoxicity through rapid systemic excretion, and importantly for gliomas, be able to cross an intact blood-brain barrier to reach infiltrating tumour cells without entering surrounding normal brain cells.

Many compounds have been synthesized and investigated as potential new generation PS for a variety of different conditions and cancers. Only a few make it through to clinical trial. These include but are not limited to Verteporfin (benzoporphyrin derivative), Purlytin (tin etiopurpirin), Foscan (*meta*-tetrahydroxyphenyl chlorin), NPe_6 (mono-aspartyl chlorine e_6), Levulan (Δ-5-aminolevulinic acid), Lutex (lutetium texaphyrin), BOPP (tetrakis-carborane carboxylate ester of 2.4 [α,β-dihydroxyethyl] deuteroporphyrin IX, abbreviated to a boronated porphyrin), Photosens (phthalocyanine) and LS11 (taloporphyrin).[31–47]

4. Photochemistry of photosensitizers

As indicated earlier, the most important cytotoxic product of the PDT photochemical reaction is singlet oxygen and the effectiveness of the PS has been shown to be directly proportionate to the amount of singlet oxygen produced.[48] Once the PS is illuminated with the appropriate wavelength of light corresponding to an absorbance maxima, the PS is converted from its stable electronic ground state to an excited singlet state (during this excitation, other processes such as scattering and reflection can also occur). The excited PS will attempt to de-excite as there are no unpaired electrons in the outer valance shell of the PS and return to its ground state by a number of different modes. This can include relaxation back to the ground state via the emission of a fluorescent photon (short-lived) or a phosphorescent photon (longer-lived) if the initial de-excitation has occurred via excited triplet states in an intersystem crossover (Fig. 2). The relaxation from the intermediate intersystem crossover states may also initiate a sequence of photochemical responses known as Type I or Type II reactions. In oxygenated environments, the PS will readily transfer its energy down to ground state molecular oxygen ($^3O_2$) which results in the production of singlet oxygen ($^1O_2$). Only a small amount of energy is required for the transition of oxygen from the triplet to singlet state and this is known as a Type II reaction, because of the dependence of the reaction on the oxygen concentration.[49] Alternatively, Type I reactions are characterized by a dependence on the PS : cellular substrate ratio. In this reaction, the triplet state PS can react directly with the cellular substrate via electron transfer that produces an oxidized substrate and a reduced PS. In less oxygenated or hypoxic environments, the reduced PS can then also react with superoxide radicals, producing superoxide ions and ultimately leading to the creation of highly reactive hydroxyl radicals. Even though it is believed that the Type II reactions dictate the outcome of a PDT reaction, in a hypoxic environment or where the PS is localized in high concentrations with the cellular substrate, Type I reactions may play a more predominant role.

5. Singlet oxygen

The extreme reactivity of singlet oxygen arises from the pairing of two electrons that have misaligned spins in one of the outermost antibonding orbitals. This is a result of the interaction of one of the electrons reacting with the excited PS, causing its spin to invert, pair up with another

