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An Alternative Treatment Modality of Diseases using Photodynamic Therapy with a Wide Range Biological Targeting Possibility

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Editorial

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INTRODUCTION

With approvals for clinical use by health agencies in most industrial countries such as the United States, the Netherlands, Canada, Japan, Australia, Russia [1-3], Photodynamic therapy [PDT] is a very promising and minimally invasive treatment modality for various types of malignant diseases, including but not limited to cancers of lung, breast, bladder, pancreas, liver, ovary, prostate, skin, head and neck, digestive tract and brain, and for wide ranges of non-malignant diseases, such as hypertrophic scarring, ulcers, rheumatoid arthritis, intimal hyperplasia, periodontitis, atherosclerotic plaques, macular degeneration, psoriasis, actinic keratosis, bacterial and fungal infections [4].

Photodynamic therapy is based on photosensitizers, light with the corresponding wavelength of the photosensitizers, and tissue oxygen to destroy the target cells and tissues [5-10]. The electronic transitions occur from a singlet ground state to a singlet excited state first, and then a triplet excited state by intersystem crossing within the photo-induced molecules which are the main agents of photodynamic therapy [7,11-12]. After that, the photosensitizers eliminate the absorbed energy by transfer to tissue oxygen forming singlet oxygen or by transfer to biological substrates, forming semi-oxidized or semi-reduced radicals, which are associated with further electron transfer reactions [13-16].

The photosensitized radical chain reactions can lead to the formation of oxidized biological molecules such as lipids, proteins, carbohydrates, nucleic acids and other biologically-relevant molecules including vitamins, natural antioxidants etc. [17]. For example, lipophilic photosensitizers can intercalate into acetyl chain department of the phospholipid bilayer and photodynamic therapy-triggered oxidative modification of lipid constituents such as peroxidation of unsaturated phospholipids or production of truncated oxidized lipids [aldehydes and carboxylic acids] can bring membrane leakage and/or lysis, resulting in unregulated necrosis-like cell death [18-26]. Moreover, the photosensitized radical-induced oxidative lesions such as 8-hydroxy-2' -deoxyguanosine [8-OHdG] and 8-oxo-7,8-dihydro-2' -deoxyguanosine [8-oxodG] can be occurred, respectively in nuclear and mitochondrial DNA [27]. Oxidative attacks on sugar moiety of nucleic acids can be also accomplished by singlet oxygen and reactive oxygen species [28-31, 9]. Photo-oxidation of proteins can lead to structural and conformational changes of the peptide skeleton, loss of enzyme activity, differentiation in ligand affinities, mechanical properties and aggregation states, oxidation of other proteins and biological molecules, and deterioration or depletion of intracellular and/or extracellular signaling pathways [32-37, 59].

On the other hand, it is also possible to see the photo-oxidations at organelle level such as mitochondria, endoplasmic reticulum, golgi apparatus and lysosomes. For example, photodynamic therapy-triggered lysosomal rupture are associated with release high concentrations of lysosomal enzymes [such as the discharge of cathepsins] into cytoplasm and increase of cytosolic acidification, resulting in lysophagy, apoptosis or non-programmed cell death [38, 39]. The proteolytic cathepsins can fracture

the pro-apoptotic member of the Bcl-protein family, BH3 interacting-domain death agonist [BID], to form truncated-BID [t-BID], which are eventuated in apoptosis [40-42, 26]. Similarly, photo-oxidized the sarcoplasmic reticulum provides a burst of calcium that has been shown to play a substantial role in inducing programmed necrosis and necroptosis signaling pathway [43-45]. It is also widely known that targeting the endoplasmic reticulum and golgi apparatus could significantly compromise the synthesis and processing of proteins [46-47, 3]. Mitochondria is the most studied organelle in photodynamic application due to its key role in apoptotic pathway. However, ATP levels depletion, drastic mitochondrial membrane permeability and disruption of mitochondria can be achieved by high PDT-dose treatment, resulting oncosis and non-programmed cell death [48-50]. Extracellular release of ATP has been assigned as a very potent find-me signal for dendritic cells, monocytes and macrophages. For instance, ATP binding to P2X7 purinergic receptors on dendritic cells can stimulate dendritic cell maturation, and then induction of an anti-tumor adaptive immune response [51-53, 26]. Furthermore, it is worth mentioning about PDT-mediated immunological responses, occurred by damage-associated molecular patterns [DAMPs], which arise from stressed and dying cells, and operate as danger signals for the host immune system. The best characterized PDT-associated DAMPs are heat shock proteins [HSPs] serve as chaperon proteins that play key roles in the actions including transport and correct folding of new synthesized proteins, prevention of apoptosis and stress conditions, promotion of proteasomal degradation [54-59]. The exist of HSPs into the extracellular environment stimulates various immune cells and anti-tumor immune response due to the binding properties of HSPs to numerous receptors, related to immune system such as Toll-like receptors [TLR 2 and TLR 4] and cluster of differentiation 91 [CD 91] [60-63, 26].

Biological outcomes of the PDT-triggered radical-mediated photo-oxidations can cause cell senescence, and autophagic, apoptotic or necrotic cell death by dependent on fluence [J/cm^2] and fluence rates [mW/cm^2] of light, and photosensitizer concentration. Mfouo-Tynga and Abrahamse [64] reviewed PDT-mediated cell death pathways. However, tumor cells can renovate the outcomes of photodynamic therapy by activating one or more survival- and stress-response pathways, including a direct early stress response that induces proliferation of tumor cells, a hypoxia stress repercussions that rehabilitates energy homeostasis and encourages angiogenesis, a pro-inflammatory signaling response that manages angiogenesis and invasion, an antioxidant response that promotes de nova synthesis of antioxidants, an endoplasmic reticulum response that rehabilitates homeostasis of endoplasmic reticulum [65]. For many years, apoptosis was regarded as the most wanted result in the PDT-triggered cell death due to the minimal side effects although tumor cells can be resistant to apoptosis, and necrosis was considered as an undesired pathway for PDT-mediated cell death due to the possible initiation of inflammatory responses in the surrounding tissue [66]. Therefore, PDT-mediated autophagy can be regarded as an alternative to provide more efficient treatments to cells deficient apoptosis [16]. Additionally, the features of photosensitizers and photo-induced reactive species such as their aggregation and diffusion in nanoenvironment, the specific targets of photosensitizer, singlet oxygen generation quantum yield capacity, fluorescence lifetime, encapsulation, lipophilic and hydrophilic features, and other photo-physical and photo-chemical properties should be considered for an efficient photodynamic therapy [67-77, 26].

Consequently, photodynamic therapy seems to be the most promising strategy with minimal damage in surrounding tissue, combination possibility with other treatment strategy, perfectible features of different photosensitizers and possible treatment applications for a wide range of diseases. To provide an efficient photodynamic therapy, the researches focused on clinical, *in vivo* and *in vitro*, therefore, should be expanded.

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