Chemistry and Biology of Bioactive Lipids—A Tribute to Prof. Viswanathan Natarajan for his 50 Years of Research in Lipid Biochemistry

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This special issue of *Cell Biochemistry and Biophysics* focuses on the “Chemistry and Biology of Bioactive Lipids” to honor Prof. Viswanathan Natarajan of the University of Illinois at Chicago for his 50 years of invaluable contributions in biochemistry and especially lipidology. This special issue is a collection of scientific papers (historical accounts, original papers, and reviews) contributed by nearly two dozen celebrities in different areas of lipid research including bioactive lipidology in health and disease honoring Prof. Natarajan for his important discoveries and profound mentoring, and vital collaborations with scores of scientists in diverse areas of biochemistry and lipidology.

Keywords Bioactive Lipids · Membrane Lipid Biochemistry · Cell Signaling · Natarajan

Prof. Viswanathan Natarajan (popular as “Nati”) of the University of Illinois at Chicago is a versatile researcher whose work spans from the chemistry, biochemistry, and molecular biology of the lipid metabolizing and signaling enzymes and synthesis, formation, and analysis of lipids to their interrelationships with other metabolic cascades including the reactive oxygen species and oxidative stress, pharmacology of drugs, and actions of toxic agents. Natarajan, in his 50 years of journey as an academician, researcher, and mentor has developed a solid field of chemistry and biology of bioactive lipids and built a sound collaborative alliance with dozens of biochemists, cell biologists, and clinician scientists toward fostering a vibrant field of research in the area of bioactive lipids in health and disease. This special issue comprises a broad spectrum of scientific articles (historical essays and original research as well as reviews) contributed by two dozen established and

highly reputed biochemists, molecular biologists, pharmacologists, and physician scientists worldwide honoring Prof. Viswanathan Natarajan for his indefatigable research and profound discoveries in the field of lipidology, especially chemistry and biology of bioactive lipids.

Prof. Harald Schmid vividly presents his association with Prof. Natarajan at the Hormel Institute and their pursuits and successes in discovering a New Metabolic Pathway, summarizing their early research in the 1980s. Prof. Schmid describes one of their exciting and important discoveries of a novel sequence of biochemical reactions in the heart and cells known as the transacylation—phosphodiesterase pathway of phospholipid metabolism, which leads to the formation of the metabolite, *N*-arachidonoyl ethanolamine, which was later established to bind and activate the cannabinoid receptors. This has now emerged as a rapidly advancing area of endocannabinoid research. Prof. David Brindley recognizes the lifetime contribution of Prof. Natarajan toward the advancement of lipid metabolism and lipid signaling, especially in the areas of understanding the mechanism(s) of action(s) of bioactive lipids including phosphatidic acid (PA), lysophosphatidic acid (LPA), sphingosine-1-phosphate (S1P) and cardiolipin in lung functions and disease. Prof. Viswanathan Natarajan’s presented an overview of his journey in academia as a mentor, teacher, and lipid scientist for ~50 years beginning as a graduate student including his early research on the biosynthesis and catabolism of phospholipids in the developing brain; his studies of the last five decades on the role of

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sphingolipids and sphingolipid-metabolizing enzymes in pulmonary endothelial cells, epithelial cells, and fibroblasts under normal conditions and in lung diseases. Prof. Natarajan believes that research in the field of bioactive lipids combined with OMICS technology can lead to the understanding of the modulation of cell function under normal and disease states by different lipid mediators.

While narrating a personal story and offering debt of gratitude to Prof. Viswanathan Natarajan, Prof. Steve Georas describes the roles of the bioactive lipid, lysophosphatidic acid (LPA), and its extracellular enzymatic generator, autotaxin (ATX) in diverse cell signaling cascades and envisions that ATX and LPA antagonists could be used to treat lung fibrosis, cancer, and lung inflammatory conditions such as asthma.