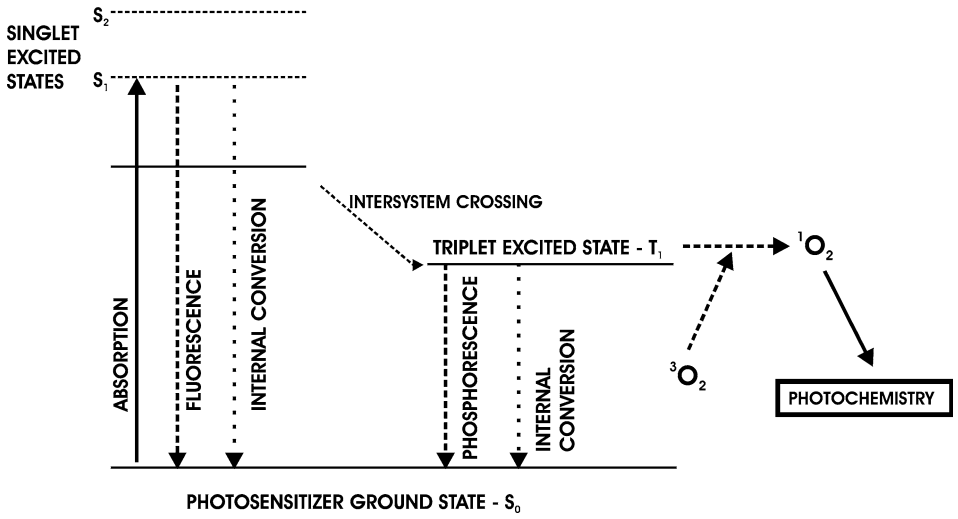

Fig. 2. A simplified energy level diagram showing the photoactivation of a photosensitizer from the ground state.

electron in this orbital and subsequently destabilize the molecule.

The highly toxic singlet oxygen exhibits short lifetimes in organic solvents (10–100 μsec) and even shorter in biological systems (40 nsec)[50–56] because of its highly reactive nature. This property of singlet oxygen means that the PDT-induced damage caused by its formation is highly localized within a short radius of action of less than 0.02 μm[50] and therefore confined to the cell in which it is produced. The initial damage is probably confined to targets near or within the localization of the PS, which in many cases can be hydrophobic regions of the cell due to the hydrophobic character of most PS, followed by the triggering of an apoptotic or necrotic response, depending on the organelle targeted by the PS localization.[50,57–59]

6. Photosensitizer transport

From a practical point of view, the main characteristics that are initially targetted when designing a new PS in a laboratory are a clinically relevant absorption peak (between 600–900 nm) and the ability to generate active molecular species such as singlet oxygen at a reasonable level. Further in vivo screening then determines those that are somewhat selectively localized within neoplastic cells or tissue. The structure of a PS will determine how it will interact in its surroundings, whether it is an in vitro or in vivo system. The hydrophobicity and charge on a PS will influence how it relates to itself in solution in vitro, that is, whether the PS will stay in a monomeric or aggregated form. In vivo is a completely different matter, as the PS structure, hydrophobicity and charge, will determine the extent of the interactions between serum proteins acting as carriers, pH gradients within tumour tissue, leaky tumour vasculature, tissue structure and location and entry into tumour cells.

Low density lipoprotein (LDL) associated PS uptake via the LDL receptor pathway is thought to be one of the main transport mechanisms of PS to tumour cells. It has been shown that components of PS can bind to either albumin or serum lipoproteins.[60,61] Serum taken from glioma patients undergoing HpD-mediated PDT has revealed binding to serum proteins as well[62] (Fig. 3). There is an increased number of LDL receptors on the surface of malignant cells which is expected as the increased rate of proliferation or membrane turnover would require an a greater amount of available cholesterol, of which LDLs are the major carrier in serum. Binding to high density lipoproteins (HDL) and albumin may also allow for a non-receptor mediated uptake of a PS into tumour stroma, or even be responsible for the extended periods of skin photosensitivity post-systemic administration.[63] Also, it is known that macrophages have an enormous capacity for LDL and therefore accumulate high concentrations of PS-LDL complexes, which then localize in the skin, also causing skin photosensitivity.[64,65] Not all tumours show elevation of LDL receptors[49] and binding of relatively hydrophilic PS to albumin and HDL can lead to tumour destruction and vascular shutdown via a non-LDL mode of PS localization.[66–69]

