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Therapeutic application of nitric oxide in cancer & inflammatory disorders, 1st edition, L. Morbidelli, B. Bonavida, editors (Academic Press, Elsevier, UK) 2019. 372 pages. Price: Not mentioned.

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The present book discusses the therapeutic applications of nitric oxide (NO) in three parts; the first in cancers, the second in inflammatory diseases and the third part involves the collection of abstracts from the conference held in Siena, Italy, on October 4-5, 2018. This book is designed to share knowledge from the highly reputed eminent researchers and clinicians in the field of NO and related bioactive nitrogen oxides, as signalling molecules in physiological and pathophysiological states.

In the first chapter, the role of NO donor nanoparticles to be used for cancer chemotherapy is discussed as it would release NO at target site, contributing to the reversal of multidrug resistance (MDR) in cancer cells, in comparison with lower doses, which given independently does not have the potential to trigger apoptosis. This nanoparticle which has the ability to induce leakiness in the blood vessels, when combined with traditional cancer chemotherapeutic

agents, has been discussed to provide effective treatment outcomes.

Baritaki has explored the anti-neoplastic roles of NO and NO donors in the contexts of tumour initiation, growth and metastasis as well as its role in tumour microenvironment and MDR. It has been discussed that the total NO levels at tumour bed, which is an additive of the contributions by the tumour milieu, along with the total cellular redox potential, in turn determine the action of NO against the tumours. Various NO donors, NO donor conjugates, NO-releasing nanoparticles and NO synthases (NOS) gene targeting for their key anti-tumour therapeutic values have also been discussed.

While an overview of the anti-tumorigenic effects of NO donors and their pathways has been discussed in the earlier chapters, a novel metal nonoate NO donor, Ni(SalPipNONO) and its anti-tumorigenic effects in human lung carcinoma have been discussed in the third chapter. It was shown to effect *via* the NO/cGMP pathway and reactive oxygen species induction, subsequently triggering the p53 upregulation, reduction of hypoxia-inducible factor 1 alpha and vascular endothelial growth factor, thereby exhibiting an anti-angiogenic effect directly on endothelial cells and indirectly on the tumour cells. This molecule has the potential to be used as anticancer drug either alone or in combination.

In the fourth chapter, the roles of NO, both endogenous and exogenously supplied, has been elaborated in angiogenesis either through direct effect on endothelial cells or as the mediator of angiogenic activity in tumour as well as stromal cells. NOS inhibition has been described as effector of anti-angiogenic and anti-tumour drugs. Further, the roles of NO in tumour angiogenesis and the innovations in the therapeutic applications involving strategies for controlled NO availability have been discussed.

The fifth chapter discusses about NO and cancer with respect to inducible NOS (iNOS) levels in the tumours and the microenvironment. Cellular NO synthesis pathways, along with the controversial role of NO and its concentration-based effects with regard to cancers, have been described. NO in cancer has been well explained in terms of iNOS induction and inhibition strategies with a clear analysis of human cancer incidence on exposure to NO. Finally, it has been concluded that iNOS induction would repolarize the tumour-associated macrophages from tumour-promoting M2 phenotype to a tumoricidal M1-like population which calls for further research.

In the next chapter, the arginine (ARG) metabolism-associated NO production in melanoma tumour microenvironment by affecting the potential effector T-lymphocytes has been elaborated, thus suppressing the local immune response. The activity of iNOS and ARG enzymes metabolizes the crucial immunosuppressive mediators which regulate T-cell infiltration, subsequent tumour growth *via* potential anti-tumour immune response than a wholesome immune suppression.

