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COMMENTARY

Molecular and Biochemical Mechanisms of Photodynamic Therapy Anti-Tumor Effects

Benjamin Bonavida[1,]* & M. Zouhair Atassi[2]

[1]Department of Microbiology, Immunology and Molecular Genetics, University of California at Los Angeles, Los Angeles, CA; [2]Department of Biochemistry and Molecular Biology, Baylor College of Medicine, Houston, TX

*Address all correspondence to: Benjamin Bonavida, Department of Microbiology, Immunology and Molecular Genetics, University of California at Los Angeles, Los Angeles, CA 90095-1747; bbonavida@mednet.ucla.edu

Several presentations were delivered on the biochemical and molecular mechanisms mediated by photodynamic therapy (PDT), both directly at the cancer cell and indirectly at the tumor microenvironment. Clearly, a thorough understanding of the PDT-mediated effects should result in improving the therapeutic potential of PDT with reduction of toxicity and development of novel applications.

The first session of the workshop was devoted to cellular uptake and photosensitizers. The plenary lecture was presented by Dr. Gomer (Los Angeles, USA). He introduced the pleiotropic effects induced by PDT in cancer models and summarized a number of gene products that are modified by PDT, including angiogenic and pro-survival factors. Emphasis was directed at the use of agents currently in clinical trials that target PDT-activated survival molecules in combination with PDT to achieve additive/synergistic anti-tumor effects. Clearly, the approaches investigated by Dr. Gomer's laboratory and others are urgently needed for their clinical application for the treatment of various cancers. A presentation was made by Dr. Barberi-Heyob (Nancy, France) on the role of nanoparticles and PDT, and she also presented Dr. Fochot's (Nancy, France) work on targeted strategies in PDT. A major limitation of the PDT application in the clinic is the poor accumulation of photo-sensitizers within the tumor tissues. In that vane, several approaches have been considered, such as the delivery of light selectively to tumor tissues, the enhancement of uptake of photoactive compounds by the target cells, and the control in the formation of singlet oxygen. Among those approaches, one may list the use of advanced optical fibers, conjugation with monoclonal antibodies or other target-binding molecules, and targeting the tumor vasculature. An example of the use of PDT in the treatment of brain tumors is critical due to the current limitations of various treatment modalities. Hence, the use of nanoparticles as photosensitizing carriers is one approach to circumvent the above

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limitations. Dr. Barberi-Heyob presented the use of nanoparticles bearing the neuropilin-1 (over-expressed in tumor vessels) and directed against the tumor vasculature. This approach was validated for its cytotoxic effects on cells over-expressing neuroplin-1. Dr. DaRos (Trieste, Italy) presented studies on the beneficial effects of photo-dynamic approaches with novel cadmium nanoparticles. Noteworthy, the physiological properties of these particles include tropism for several tissues, an advantage for their application for anti-tumor activity. These aforementioned new technologies with modified nanoparticles are good examples for their beneficial effects in clinical applications not only for brain tumors but also for other tumors.

Three presentations were made on the signal transduction pathways induced by PDT. Dr. Korbelik (Vancouver, Canada) described his work on the acute inflammatory response induced by PDT. A family of proteins, namely pentraxins and complement proteins, play a role in the removal of cells in PDT-treated tumors and participate in the initiation of an adaptive anti-tumor immune response. Using *in vitro* cell lines, he showed that following PDT treatment, the PI3K/AKT pathway was activated as well as transcription factors involved in the regulation of the expression of several gene products that are up-regulated by PDT. Clearly, such approaches to identify gene products regulated by PDT may provide novel means for their role in tumor responsiveness or tumor unresponsiveness following treatment with PDT. Such studies also offer the identification of novel biomarkers. Dr. Rapozzi's presentation investigated the molecular mechanism of PDT-mediated effects under conditions of tumor cell death or tumor cell recurrence. She analyzed the role of nitric oxide (NO) induced by different doses of PDT on both cell survival and cell death. She described the role of activation of the NF-κB pathway in conditions of PDT-mediated cell recurrence as well as the inhibition of the NF-κB pathway in conditions of PDT-meditated cytotoxicity. She proposed to use the combination of NO donors, which inhibit NF-κB activity, with low doses of PDT to enhance anti-tumor activity. Dr. Zawacka-Pankau (Gdansk, Poland) presented her studies on the interrelationship between the p53 tumor-suppressor protein and protoporphyrin IX (PpIX), and demonstrated how PpIX directly targets p53, resulting in its release from the p53/MDM2 complex and leading to cell death in a human colon cancer cell line used as model. She also reported on the role of PpIX or PpIX-PDT on the activity of p73, resulting in the induction of cell death in p53 null cells. This approach is relevant for most cancers since they express either an inactive p53 mutation or absence of p53. Clearly, these studies await their *in vivo* validation in mice bearing various appropriate tumor xenografts.