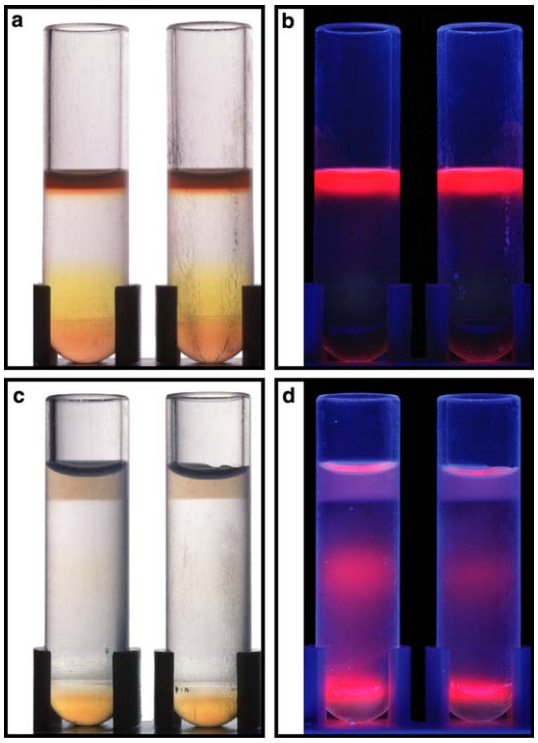

Fig. 3. Lipoprotein isolation from patient serum (62). Total protein isolation in panels (a) and (b). (a) A photo taken under normal white light conditions, whereas (b) was taken under a UV light source. The brown layer in (a) and the pink layer in (b) are the total lipoproteins (VLDL, very low density lipoproteins, LDL, low density lipoproteins and HDL, high density lipoproteins). Gradient separation of lipoprotein classes in panels (c) and (d). (c) A photo taken under normal white light conditions, whereas (d) was taken under a UV light source. The cloudy top layer is comprised of chylomicrons and VLDL's, the middle layer LDL's and the HDL's are located directly above the bottom yellow layer (dense serum proteins, in (c) and are fluorescing in (d)[62]).

7. Photosensitizer intracellular localization

The cellular mechanisms involved in PDT have been studied extensively. The transport and entry of a PS into a cell are affected by the complex extracellular and cellular environments and many factors including polarity of the PS, chemical nature of the side-groups, presence of a chelated metal ligand, aggregation properties and binding to proteins. To aid in the development of the next generation of PSs, it is necessary to identify the targets of current PS. Subcellular localization is also dependent on the physicochemical properties of the PS once it enters the cell. The plasma membrane, lysosomes, mitochondria and cytoplasm have been shown as areas of localization within a cell. Due to the short distance (0.02 μm) travelled by singlet oxygen[50] as a result of quenching in biologic systems,[70] the cellular structure that has localized PS or that is close to the

PS and a high concentration of oxygen will be preferentially damaged by the PDT process on illumination.

Fluorescence microscopy has been the main tool used in the determination of PS subcellular localization. Conventional epifluorescent microscopes, microscopes with charge-coupled devices or video cameras and confocal laser scanning microscopy, have been used to examine PS localization within cells.[71–79] Many PS, including the heterogeneous HpD and Photofrin, have been shown to localize mainly within mitochondria.[80–85] This may be important as the benzodiazepine receptor is present in higher numbers on the membrane of certain neoplastic cell types and it has a high affinity for some porphyrins in addition to binding benzodiazepines.[86,87] The activation of PS that have localized in mitochondria, results in the rapid induction of apoptosis (Fig. 4) through the release of cytochrome C through the mitochondrial transition pore into the cytosol.[88,89] One of the first links between PDT and apoptosis was demonstrated by Agarwal et al. in 1991.[90] A necrotic cellular response is generally the result from PS that localize in lysosomes and plasma membranes,[91–94] although it is possible that lysosomally localized PS may relocate to more susceptible organelles, such as the mitochondria in the early stages after light activation.[95–97] Commonly, the type of damage that is manifested by these types of PS is cellular swelling, blebbing, depolarisation of membranes, release of cytosolic and lysosomal enzymes and lipid peroxidation.[98–102]

8. Biological mechanisms of tumour destruction

The three main mechanisms of PDT-mediated tumour destruction involve a direct cellular toxic effect, vascular damage or immune reaction. All of these mechanisms are dependent on a number of factors that will determine their degree of involvement in the PDT process. The tumour cells, tumour and normal tissue vasculature and the host immune and inflammatory system are all targets of the PDT process. It is evident that a complex system of interrelated events occur during the PDT process and that it is not only the nature and structure of the PS, its localization within the tumour tissue and oxygen concentration,

