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Introduction to the special issue on sphingolipid signaling in chronic disease

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Sphingolipids are important components of all eukaryotic cell membranes. In the past decades, we have begun to appreciate that they also generate metabolites with important biological functions to regulate specific downstream effectors and targets. Recent studies on bioactive sphingolipids have shown the complexity of the sphingolipidome and also greatly advanced understanding of their biological functions and roles in diseases. Research on bioactive sphingolipids has accelerated in recent years by the discovery of beneficial drugs that target their signaling and are now in use to treat diseases. This Special Issue on Sphingolipid Signaling in Chronic Disease covers areas of bioactive sphingolipid metabolism and particularly their roles in human physiology and diseases.

This first article in this issue, from **Drs. Davis, Kannan, and Wattenberg** (Virginia Commonwealth University) covers the basic biochemical mechanism that controls the initiating step in the synthesis of all of the sphingolipids, the condensation of serine and palmitoyl CoA by the enzyme serine palmitoyltransferase (SPT). It focusses on the newly discovered regulator of SPT, the Orms (in yeast) and ORMDLs (in higher eukaryotes). They discuss how this regulation occurs, how it can go awry in disease and what we need to know in the future to harness this regulation to treat diseases where control of sphingolipid biosynthesis will be a new avenue for therapy. This is followed by a discussion of sphingolipids in asthma by **Dr. Sturgill** (University of Kentucky). She discusses the complex roles that sphingolipid signaling molecules, including ceramides and sphingosine-1-phosphate impact this complex disease. This impact may be on the immunologic components of asthma, the airway epithelium, and the smooth muscle. She outlines the fascinating progress of our understanding of the role of these signaling lipids and the opportunities they present for novel therapeutic approaches. **Dr. Spassieva** (University of Kentucky) presents a comprehensive review of how dysregulation of sphingolipids, in particular the sphingoid bases, is the root of a number of neurodegenerative diseases. The range of diseases is broad, but Dr. Spassieva's review emphasizes that neuronal tissues are particularly sensitive to the over and underproduction of specific sphingolipids and the derangement of their metabolism. This theme is emphasized in the article by **Drs. Wang**

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and Bieberich (University of Kentucky) who explore the dual, and often opposing, roles of sphingosine-1-phosphate and ceramide in the generation of neurodegeneration. They explore the mechanisms through which these signaling lipids operate and how those mechanisms are often fundamental cellular processes which, when over-stimulated, can lead to these devastating diseases. A specific neurological disease, Niemann-Pick type C, is the focus of the review by **Drs. Newton, Milstein, and Spiegel** (Virginia Commonwealth University). These authors carefully analyze the literature to explore the dogma that has grown up around experiments studying the molecular mechanism underlying this disease. The work of a number of groups, including theirs, has begun to build a detailed picture of how basic cell biological processes are vulnerable to changes in sphingolipid metabolism. However neuronal tissues are not the only site where pathology occurs due to alterations in sphingolipid levels and signaling. The ability of adipose tissue to perform its function to store and distribute lipids is profoundly sensitive to changes in sphingolipids, as outlined extensively by **Lambert, Anderson, and Cowart** (Virginia Commonwealth University). They document the numerous ways in which alterations in sphingolipids, both experimentally and in disease states, leads to dysfunction in adipose tissue and can have serious clinical consequences. The sensitivity of adipose tissue to sphingolipid accumulation is especially evident in alchoholic and non-alchoholic fatty liver disease, as reviewed by **Dr. Nikolova-Karakashian** (University of Kentucy). In that article Dr. Nikolova-Karakashian discusses how elevation of ceramide in particular is a key trigger in the pathology of these diseases and delves into the biochemical basis for generating that ceramide. Similarly, acute kidney injury, from a number of insults, appears to be strongly dependent on alterations in signaling sphingolipids, as outlined by **Drs. Dupre and Siskind** (University of Louisville). The changes can occur in several essential sphingolipid signaling pathways and their focus on the injury due treatment with the chemotherapeutic drug cisplatin has direct clinical consequences.

Together this collection illustrates the important roles that sphingolipids play in a variety of disease phenotypes and the important progress we have made in understanding the basic changes in the metabolic enzymes that drive pathological changes in sphingolipid levels. That understanding brings to reality novel strategies to treat these diseases by capitalizing on inhibitors that target those enzymes. These approaches are in progress and we look forward to exciting new basic and clinical discoveries that will drive the field of sphingolipid biology towards the future.