

Preface

The Nobel Prize in Physiology and Medicine was awarded in 1998 to Drs. Furchgott, Ignarro, and Murad for their discoveries concerning the “Nitric oxide as a signaling molecule in the cardio-vascular system.” Nitric oxide (NO) is a short-lived, endogenously produced gas that acts as a signaling molecule in the body. NO-induced signaling events within the cell producing it and its diffusibility to other cells has led to the discovery of many other physiological functions in many other types of cells including cancer cells. Noteworthy, nitroglycerin, invented by Alfred Nobel, has been used for the treatment of chest pain and associated cardiovascular diseases and has now started to be used in clinical studies including cancer (see below).

Several reports have addressed the roles of tumor-expressing iNOS and NO donors on tumor behavior in vivo. Data reported demonstrated the contrasting roles of NO mediating either tumor promotion or tumor regression. In an effort to sort out the roles of iNOS and NO in cancer, the “First International Conference on Nitric Oxide and Cancer” was held in Paris, France, November 26–28, 2007. This conference was attended by leaders in the field and Dr. Wink and collaborators presented convincing data demonstrating that the levels of NO dictate the outcome of tumor cell response. This conference resulted in the publication of a special issue “Nitric Oxide and Cancer: Clinical and Therapeutic Implications” (Nitric Oxide, Vol 8/19, September 2008). The rapid advances made in the field of nitric oxide and cancer were the impetus to develop this special volume summarizing the current status of NO and cancer to be published by Springer and contains over 25 chapters that have been contributed by leaders in this field.

This volume was divided arbitrarily into seven parts, namely (I) General overview, (II) Nitric Oxide and the pathogenesis of cancer, (III) Dual roles of NO in protecting against or inducing cell death, (IV) Role of NO in metastasis, (V) Nitric oxide as a sensitizing agent for chem-radio-immunotherapy, (VI) Prognostic applications of iNOS in various cancers, and (VII) The application of nitric oxide as a therapeutic. Briefly below, I will discuss the highlights presented by each contributor in each section.

In Part I, Drs. Harris, Wink, and colleagues from the National Cancer Institute present an overview of the field and provide chemical and molecular analyses

underlying the pleiotropic activities observed with NO in cancer. They also discuss the roles of NO in the modulation of host immune responses and suggest novel strategies to develop new applications of NO as a therapeutic drug. In Part II, Drs. Counter, Chadhuri, and Masini describe the role of NO in the pathogenesis of cancer. Dr. Counter discusses the role of eNOS in tumorigenesis through the activation of the Ras family of proteins. Several experimental models are presented to corroborate their findings. They also raise several questions that need to be explored regarding the underlying mechanism(s) of the eNOS/Raf interaction in tumors. They also suggest novel targets for therapeutic interventions and show an inhibitor of eNOS inducing an anti-tumor activity. Dr. Chadhuri also describes the multifaceted roles of NO in cancer, namely, in cell growth and apoptosis and highlights several other gene products that are regulated by NO. Dr. Masini discusses the dual roles of NO in cancer as well. In addition, the coordinate expression of iNOS, COX2, and VEGF in certain tumor cells are shown to promote new blood vessel formation and tumor growth. In addition, contrasting findings are presented and overall the iNOS/COX2 pathway is considered as target for cancer treatment. In Part III, five contributors review the dual roles of NO in protecting or inducing cell death. Dr. Rojanasakul and colleagues describe the role of S-nitrosylation by NO in cell death. In addition, they review the involvement of NO in the tumor microenvironment and mechanisms of tumor progression toward metastasis. The role of NO-mediated cysteine nitrosylation on carcinogenesis is also discussed. Dr. Soma reviews the recent literature and presents several schematic and illustrative diagrams summarizing the various pathways that regulate the various pro- and anti-apoptotic roles of NO. Dr. Chung and colleagues review the reported studies and theirs on the effects of NO concentrations, sources, half-life, chemical interactions, and the microenvironment all of which would influence the outcome. Dr. Weinberg reviews the dual roles of NO and emphasizes the role of iNOS overexpression in hematological malignancies, particularly CLL. In these tumor cells the overexpression of iNOS is protective and inhibition of iNOS results in significant cell death in CLL. It is suggested that overexpression of iNOS results in NO-induced inhibition of caspases which leads to resistance to apoptotic stimuli. It is suggested that the use of specific inhibitors targeting iNOS in this cancer may be therapeutic. Dr. Kolb and colleagues also describe the anti-apoptotic role of NO in CLL. The overexpression of iNOS in CLL is regulated by the toll-like receptor 7 (TLR-7). While NO exerts contrasting effects on apoptosis in many tumor cells, however, in CLL it is protective against apoptosis. In Part IV, Drs. Estrala and Baritaki describe the role of NO in metastasis. Dr. Estrala reviews the intravascular origin of metastasis, the cytotoxic effect of NO derived from the vascular endothelials in the tumor microenvironment and tumor survival. Also, the role of anti-apoptotic gene products including NOS in the regulation of metastasis as well as the role of NO in the regulation of angiogenic factors is reviewed. Dr. Baritaki, in contrast, describes a novel mechanism of tumor cell inhibition of metastasis by NO donors. Treatment of metastatic human prostate cancer cell lines with the use of high levels of the NO donor, DETANONOate, results in the inhibition of constitutive survival pathway such as NF- κ B and downstream the metastasis-inducer transcription factor,

