

Preface

Photodynamic therapy (PDT) represents an already well consolidated but still gradually expanding approach to the treatment of solid tumors, which is based on the combined action of three elements—a tumor-localizing photosensitizing agent, oxygen and specific intervals of visible light wavelengths, which leads to the generation of highly cytotoxic reactive oxygen species (ROS) (that is, *in primis* singlet oxygen). This technique has so far obtained the approval in several countries for the palliative or curative treatment of tumors localized in different organs, and in particular, the non-melanoma skin cancer, head and neck, gastroenteric apparatus, lungs, prostate and brain. Moreover, the application of PDT is also gaining attention for the treatment of diseases outside the oncological field, such as blood sterilization, age-related macular degeneration, and a variety of infectious diseases including those caused by antibiotic-resistant bacteria, recalcitrant rheumatoid arthritis and a number of cutaneous pathologies.

For many years, one favorable aspect of PDT has been assumed to be represented by the low probability of selecting photoresistant strains of malignant cells, a consequence of the multi-target mode of action of photosensitized processes; in most cases, an irreversible damage is induced to different proteins, unsaturated lipids and nucleotides. This should minimize the possibility for cells to develop protective strategies, including the activation of anti-oxidant processes. However, the development of thorough in-depth studies on the factors controlling the response of cells to repeated PDT treatment has provided different examples pointing out the not-too-rare gradual generation of cell clones poorly susceptible to the damaging effects of photosensitizing agents. Such observations raised the question of the consequences of cell resistance to PDT in a clinical scenario, especially when the PDT treatment needs to be repeated in the case of recurrences or insufficient response of the neoplastic lesion to the primary PDT treatment.

This volume addresses this above issue by assembling selected contributions from investigators who are authoritatively involved in front-running studies focused on the basic mechanisms of PDT and the translation of the results obtained in such studies to the clinical utilization of this technique. The volume starts with a chapter providing an overview of the main features of PDT at molecular, cellular and tissue levels. In addition, the response of various types of tumors to PDT in

human patients is described and the advantages or limitations of the utilization of PDT in the individual fields are discussed. In order to provide an exhaustive description of the current “state of art” of our knowledge on the modalities by which photosensitized processes can promote the selection of cells clones exhibiting poor susceptibility to the attack by ROS and the practical importance of such processes, the volume contains a total of ten additional chapters which deal with three aspects of tumor resistance to PDT.

Part 2 is centered on the mechanisms which have been shown to be most frequently responsible for the induction of cell resistance to PDT. In particular, a correlation is attempted between the probability and rate of the formation of resistant cells and the sequence of the main physical, chemical and biological events which lead to the eventual cell killing after the initial electronic excitation of the photosensitizer: according to the currently available information, cell death after photodynamic inactivation can occur via three concurrent pathways—random necrosis, apoptosis, and autophagy. Moreover, the possible involvement of tissue vasculature in the development of resistance to PDT is taken into attentive consideration, since the impairment of neo-formed blood vessels is well known to often play a major role in the PDT-induced damage to neoplastic lesions. Finally, methodologies are described for the isolation of PDT-resistant cells in order to facilitate a detailed examination of the most prominent characteristics of such cells at both functional and morphological levels. Such observations are essential to devise optimal ways for preventing the generation of PDT-resistant cells or obtaining their specific inactivation.

Part 3 of the volume reviews different strategies currently used to sensitize tumor cells to PDT with an aim to pilot the photosensitized process for counteracting or at least minimizing the probability to stimulate the selection of resistant malignant cells. The information provided by the investigations carried out at molecular and subcellular levels are being exploited in order to identify modes of regulation of PDT resistance that depend on the targets of the photosensitized processes, most of all the nature of the subcellular compartments which represent the binding sites of the added photosensitizer, since they are involved in the early stages of the photoprocess. Specific examples are given based on the involvement of specific factors, such as GRP78-targeting subtilase cytotoxin and survivin gene knockdown.

Part 4 of the volume outlines emerging and apparently very promising approaches to adequately control the tendency to induce resistance of tumor cells to PDT. One approach is based on the manipulation of the mechanisms regulating the intracellular formation of the tumor sensitizer protoporphyrin IX from the exogenously administered pro-drug 5-aminolevulinic acid (ALA); this approach is usually known as ALA-PDT and is increasingly utilized for the treatment of skin tumors. An alternative approach exploits the novel possibilities opened in the field of PDT by the introduction of multi-functional nanoparticles as carriers of photosensitizing agents to tumor tissues. In particular, the possibilities to utilize such nano-vehicles to target specific receptors preferentially expressed by malignant cells, thus, enhancing the selectivity of the PDT action and, thus, the scope of this approach

is critically outlined. Finally, the practical applications of such approaches for the PDT treatment of melanoma are exemplified.

We wish to mention that one potentially very important contribution to this volume, dealing with the relationship between the chemical structure of the photosensitizing agents and the development of tumor cell resistance to PDT by Janet Morgan, a well-known expert on this topic, is unfortunately missing since the author regrettably passed away while she was engaged in the preparation of her chapter.

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