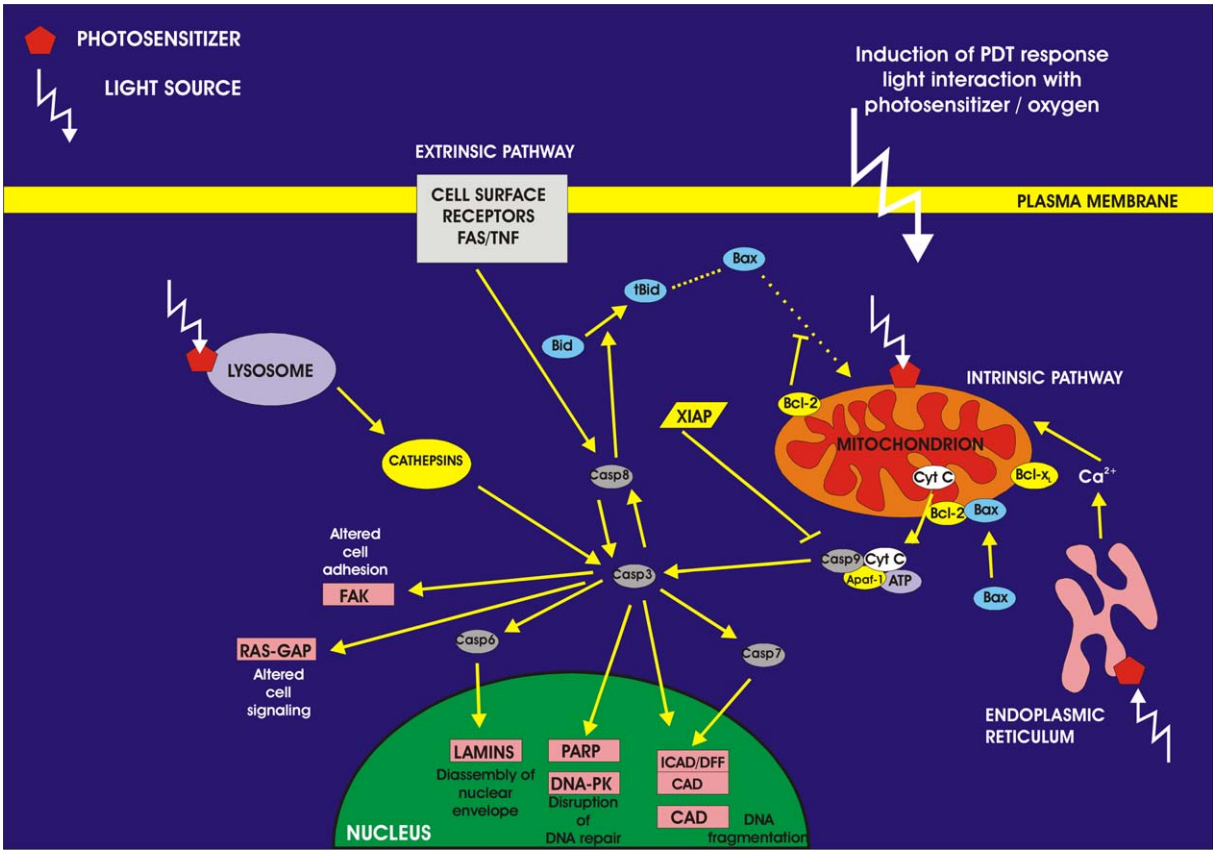

Fig. 4. Schematic of some of the molecular events that occur during photodynamic therapy (PDT) induced processes. The intracellular uptake of a photosensitizer (PS) may allow it to bind to the mitochondria, lysosomes, endoplasmic reticulum or other intracellular membranes. Once the PS is photoactivated, cytochrome C (cyt c) is released from the mitochondria into the cytosol which becomes part of a complex with ATP, APAF-1 to initiate the activation of caspase 9. This then leads to the activation of the central effector caspase, caspase 3 which cleaves and activates other caspases. They ultimately instigate the cleaving of other intracellular proteins that lead to nuclear inhibition of DNA repair, nuclear breakdown, degradation of DNA and cell structure and adhesion alteration. The Bcl-2 family family of proteins can promote or inhibit the apoptotic process as shown.

but also the tumour type, vascularity and even its macrophage content[103–108] that are involved in the PDT process.