Several presentations were directed at the mechanisms of cell death mediated by PDT. Dr. Krammer (Salzburg, Austria) presented studies on the naturally occurring photosensitizer hypericin (Hyp). She showed that Hyp destroys tumor cells via the induction of reactive oxygen species (ROS). She demonstrated how the dose of Hyp-PDT can dictate cell growth or cell death. At low doses, cell growth is observed, whereas at high doses, autophagy takes place. However, with very high doses, apoptosis is observed via activation of the mitochondrial pathway. Hence, one

may select the mode of death by calibrating the doses of PDT for different tumors. Dr. Garg (Leuven, Belgium) presented his laboratory's research on the effect of hypericin-PDT (Hyp-PDT) on cell death and reported that the cells undergo immunogeneic apoptosis (IA), as assessed by the induced maturation of dendritic cells and the induction of a protective adaptive immune response *in vivo*. Dr. Ricchelli (Padova, Italy) presented studies on PDT-mediated targeting to the mitochondrion to stimulate cell death. A target of PDT, the outer mitochondrial membrane, the 18-kDa translocation protein (TSPO) binds photosensitizers, and TSPO is expressed at high levels in cancer cells. The cellular phototoxicity correlated with the density of TSPO. Based on the sensitizer/light doses she showed switching from inhibition to activation of the mitochondrial permeability transition. Dr. Gamaleia (Kiev, Ukraine) presented his studies on how to avert the limitation of PDT-induced small depth of penetration into biological tissues. He approached this limitation by using nanoparticles targeting specifically to tumor tissues. Dr. Krzykawska (Krakow, Poland) presented the use of synthetic bacteriochlorine derivatives in PDT to stimulate the local immune response. Dr. Bergamo (Trieste, Italy) presented water-soluble ruthenium-porphyrin conjugates and demonstrated their cytotoxic effects in the low micromolar range on tumor cell lines.

One of the challenges in cancer therapies currently used is the failure of most cytotoxic therapies to kill the cancer stem cells/cancer-initiating cells. Therefore, novel therapies are urgently needed to target these cells, which have been shown to be responsible for relapse and metastasis. Dr. Selbo (Oslo, Norway) presented results on photochemical internalization (PCI), which is a novel, efficient, and specific drug and gene delivery methodology developed in his lab. For instance, photochemically internalized antibody-drug conjugates targeting cancer stem cell markers have been shown to be potent cytotoxic agents. These novel approaches are clearly clinically relevant in the elimination of drug-resistant cancer stem cells. Dr. Xodo (Udine, Italy) presented studies on the ability of photoactivated cationic porphyrins to bind to RNA quadruplexes, resulting in the inactivation of specific cancer-associated gene products. He presented data on the inhibition of the mutant KRAS, which is usually expressed in cancer cells and is responsible for progression as well as resistance. Dr. Jori (Padova, Italy) presented studies on the utilization of photodynamic processes in the elimination of various infections. The cationic photosensitizers have been shown to bind efficiently on negatively charged functional groups at the surface of various microbes, bacterial and fungal, resulting in their growth inhibition. Advantages of this methodology are its wide spectrum of action towards native and antibiotic-resistant strains and the mild radiation exposure as well as the utilization of visible light sources. Dr. Magaraggia (Padova, Italy) presented studies on the utilization of porphyrin photosensitizers in the elimination of water infections in large-scale reservoirs.

All of the aforementioned studies that were presented in this workshop clearly recognize novel molecular pathways that are modulated by PDT and the potential of extending their therapeutic applications in cancer and in other diseases, as well as their commercial applications. There are several

advantages for the use of PDT technologies and it is essential that research in this field continue on its applications and on the development of more efficient PDT approaches to overcome current limitations.

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