In the next chapter, the authors broadly discuss on the various multifaceted effects of NO in different cells and at varying concentrations, along with the structure, activity and mode of action in detail of three potential NO donors, namely NBS1120 that releases NO and H_2S, JS-K an arylating NO donor and RRx-001 an immune stimulatory agent as potential therapeutics. While RRx-001 has reached at clinical trials phase III, the others are at initial phases. This chapter also mentions their prospective effects on diseased conditions other than cancers, which include neurodegenerative disorders, haemorrhagic shock, sickle cell disease and malaria, which can open the doors towards therapeutic application of these NO donors beyond cancers. In the next chapter the role NO-scavenging therapies has been elaborated for colorectal cancer. Endothelial NOS is the most relevant source of NO which can enhance the cancer stem cell (CSC) phenotype in colorectal tumours. The authors have provided experimental proof for the NO scavenger named c-PITO showing efficacy of immunotherapy to impair this CSC phenotype by altering the stem-related signalling pathways. S-nitrosylation is an important process in protein modifications triggering many of the pathological disturbances including cancers. This chapter focuses on denitrosylases being used as an effective therapeutic target to act against these S-nitrosylations of proteins based on two main systems, *i.e*. S-nitrosoglutathione reductase (GSNOR) and thioredoxin. Thioredoxin inhibition and targeting of GSNOR dysfunctions have been described as effective therapeutic targets for cancer.

The last chapter in the first part of the book describes NO-releasing nanomaterials being used as anticancer therapeutic agents. In this chapter, the authors have explained the various therapeutic NO donors such as the NONOate, S-nitrosothiols,

organic nitrates, metal-nitrosyl complexes, photo-triggered organic NO donors and their roles in cancer therapy. The authors discuss the roles of NO in inducing cellular cytotoxicity, chemosensitization and radiosensitization. Various nanoplatforms made by combining these NO donors and nanomaterials and their actions are also explained, which enhances the NO concentrations at the target site by site-directed delivery.

The second part of the book has four chapters. The first chapter describes the role of NO on vascular dysfunction-related properties, especially during ageing and Alzheimer's disease (AD). The pathophysiological mechanisms of AD include amyloid plaques and neurofibrillary tangles. The authors discuss how NO depletion results in the reduction of extracranial blood flow and impairment of circulation leading to AD. This chapter also discusses on novel therapeutic approaches to consider NO homeostasis for the AD treatment. The next chapter describes on carbonic anhydrase (CA) enzymes which are widely overexpressed in many diseases and their inhibitors which are used in therapy. The chapter discusses on the potential role of CA inhibitor sulphonamide coupled with NO donor moieties as therapeutic agents, where these hybrids are studied to be effective against glaucoma as well as many other diseases such as neuropathic pain, arthritis and cerebral ischemia.

The role of NO, contributing to reactive oxygen intermediates, leading to sepsis-mediated vascular dysfunction, immune modulation and resultant organ dysfunction has been described in the chapter which has elaborated on features of inflammation, sepsis, types of immunity, immune suppression, sepsis-induced metabolic defects as well as NO and its role in oxidative stress. Since iNOS (NOS2) isoform is overexpressed in sepsis, its inhibitors have been discussed as a therapeutic strategy keeping in mind the regulatory parameters of NO within the host system.

The final chapter in this part elaborate on nanoporous materials as key NO donors which can be exploited for therapeutic purposes. Since NO has short half-life and NO donors being unstable and soluble in physiological medium, their targeted delivery was not possible for effective therapy at target site. This has been overcome now using nanoporous materials which act as NO donors. Various NO-releasing platforms and NO donor porous materials along with their mode of action and mechanisms are extensively described in this chapter.

As a third part of this book, 16 abstracts of presentations at the Conference in Siena are included which span basic molecular studies *in vitro* and *in vivo* studies as well as population-based studies on NO signalling, leading to pathogenesis as well as NO-based therapeutic strategies.

Overall, this book is a good start for a novice in the field of NO and associated biological effects but lacks depth to cater to the scientific community working in the specific sub-domains of NO biology. Many chapters give more of an introductory view but do not give deeper mechanistic basis on the pathophysiological changes elicited by NO.

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