9. Cellular effects

PDT-mediated cellular effects have been proposed to be the main contributors to cell death, provided there is a sufficient concentration of localized PS in the tumour cells and if lethal quantities of singlet oxygen are produced following activation by a suitable light source.

As mentioned previously, the cellular pathways initiated during PDT-mediated photodamage include apoptosis or necrosis. As mitochondria have been found to be one of the sites of localization for many PS, it is possible that a protein found in the outer membrane of mitochondria (Bcl-2), which is known to be anti-apoptotic, may influence the cellular effects of apoptosis. The overexpression of this protein is known to confer some resistance to chemotherapy and radiation regimens[109–112] and this is also evident in the photodynamic process.[113–116] It is speculated that it is the antioxidant effect of Bcl-2 or the interference with cellular calcium homeostasis[117] that plays a role in PDT, however its major role in apoptosis is the inhibition of cytochrome C release from the mitochondrial membrane[118–120] which is an activator of one of the central caspases in apoptosis, caspase 3. Xue et al.[121] have shown that Bcl-2 is highly sensitive to the PDT process, using a phthalocyanine PS. Damage produced the loss of the native Bcl-2 protein which would then contribute to the efficient induction of the apoptotic process by increasing the Bax (pro-apoptotic) : Bcl-2 (anti-apoptotic) ratio. Oxidation of unsaturated fatty acids and cholesterol in the cellular membranes of the plasma and mitochondrial membranes[122–124] as a result of activated PS localized in these regions can drastically affect cellular energy-consuming processes, replication and repair. Lysosomal localized PS may not produce direct cellular toxicity but the rupturing of the lysosomes by the production of singlet oxygen may have a twofold effect. First of all, the possible release of lysosomal enzymes may degrade other cellular components[125] or the release of PS from the lysosomes may relocate to other cellular sites such as mitochondrial membranes and cause photodamage at the new site.[126] Other cellular signalling molecules, growth factors and cytokines have also been implicated as either affecting or being affected by the PDT process.[127–129] These include the mitogen activated protein kinase family (MAPKs), ERKs (extracellular receptor-stimulated kinase), JNKs (Jun NH_2-terminal kinase) and p38 MAPKs,[130,131] protein tyrosine kinase activity of the epidermal growth factor (EGFR) receptor[129,132] which is elevated in glioblastoma multiforme,[133–137] NF-κB (nuclear factor kappa-b)[138] which has been shown to be constitutively activated in glioblastoma samples[139] and ceramide accumulation,[140] which may induce diverse biological responses, including apoptosis or cell cycle arrest.

10. Vascular effects

PDT-mediated cellular events can trigger an apoptotic or necrotic response, initially through loss of mitochondrial membrane potential, disruption of lysosomal membrane, enzyme inhibition or membrane lipid peroxidation, but vascular destruction within a tumour has also been shown in vivo. Fingar et al.[141] demonstrated that when using Photofrin to treat tumour-bearing animals, the PDT damage was confined to the tumour vasculature. Following PS accumulation and irradiation, damage occurred in the sensitive sites within the microvasculature, namely the endothelial cells and the vascular basement membrane. This allows for the establishment of thrombogenic sites within the vessel lumen, which in turn instigate events such as platelet aggregation, the release of vasoactive molecules, leukocyte adhesion, increases in vascular permeability, vessel constriction and haemorrhage. Ultimately, there is the stasis of blood flow and tumour microvasculature collapse.[142] This is not the case with all PS as McMahon et al.[143] showed, that the vascular effect can differ depending on the PS and may be reliant on the level of thromboxane production in response to the PDT process.

