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New Insights into a Classical Pathway: Key Roles of the Mevalonate Cascade in Different Diseases (Part II)

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The mevalonate (MVA) cascade is also known as the cholesterol biosynthesis pathway. This critical cellular pathway is not only responsible for the biosynthesis of cholesterol but is also the source of several essential intermediate metabolites such as geranylgeranylpyrophosphate (GGPP) and farnesylpyrophosphate (FPP) which are vital for normal cell metabolism and function [1]. As with cholesterol, the isoprenoids GGPP and FPP also play a fundamental role in human disease.

The statin drugs (a.k.a. ‘statins’) are competitive inhibitors of hydroxyl-methyl-glutaryl coenzyme-A (HMG-CoA) reductase (HMGCR), which converts HMG-CoA into mevalonic acid (or mevalonate). HMGCR is also the rate-limiting step in cholesterol biosynthesis. In eukaryotes, the MVA pathway is the only biochemical mechanism capable of generating the isoprenoids, FPP and GGPP, as well as cholesterol. The chemical structure of statins has an HMG-like moiety that binds to a portion of the HMG-CoA binding site, thus blocking access of the HMG-CoA substrate to the enzymatic active site. This inhibition in turn effectively and directly reduces the rate of MVA production [2].

The statins were first discovered in 1976 when a fungal metabolite isolated from Penicillium citrinium was observed to inhibit HMGCR [3]. Soon after, several different statins were discovered and isolated, and further classified for broader use in the clinical arena. The statins are typically divided into several different classes based on whether they are naturally produced by fungi (type 1; *e.g.* lovastatin, pravastatin, and simvastatin) or synthetically produced (type 2; *e.g.* atorvastatin, fluvastatin, pi-tavastatin, and rosuvastatin). The

conserved HMG-like moiety seen on all statins, is covalently bound to an extended hydrophobic group which stabilizes statin binding to HMGCR.

While statins are widely known to reduce cholesterol biosynthesis, they also decrease critical MVA cascade intermediates such as FPP, GGPP, and downstream squalene, dolichols, and coenzyme Q10 [4, 5]. Currently, MVA cascade inhibitors such as the statins are considered amongst the safest drugs, and are widely used for the treatment of cardiovascular diseases where they have long-standing established clinical benefits.

We have been investigating the various roles of the MVA cascade in models of respiratory, cardiovascular, and cancer diseases and have contributed to the understanding of how MVA metabolism and the statins participate in the development and treatment of disease [1, 6–12]. Furthermore, there is increasing interest in the diverse applications of MVA cascade inhibitors, and a desire to better understand the role of MVA metabolism in common chronic human diseases.

Hence, in collaboration with “Current Molecular Pharmacology” we have prepared a two-part volume of selected papers that cover various aspects of the MVA cascade as it relates to several prevalent conditions. As Editors, we feel privileged to have world-class clinicians and scientists share their expertise through this unique volume. While not comprehensive of all the diseases that MVA metabolism is known to affect, this volume specifically covers the latest knowledge of how the MVA pathway modulates pathogenic mechanisms relevant to respiratory science, developmental biology, cancer, and neuroscience.

In Part 2 of 2 of this volume, we turn our attention to the role of the MVA pathway in human cancers, neuroscience, and developmental biology in health in disease. In the first article of this Part 2, Bathaie *et al*. review the *in vitro* and *in vivo* application of MVA cascade inhibitors in various cancers including breast, prostate, pancreas, lung, esophagus, hepatic, and hema-tologic malignancies. The authors discuss regulation of the MVA cascade focusing on hypoxia inducing factor-1, p53, and negative feedback regulation of the pathway by sterol-regulatory element binding protein, protein kinase B and Akt, and AMP activated protein kinase (AMPK). Since the regulation of MVA metabolism in cancer remains a hotly debated issue within the scientific community, this article provides some insights into how certain MVA cascade inhibitors, such as the statins, are being utilized in different cancers. This review also delves into dysregulation of MVA regulatory mechanisms in different cancers.

Cholesterol is the chemical backbone required for the biosynthesis of sex hormones and plays essential roles in the regulation of sex hormone production [13, 14]. It is well-known that hormone-dependent breast and prostate cancers are strongly affected by sex hormone levels. Mokarram *et al*. present a comprehensive review on the role of MVA in the development and progression of breast and prostate cancers. The authors first provide an overview of the state of knowledge regarding sex hormone biosynthesis in males and females. Then, they explain how estrogens and progesterone are involved in sex hormone-dependent cancers. They also provide the latest in-depth information on MVA pathway dysregulation in breast and prostate cancers. They carefully review the current literature on

the application of different statins in breast and prostate cancers. Finally, they suggest possible therapeutic approaches in these cancers based on the modulation of the MVA cascade.

Jiao *et al.* provide a focused review on the importance of the MVA cascade in neurodevelopment and neurodegeneration. They discuss the key differences between brain and plasma lipoproteins. They then provide a comprehensive literature review regarding the role of cholesterol and cholesterol metabolism in neural development and neurodegenerative diseases including, Alzheimer's Disease, Huntington Disease, Parkinson's Disease, Niemann-Pick type C, and Smith-Lemli-Opitz Syndrome. To conclude, the authors discuss the importance of MVA cascade inhibitors such as the statins and small Rho GTPase inhibitors as potential novel therapeutic strategies for some of these conditions.

In a related topic, Eftekharpour *et al.* focus on spinal cord injury and the role of MVA metabolism, which is a fresh perspective on neural injury. They discuss the mechanism(s) and pathophysiology of primary and secondary cord injuries. They provide an overview on the therapeutic strategies which are being used in spinal cord injury including inhibition of small Rho GTPase protein. They also review the application of statins in spinal cord injury as compared to non-steroid anti-inflammatory drugs.

Finally, we include a paper relevant to placental development, pregnancy, and pre-eclampsia. The placenta is also involved in sex hormone production [15, 16] and plays an important role in embryonic development. Ermini *et al.* provide an inclusive review on the role of the MVA cascade in placental development and discuss how this pathway can affect pre-eclampsia in pregnancy. They also address how MVA cascade inhibitors could be used in pregnancy and how they may prevent the serious complication of pre-eclampsia. This review is important because it focuses on a novel and underappreciated intersection between development and MVA biology. This review also covers the most updated information regarding MVA cascade inhibitors and related intermediates in pre-eclampsia, relevant for both basic scientists and clinicians.

Collectively, this volume of ten articles addresses the basic science that underlies the clinical importance of the MVA cascade and how targeting this important pathway may offer novel therapies for various conditions. The underlying premise is that many of these chronic diseases partially share a common endotype in the form of MVA metabolism that underlies many of the pathologies observed in different diseases. Additionally, this volume further provides an updated platform where both basic and clinical scientists can access the latest developments in cholesterol/isoprenoid metabolism, and apply this knowledge in the service of drug development and the treatment of patients.

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