Chapter XXXV
Photodynamic Therapy:
A Systems Biology Approach

Michael R. Hamblin
Massachusetts General Hospital - Boston, USA; Harvard Medical School, USA; and Harvard-MIT Division of Health Sciences and Technology, USA

ABSTRACT

Photodynamic therapy (PDT) is a rapidly advancing treatment for multiple diseases. PDT involves the administration of a nontoxic drug or dye known as a photosensitizer (PS), either systemically, locally, or topically, to a patient bearing a lesion (frequently but not always cancer), followed after some time by the illumination of the lesion with visible light; in the presence of oxygen, leads to the generation of cytotoxic species and consequently to cell death and tissue destruction. The light is absorbed by the PS molecule and the excited state PS transfers energy to ground state molecular oxygen, forming a reactive oxygen species that oxidize lipids, proteins, and nucleic acids. The resulting damage to essential biomolecules kills target cells by necrosis, apoptosis, or autophagy. When used as a cancer treatment PDT is known to cause direct tumor cell killing, severe damage to tumor blood vessels, and also produce an acute inflammatory reaction that can stimulate the immune system to recognize, track down, and even kill distant tumor cells that could cause metastases. This chapter focuses on studies of PDT that have employed a systems biology approach. These experiments have been frequently carried out using gene-expression micro-arrays. We will cover protective responses induced by PDT that include activation of transcription factors, heat shock proteins, antioxidant enzymes, and antiapoptotic pathways. Elucidation of these mechanisms might result in the design of more effective combination strategies to improve the antitumor efficacy of PDT. Specific pathways shown to be activated after PDT are heat shock proteins 90, 70, and 27, heme oxygenase, and cyclooxygenase-2.

INTRODUCTION

Photodynamic therapy (**PDT**) is a rapidly advancing treatment for multiple diseases. **PDT** involves the administration of a nontoxic drug or dye known as a photosensitizer (PS) either systemically, locally, or topically to a patient bearing a lesion (frequently but not always cancer), followed after some time by the illumination of the lesion with visible light, which, in the presence of oxygen, leads to the generation of cytotoxic species and consequently to cell death and tissue destruction. The light is absorbed by the PS molecule and the excited state PS transfers energy to ground state molecular oxygen to form reactive oxygen species that oxidize lipids, proteins and nucleic acids. The resulting damage to these essential biomolecules kills target cells by processes characterized by necrosis, apoptosis or autophagy. When used as a cancer treatment **PDT** is known to cause combinations of direct tumor cell killing, together with severe damage to tumor blood vessels. In addition **PDT** can produce an acute inflammatory reaction that can stimulate the immune system to recognize, track down and kill distant untreated tumor cells that could cause metastases. This chapter will focus on studies of **PDT** that have employed a systems biology approach. Many cell pathways and signaling systems are engaged after **PDT** and although many of these cellular changes have been elucidated by traditional biochemical and cell biology techniques, the newer technologies of "omics" are increasingly being brought to bear on this problem. In particular these technologies involve the use of gene-expression micro-arrays. We will cover protective responses induced by **PDT** that include activation of transcription factors, heat shock proteins, antioxidant enzymes and antiapoptotic pathways. Elucidation of these mechanisms might result in the design of more effective combination strategies to improve the antitumor efficacy of PDT.

OVERVIEW OF PHOTODYNAMIC THERAPY

PDT dates from the early days of the twentieth century when workers used dyes such as eosin together with light to treat skin cancer (Jesionek, 1903). Hematoporphyrin (HP) was also first used at this time (Hausman, 1911) and sporadic reports (Figge, 1948) of both selective localization of porphyrins in tumors and regression after exposure to visible light appeared until the 1960s. The modern explosion of interest in PDT dates from the discovery of hematoporphyrin derivative (HPD) by Lipson and Baldes in 1960 (Lipson, 1960), and was fueled by pioneering studies in both basic science and clinical application (Dougherty, 1974, Dougherty, 1978, Dougherty, 1979) by Dougherty et al. (notable among many groups). A semi-purified preparation of HPD known as Photofrin® (PF) was the first PS to gain regulatory approval for treatment of various cancers in many countries throughout the world, including the United States. After experience of treating tumors with HPD-PDT was accumulated, it was realized that this compound had significant disadvantages, including prolonged skin sensitivity necessitating avoidance of sunlight for many weeks (Baas, 1995), sub-optimal tumor selectivity (Orenstein, 1996), poor light penetration into the tumor due to the relatively short wavelength used (630 nm) (Spikes, 1990) and the fact that it was a complex mixture of uncertain structure (Kessel, 1987).

In recent times much work has been done on developing new PS (Gaullier, 1995, Gomer, 1991a), and at the present time there is such a great number of potential PS for PDT that it is difficult to decide which ones are suitable for which particular disease or application. Some PS can easily be prepared by partial syntheses starting from abundant natural starting materials, such as heme, chlorophyll and bacteriochlorophyll. This route leads to both economical and environmental advantages compared to