Snail, and inhibition of the epithelial–mesenchymal transition (EMT). Also, in this chapter, she describes NO-induced expression of the metastasis suppressor gene product, RKIP. This study suggests the potential therapeutic application of NO donors in the regulation of metastasis. In Part V, four contributors discuss the role of NO as a sensitizing agent to reverse tumor cell resistance to cytotoxic therapies. Dr. Siejo discusses the role of NO as a sensitizing agent for radio-chemo- and immuno-therapy. Irradiated tumor cells result in the release of NO and ROS that potentiate the cytotoxic effect of radiation. Likewise, the addition of NO donors to irradiated tumor cells potentiates the cytotoxic effect. Similar findings are discussed with respect to tumor therapy and NO. Dr. Jeannin discusses the primary role of NO as an enhancer for cancer therapy. In this review, he also discusses the mechanism by which NO exerts its sensitizing effect to both chemo- and immuno-therapy. Dr. Effert reports on the resistance induced in cancer cells by hypoxia and how NO inhibits the transcription factor, HIF-1 α . The inhibition of HIF-1 α results in the inhibition of many resistance gene products and, hence, the tumor cells become sensitized to chemotherapeutic drug-induced apoptosis. Dr. Garbán reviews the role of NO in reversing tumor cell resistance to cytotoxic drugs. He postulates that NO induces oxygenation of tumor cells by increasing blood flow and resulting in the increase of the delivery of the cytotoxic drug to the tumor. Further, NO modulates the host immune response by regulating the expression of death receptor on the tumor cells and, thus, potentiating their sensitivity to host-immune cytotoxic lymphocytes. In addition, Dr. Garbán presents his expert opinion on the above chapters. In Part VI, four contributors review the prognostic significance of iNOS expression in various cancers. Drs. Ekmekcioglu and Grimm present the prognostic significance of iNOS in human melanoma. Their findings demonstrate that iNOS overexpression in melanoma is an independent prognostic factor for Stage III melanoma. Drs. Pascale and Feo review the molecular increase in the alteration of iNOS and NO and, in particular, the high level of iNOS in a subgroup of hepatocellular carcinoma and correlation with poor prognosis. Drs. Matsumoto and colleagues describe the prognostic significance of iNOS in nasopharyngeal cancer. They demonstrate that overexpression of iNOS is associated with p53 overexpression but not associated with prognosis. They suggest that iNOS contributes to tumorigenesis but not to tumor progression. Drs. Hiraku and Kawanishi discuss the overexpression of 8-nitroguanine. In patients with nasopharyngeal carcinoma infected with EBV, the prognostic significance of 8-nitroguanine is reported. They also found that in patients with soft tissue tumors strong 8-nitroguanine formation was associated with poor prognosis. In Part VII, the therapeutic application of NO in cancer is reviewed by six contributors. Drs. Thatcher and Anand describe the therapeutic potential and cancer prevention of nitric oxide-releasing molecules. They review the activities of various classes of NO donors, and in particular, the new generations of NORMs, nitric oxide redox molecules. Drs. Hirst and Robson discuss the anti-tumor properties of NO donors in both experimental and clinical trials in patients. They also describe the physiological effects as single agents or in combination with other agents. They summarize in a table format all the reported studies undertaken to-date by nitric oxide against

tumor cells, both in vitro and in vivo. Drs. Bonavida and associates describe the role of various NO donors and their mechanisms of action on the reversal of tumor cell resistance to various cytotoxics. They discuss the beneficial effects of NO donors as sensitizing agents and that they can be considered as universal sensitizing agents when compared to specific targeted agents. NO donors perturb many survival anti-apoptotic pathways in the tumor cells and act upstream to various pathways in contrast to various specific inhibitors which act downstream. Drs. Nicoletti and colleagues describe an NO donor compound, GTT-27NO, as a tumor-specific cytotoxic drug and its ability to reverse resistance of tumor cells. They also discuss the induction by GTT-27NO of ROS, RNS, and nitration of tyrosine residues. They suggest the potential application of this drug in the clinic. Drs. Yasuda and colleagues describe the therapeutic application of NO in in vitro models and in humans. They describe the current clinical trials of the use of nitroglycerin in combination with cytotoxic drugs in patients with non-small cell lung carcinoma. Both randomized and non-randomized studies are described. Dr. Rustum describes his opinion of the preceding chapters in Part VII and also describes his own studies with the compound SE-methyl selenium and its ability to inhibit HIF-1 α .



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