11. Immunologic effects

It is realized that PDT can elicit tumour destruction via the modulation of the host immune system. PDT can either activate or suppress the immune system as the immune system produces cytokines that have a variety of roles within the host. The interleukins (IL) are a class of these immune system modulators. IL-6 expression in a murine tumour model increased after PDT exposure, whereas IL-10 was seen to decrease, prompting the investigators to suggest that the general inflammatory response to PDT in the tumour may be partly due to the increased expression of IL-6.[144] Bellnier[145] showed that tumour necrosis factor-α (TNF-α), when administered as an adjuvant to Photofrin-mediated PDT, increased phototoxicity and selectivity. This led to the theory that an increase in the inflammatory response at the treatment site was instigated by TNF-α , as one of its roles is to stimulate macrophage growth and differentiation. Korbelik has also reported TNF-α mediation of phototoxicity through macrophage involvement, especially as it was observed that tumour-associated macrophages accumulated up to nine times the Photofrin levels in comparison to the neighbouring tumour cells,[146,147] thus increasing the amount of available PS and subsequently singlet oxygen at the treatment site. The PDT effect would release TNF-α, mediating the PDT process as an indirect mechanism of cytotoxicity. Gollnick and colleagues[145] showed that monocyte/macrophage and neutrophil infiltration and activity were involved in the destruction of tumour cells after Photofrin-based PDT. The release of heat shock proteins (HSP) from the tumour cells or macrophages may also play an important role. HSP can alert the host immune

system to the presence of a possible threat and induce a variety of immune and inflammatory responses[148,149] that can act upon the cells that have not undergone necrosis from the PDT process.

12. PDT dosimetry

Dosimetry discussions in the PDT field have generally revolved around the importance of light. But a PDT response is obtained when there is an interaction between the localized PS, activating light and oxygen at the treatment site. Therefore, PDT dosimetry can be altered as each of these factors contribute to the final result.

The aim of PDT is to achieve selective destruction of the tumour tissue without damaging surrounding normal tissue. A PS that accumulates in tumour tissue to a greater degree than adjacent normal tissue along with the delivery of the appropriate light to the tumour site and not the normal tissue, will assist in administering an efficacious PDT dose. In general, the PDT dose is a measure of the energy absorbed by the PS in a given volume of tissue. PS quantification within tissue has usually been via chemical extraction and subsequent analysis via spectrophotometric or fluorometric methods.[14,150–152] In vivo methods have also been utilized to directly measure the concentration of PS present in the tumour tissue, even though PS aggregation, photobleaching and tissue optical properties can ultimately confuse the issue.[153–158]

Light delivery and penetration to the target tissue containing the accumulated PS is the next important step in the process. The wavelength of light used, as well as the optical properties of the tissue, will have a bearing on the PDT process. Light entering tissue can be reflected at the surface or scattered internally within the tissue until some of the light escapes the tissue again or is absorbed by an internal chromophore within the tissue.[159] The internal chromophore may be haemoglobin contained within blood present within the tumour or in terms of the PDT process, the selectively accumulated PS within the tumour cells or vasculature. Absorption of a light photon by a PS molecule allows for the excitation of local ground state molecular oxygen within the tumour to the active singlet oxygen and subsequent destruction of the tumour cells.

The abolition of the PDT effect has been shown under anoxic conditions,[160] and changes in the oxygen concentration during PDT have also been observed.[161,162] The implication of a reduction in the concentration of available oxygen during PDT would ultimately limit the generation of singlet oxygen and diminish the PDT effect, especially in less vasculature or hypoxic regions of the tumour. Fractionated irradiation or lower fluence rates have been proposed as higher fluence rates tend to consume oxygen in most cases at a higher rate than it is being replenished from the circulating blood[163–167] and that the lower fluence rates should produce a more efficient PDT response. This may not be practical in the clinical environment as the introduction of intervals (seconds or minutes) allowing re-oxygenation may dramatically increase total treatment times.

13. Conclusions

The future of PDT relies on the generation of new PS synthesized to target different types of cancers that have varying characterstics. This may allow for custom manufacturing of PS tailored towards certain types of malignancies, depending on their location and the depth of treatment required. PS which possess activation wavelengths beyond those of the first generation PSs, efficient singlet oxygen generation, low systemic toxicity, a purified composition and high tumour tissue selectivity, will improve the efficacy of the treatment. The development of inexpensive and simplified light sources have been helpful in making the treatment more available generally. The clinical aspects of PDT will be discussed in Part II of the review to be published in the next issue of this journal.

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