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Arunabha Ray
Kavita Gulati *Editors*

Nitric Oxide: From Research to Therapeutics

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Chapter 3
Nitric Oxide and Cardiovascular Diseases: Cardioprotection, Complications and Therapeutics

Gaurav Kumar, Sanjay Kumar Dey, and Suman Kundu

Abstract Perpetually increasing cardiovascular complications significantly contribute to economic slow-down in developing nations. Indeed, adverse cardiovascular events are among the world's greatest mortality factors. The underlying cause behind these events is hypertension, which in advance stages, manifests with the development of multifactorial outcomes ultimately leading to organ damage and subsequent death of the individual. One of the major reasons behind the onset of hypertension is endothelial dysfunction, a physiological and clinical situation where normal functions of vascular endothelium are altered. This alteration results in a lack of proper production as well as the distribution of nitric oxide, which is a potent vasorelaxant. Efforts to maintain adequate NO signaling are always in practice. One of such approaches is targeting cytochrome b5 reductase3 at the myoendothelial junction, an anatomical location between endothelial cells and vascular smooth muscle cells. This chapter highlights the production and distribution of NO by nitric oxide synthases and cytochrome b5 reductase3, respectively, its contribution in various cascades of vascular homeostasis and its established role in cardiovascular disorders followed by different strategies and a glimpse of the clinical studies considered to improve NO signaling in vivo.

Keywords Nitric oxide · Endothelium · Hypertension · Cardiovascular homeostasis · Cytochrome b5 reductase3 · Nitric oxide synthase

Gaurav Kumar and Sanjay Kumar Dey have contributed equally.

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Circadian System

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CHAPTER ELEVEN

The interplay between circadian clock and viral infections: A molecular perspective

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Contents

Abstract

The circadian clock influences almost every aspect of mammalian behavioral, physiological and metabolic processes. Being a hierarchical network, the circadian clock is driven by the central clock in the brain and is composed of several peripheral tissue-specific clocks. It orchestrates and synchronizes the daily oscillations of biological processes to the environment. Several pathological events are influenced by time and seasonal variations and as such implicate the clock in pathogenesis mechanisms. In context with viral infections, circadian rhythmicity is closely associated with host susceptibility, disease severity, and pharmacokinetics and efficacies of antivirals and vaccines. Leveraging the circadian molecular mechanism insights has increased our understanding of clock infection biology and proposes new avenues for viral diagnostics and therapeutics. In this chapter, we address the molecular interplay between

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Application of functional proteomics in understanding RNA virus-mediated infection

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Contents

Abstract

Together with the expansion of genome sequencing research, the number of protein sequences whose function is yet unknown is increasing dramatically. The primary goals of functional proteomics, a developing area of study in the realm of proteomic science, are the elucidation of the biological function of unidentified proteins and the molecular description of cellular systems at the molecular level. RNA viruses have emerged as the cause of several human infectious diseases with large morbidity and fatality rates. The introduction of high-throughput sequencing tools and genetic-based screening approaches over the last few decades has enabled researchers to find previously unknown and perplexing elements of RNA virus replication and

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Cyanobacteria - Recent Advances in Taxonomy and Applications

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Chapter

Novel Hemoglobin from *Synechocystis* sp. PCC 6803: Shedding Light on the Structure-Function Relationship and Its Biotechnological Applications

Mohd. Asim Khan, Sheetal Uppal and Suman Kundu

Abstract

Cyanobacteria are oxygenic photosynthetic prokaryotes, practically present in every plausible environment on the earth. In 1996, the first cyanobacterial genome was sequenced from *Synechocystis* sp. PCC 6803 and the cyanobacterial genome database has been continuously growing with genomes from more than 300 cyanobacterial and other related species, so far. *Synechocystis* sp. PCC 6803 is one of the best-characterized cyanobacteria and has developed into a model cyanobacterium that scientists are using throughout the world. At the same time, the field of hemoglobin was undergoing a breakthrough with the identification of new globins in all three kingdoms of life including cyanobacteria. Since then, the newly identified globins in the cyanobacteria are raising intriguing questions about their structure and physiological functions, which are quite different from vertebrate's hemoglobin and myoglobin. These hemoglobins have displayed unprecedented stability, unique heme coordination, novel conformational changes, and other properties that are not often observed in the globin superfamily. This chapter provides an overview of the unique globin from *Synechocystis sp.* PCC 6803, its interacting protein partners, proposed functions, and its biotechnological implications including potential in the field of artificial oxygen carriers.

Keywords: Cyanobacteria, *Synechocystis* sp. PCC 6803 hemoglobin, Structural features, Heme stability, Physiological function, Biotechnological application

1. Introduction

The ancient cyanobacteria played a fundamental role in changing the composition of the early, oxygen-poor reducing atmosphere into an oxidizing atmosphere of the earth. These tiny oxygenic phototrophs inhabit varied ecosystems and habitats ranging from oceans to hot springs and deserts [1]. They can also be found in extreme environments, such as acidic bogs and volcanoes. The plethora of available

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Frontiers in Protein Structure, Function, and Dynamics

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17 An Insight into the Importance of Ferritins in the Physiology of *Mycobacterium tuberculosis*: Unique Structural and Functional Properties