In their review on “Lipid-Derived Mediators are Pivotal to Leukocyte and Lung Cell Responses in Sepsis and ARDS”, Dr. Julie Nijmeh and Prof. Bruce Levy, celebrate Prof. Natarajan’s contributions to their understanding of lipid-derived mediators and metabolism in lung cell responses to inflammation, infections, and mechanical stresses and further add that Prof. Natarajan’s fundamental discoveries in cell biochemistry and biophysics lead to the discovery of the underlying mechanism(s) of debilitating human diseases. In addition, Dr. Julie Nijmeh and Prof. Bruce Levy present a review on the cellular and biochemical mechanisms, especially focusing on the pro-resolving mediators in health and in sepsis and ARDS.

Prof. Susan Pyne and Prof. Nygel Pyne and their team have presented their original research on “Dihydroceramide desaturase (Dggs1) functions as an inducer and rectifier of apoptosis: Effect of retinol derivatives, antioxidants and phenolic compounds”. From their findings, the authors conclude that the *de novo* synthesis of ceramide or the ubiquitin-proteasomal degradation of Dggs1 in response to antioxidants, retinol derivatives, and phenols apparently involve sensors.

Dr. Jing Zhao, Dr. Thomas Stephens, and Prof. Yutong Zhao present a review on the “Molecular regulation of lysophosphatidic acid (LPA) receptor 1 (LPA1 which belongs to the G protein-coupled receptor family) maturation and desensitization”. In their review, the authors discuss the LPA1 glycosylation, maturation, and trafficking from the endoplasmic reticulum (ER)/Golgi to the plasma membrane and further add to the molecular regulation of LPA1 internalization and stability. Also, Prof. Yutong Zhao and team present their original research on “USP13 deficiency aggravates cigarette-smoke-induced alveolar space enlargement in mice” and show that USP13 deficiency plays a role in alveolar space enlargement. In a review entitled “Lysophosphatidic acid regulates Rho family of GTPases in lungs”, Dr. Kevin Tran and Dr. Jing Zhao discuss the interplay between LPA and three Rho family proteins, focusing on their interplay within the lung

endothelial and epithelial cells, contributing to the proinflammatory states.

In a review on “Current knowledge on the biology of lysophosphatidylserine (LysoPS) as an emerging bioactive lipid”, Prof. Junken Aoki and team discuss the modulation of LysoPS signaling as a promising method for therapies to treat immunological diseases. In this review, the authors give an overview of the biology of LysoPS-generating enzymes, LysoPS receptors, LysoPS signal modulators, and future therapeutic strategies in this field.

Prof. Jeffery Jacobson presents that sphingolipids can be novel therapeutic targets in the radiation-induced lung injury (RILI) and further emphasizes that targeting the endothelial cell (EC) sphingosine signaling augmenting the EC function could attenuate EC permeability and inflammation, which could be a novel and promising therapeutic strategy for the prevention or treatment of RILI.

Prof. Roberto Machado and team present their original research on “Sphingosine kinase 1 regulating the pulmonary vascular immune response”. From their study, the authors conclude that their results suggest a role of sphingosine kinase 1 (Sphk1) that regulates pulmonary vascular immune response in pulmonary hypertension (PAH).

Prof. Denise Hemmings and Prof. David Brindley and team present their original research on lysophosphatidate (LPA) promoting sphingosine-1-phosphate (S1P) metabolism and Signaling with implications for breast cancer and doxorubicin resistance. The authors conclude from their current and earlier studies that LPA promotes S1P metabolism and signaling enhancing the tumor growth and metastasis, and further lessening the efficacy for the chemotherapy and radiotherapy of breast cancer.

In a review entitled “Genotype/phenotype interactions and first steps toward targeted therapy for sphingosine phosphate lyase insufficiency syndrome (SPLIS)”, Prof. Julie Saba and team discuss that SPLIS is a rare metabolic disorder caused by a deficiency in sphingosine-1-phosphate lyase (SPL), the ultimate enzyme catalyzing the catabolism (degradative pathway) of the sphingolipid. The authors suggest that gene therapy appears promising in the treatment of SPLIS.

In original research on “Hyperoxia (HO)-induced S1P1 signaling reduces angiogenesis by suppression of TIE-2 leading to experimental bronchopulmonary dysplasia”, Dr. Anantha Harijith and team present results which reveal that HO induces S1P1 followed by reduced expression of angiogenic factors. The investigators further show that reduction of S1P1 signaling restores ANG-1/ TIE-2 signaling towards improvement of angiogenesis and alveolarization, leading to protection against hyperoxic lung injury in the newborn.