Garima Khare, Prachi Nangpal, and Anil Kumar Tyagi

Abstract

Iron is an essential element required by most of the living organisms and acts as a cofactor for many enzymes involved in various essential cellular processes such as respiration and DNA replication. As much as it is crucial for performing major cellular functions, its excess can be detrimental to the cell by its participation in Fenton reaction, which results in the production of harmful hydroxyl radicals. Hence, iron homeostasis is a vital part of cellular physiology, which is tightly regulated by various genes involved in iron acquisition and storage. Ferritins belong to the major superfamily of iron storage proteins having a spherical macromolecular structure with a cage-like cavity and play a pivotal role in the maintenance of iron homeostasis. These proteins play a dual role by acting as a source of iron under conditions of iron scarcity as well as serving as iron quenchers under excess iron conditions. The family of ferritin proteins comprises of three subtypes, namely ferritin (Ftn) present across both eukaryotes and prokaryotes, heme-bound bacterioferritin (Bfr), and DNA-binding protein from starved cells (Dps) found only in prokaryotes. *Mycobacterium tuberculosis*, one of the most deadly pathogens, is responsible for killing millions of humans, possesses both kinds of iron-storing proteins-ferritin (BfrB) as well as bacterioferritin (BfrA), both of which are required for the pathogenesis of this deadly bacteria. Besides, the presence of both kinds of ferritin-like molecules in the pathogen is linked to distinct functions they perform in *M. tuberculosis* physiology. Moreover, structural properties of BfrB, including certain key residues at its threefold and fourfold channels, are considered as interface hot-spot residues required for BfrB oligomerization and assembly formation. Additionally, unlike other ferritins, BfrB of *M. tuberculosis* possesses an extended C-terminus region, which is implicated in playing a role in providing thermal stability to the protein.

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Dopamine Beta Hydroxylase: An Enzyme with Therapeutic Potential to Combat Neural and Cardiovascular Diseases

14

Swati Kundu, Manisha Saini, Sanjay Kumar Dey, and Suman Kundu

Abstract

The brain and the heart are arguably the two most important organs of the human body. It is thus no surprise that diseases of the brain and heart are of the highest concern and are the major causes of mortality and morbidity worldwide. A physiological process that is common to both of these major organs is the catecholamine biosynthetic pathway, where the products of the pathway regulate several major events in the human body. The changes in the levels of catecholamines are originators of several neural and cardiovascular diseases. Dopamine beta hydroxylase (DBH), an enzyme that plays a central and critical role in the catecholamine biosynthetic pathway, regulates the concentrations of dopamine and norepinephrine, whose deficiency or overproduction causes several diseases related to the brain and the heart. This enzyme is thus of great therapeutic significance. Insight into the genetics, structure, function, and dynamics of the protein will provide scope for discovery and design of potential small molecule drugs to treat neurological or cardiovascular disorders utilizing structure-based, rational drug discovery approaches.

Keywords

Dopamine beta hydroxylase · Catecholamine · Dopamine · Norepinephrine · Hypertension · Depression · Cocaine addiction

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Mycobacterium tuberculosis: Molecular Infection Biology, Pathogenesis, Diagnostics and New Interventions

Springer

Challenges and Advances in TB Drug Discovery

25

Garima Khare, Prachi Nangpal, and Anil K. Tyagi

Abstract

In this chapter, we provide a comprehensive review of the recent developments and challenges associated with tuberculosis drug discovery. The chapter begins with an overview of the global TB burden with an emphasis on the high-burden countries such as India and the probable reasons associated with high disease burden. We have discussed the targets for the WHO End TB Strategy along with the requirements to achieve them. The chapter further provides an insight into the major obstacles of TB control, the problems associated with the current chemotherapy, the need for new anti-TB drugs and expectations from an ideal TB therapy. The chapter also provides a comprehensive review of the candidate drugs in the TB drug clinical pipeline with description of their identification, mechanistic action and in vitro and in vivo efficacy data along with clinical trial progress. We then provide details about the commonly employed approaches like whole cell phenotypic approach, target-based virtual screening and repurposing of drugs for TB drug discovery along with the advantages and major challenges associated with these approaches. In this regard, the success of whole cell-based phenotypic screening has been highlighted in view of discovery of the two recently FDA-approved anti-TB drugs, namely, bedaquiline and delamanid. The chapter also deals with another promising strategy for TB drug discovery based on rational drug design with a focus on some of the leads identified by this

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Bioactive Natural Products for the Management of Cancer: from Bench to Bedside

Springer

Drug Resistance in Cancer and Role of Nanomedicine-Based Natural Products

9

Deeptashree Nandi, Aakriti Singal, and Alo Nag

Abstract

Cancer is an age-old malady that has claimed millions of lives across the globe and the death toll is ever increasing. Despite intensive research for over a decade, contemporary anticancer treatment regimens still suffer from certain shortcomings, with drug resistance posing as a major hurdle. In this aspect, natural anticancer products have attracted attention as suitable chemopreventive agents over other synthetic compounds. However, the potential application of such natural compounds has been restricted due to their low bioavailability, poor efficacy amongst other limitations. An exciting advancement in the field of medicine has been the advent of nanoparticles that have reformed the usage of natural products as innovative anticancer therapeutics. This chapter elaborates the role of nanoparticle based natural products as potent and efficacious therapeutic agents for treatment and management of cancer.

Keywords

Nanomedicine · Nanoparticle · Nanoscience · Cancer · Natural products · Drug resistance · Anti-cancer · Therapy

9.1 Introduction

In the combat against a deadly menace popularly known as cancer, natural products have had a massive contribution, especially over the past few decades. Natural anticancer products have procured preference as particularly suitable candidates for chemoprevention over other synthetic compounds, largely because the associated adverse side effects are reported to be minimal. However, such natural anticancer

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