Prof. Viswanathan Natarajan and team present their original study on “Nuclear sphingosine-1-phosphate (S1P) lyase (S1PL)-generated Δ^2 -hexadecenal (Δ^2 -HDE) as a regulator of histone deacetylase (HDAC) activity and

chromatin remodeling in the lung epithelial cells.” The authors have concluded that their results reveal an important role for the nuclear S1PL-derived Δ^2 -HDE in the modification of HDAC activity, histone acetylation, and chromatin remodeling in the lung epithelial cells.

In a review entitled “PTEN as a therapeutic target in pulmonary hypertension (PH) secondary to left-heart failure: Effect of HO-3867 and supplemental oxygenation”, Prof. Periannan Kuppusamy and team discuss the important pathology and mechanisms in the development of PH by showing the results from their earlier reported studies and novel results on PH secondary to the left-heart failure.

Prof. Steven Dudek and team, in a review entitled “Secretory phospholipase A₂ (sPLA₂) enzymes in acute lung injury (ALI)” discuss the contributions of specific sPLA₂ isoforms as markers and mediators of ALI, emphasizing on a possible therapeutic role for targeting the isoforms of sPLA₂ in the treatment of acute respiratory distress syndrome (ARDS).

In an original study on “Thermally oxidized coconut oil (TCO) as a fat source in the high-fat diet (HFD) that induces hepatic fibrosis in diabetic rat model”, Dr. Achuthan Raghavamenon and team show that HFD incorporated with TCO as a fat source, combined with STZ injection, is an efficient dietary model to develop hepatosteatosis with hepatic fibrosis in the rat model. In another original research study, Prof. Rao Uppu and team from their study on “Atherogenic oxoaldehyde of cholesterol that induces innate immune response in monocytes and macrophages” have shown the proinflammatory action of the cholesterol oxidation product, 3 β -hydroxy-5-oxo-5,6-secocholestan-6-al (cholesterol 5,6-secoesterol, ChSeco or Atheronal-A) and further suggest the underlying pro-atherogenic mechanisms of the cholesterol oxidation product.

In a review on the “Regulation of neutrophil function by marine n-3 fatty acids”, Dr. Jodi McDaniel discusses the metabolism of marine n-3 fatty acid metabolism with an impact on the neutrophil function focusing on the actions of marine n-3 fatty acid supplementation on neutrophil function from the clinical trials conducted in the past 15 years.

Dr. E. Berdyshev and team in their review entitled “Methodological considerations for lipid and polar component analyses in human skin stratum corneum” present an

overview of current knowledge of the skin lipid and polar molecules focusing on the challenging lipid analysis with solutions and approaches that lead to the purpose of analysis of stratum corneum components in the clinical trials.

Dr. Narasimham Parinandi and team present a comprehensive review entitled “Lipid nutrition in asthma” and discuss various aspects of nutritional lipids and lipidic species such as n-3 and n-6 fatty acids, oxidized fatty acids, lipid-soluble vitamins, and natural and processed foods. The review emphasizes that there is growing interest into the link between diet and asthma symptoms, with mounting evidence for an important modulatory role for dietary lipids as lipids can act as mediators in both a proinflammatory and proresolution capacity.

Bioactive lipids are rapidly emerging as important cellular mediators of mediation of inflammation, anti-inflammation, induction and mediation of tissue injury, and protection against tissue injury in various disease states (Chiurchiù et al. [1]; Zhang et al. [2]). We congratulate Prof. Viswanathan Natarajan for his continued contribution in understanding the underlying mechanisms of actions of bioactive lipids in normal biology and pathological states of vascular and lung tissue and discoveries he and his team have made on the biochemistry, biology, and molecular biology of the bioactive lipids for ~50 years. We also thank Prof. Natarajan’s mentees, collaborators, and colleagues who have contributed invaluable papers (original research and reviews) on biochemistry, molecular biology, pathobiology, and pharmacology of bioactive lipids honoring Prof. Viswanathan Natarajan’s research in biochemistry and lipidology making this issue of *Cell Biochemistry and Biophysics* a Special Edition.

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