Sphingolipids, new kids on the block, promoting glomerular fibrosis in the diabetic kidney

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Siskind and colleagues have contributed greatly to our knowledge of the role of plasma membrane lipids, particularly glycosphingolipids, to the etiology of various kidney diseases. Using sophisticated methodologies for measuring kidney tissue and urinary levels of lipid biosynthetic substrates and products as well as catabolic and anabolic enzymes, they have provided evidence supporting a mechanism by which accumulated glycosphingolipids contribute to kidney disease. Most importantly, their data, collected in animal models of human diseases and cell culture systems, parallel evidence obtained from urinary and tissue biopsy samples obtained from human patients with kidney diseases of inflammatory (4), genetic, and diabetic (7) origins.

What are glycosphingolipids and what is their role in the kidney? Sphingolipids, discovered by J. L. W. Thudichum in 1883 (8) and named for the mythological Sphinx because of their enigmatic nature, are a family of lipids that play essential roles as structural plasma membrane components and as substrates for enzymes that generate second messengers involved in intracellular signaling. In mammalian cells, there are two major classes of sphingolipids, sphingomyelin and glycosphingolipids, both of which are synthesized from the hydrophobic molecule ceramide (for a review, see Ref. 3). Sphingosine is an 18-carbon amino alcohol with an unsaturated hydrocarbon chain. A sphingosine and fatty acid are categorized as a ceramide. Sphingomyelin consists of a phosphocholine head group, a sphingosine, and a fatty acid. Sphingomyelin, a ceramide-based phospholipid, is found in eukaryotic plasma membranes, especially in the plasma membrane of oligodendrocytes and Schwann cells that form the membranous myelin sheath that surrounds axons (1). Additionally, the lecithin-to-sphingomyelin ratio (L/S ratio) is a test of fetal amniotic fluid to assess the production of surfactant and fetal lung maturity. The addition of sugar moieties to the sphingolipid ceramide results in the formation of glycosphingolipids. Glycosphingolipids are a special class of cell membrane lipids and a subtype of glycolipids containing the amino alcohol sphingosine (for a review, see Ref. 6). Glycosphingolipids are organized in signaling domains on the cell surface. They are required for cellular differentiation and are of vital importance to embryonal development. There are two major categories of glycosphingolipids: glucospongolipids, in which the first sugar moiety attached to ceramide is glucose, and galactospongolipids, in which the first sugar moiety attached to ceramide is galactose. In the kidney, podocytes, mesangial cells, and tubular epithelial cells express an abundance of glycosphingolipids under normal, healthy conditions (2). The role of aberrant glycosphingolipid synthesis in renal mesangial and tubular cells in renal disease is an emerging concept.

What do glycosphingolipids do? Cellular growth and proliferation are regulated by changes in the endogenous levels of specific glycosphingolipids. Renal glomerular hypertrophy, a hallmark of early diabetic nephropathy, may involve overproduction and/or reduced degradation of glycosphingolipids. Sphingolipids are known to function in a variety of important cellular events, including embryogenesis, cellular growth, proliferation and differentiation, cell-cell and cell-matrix interactions, second messenger generation and signal transduction, ionic transport, and hormonal signaling (6). An emanating hypothesis from these studies is that augmented glycosphingolipids as a contributing role to the pathological processes of renal disease is an emerging concept.

In a recent issue of the American Journal of Physiology-Renal Physiology, Subathra et al. (7) present evidence in support of elevated glomerular glycosphingolipid-induced fibrosis in the early stages of the development of type II diabetic kidney disease. The authors propose that hyperglycemia leads to increased glucose metabolism and prominent de novo formation of fatty acylglycerides. The model presented involves abnormally high levels of glycosphingolipids produced in the glomerulus that contribute to cell hypertrophy, fibrosis, and extracellular matrix production, causing early diabetic kidney disease. Evidence for a role for glycosphingolipid accumulation in renal hypertrophy in type I diabetic kidney disease was published in 1993 by these authors (9); however, since then, there has been a lack of investigation into the role of glycosphingolipids in type II diabetic kidney disease. In this important new study (7), the authors demonstrate that humans with diabetic nephropathy exhibit higher levels of urinary glycosphingolipids compared with those of healthy control subjects, suggesting that these lipids may be novel biomarkers of early diabetic kidney disease.

The conclusions made by the authors that glycosphingolipids are elevated under high glucose conditions are based on data obtained from glomeruli of type II diabetic (db/db) mice, urine samples from human patients with type II diabetes, and mesangial cells cultured in hyperglycemic conditions (7). Renal cortical accumulation of glycosphingolipids was found in both the early and later stages of diabetic kidney disease in db/db mice. These translational experiments performed in mice correspond with findings that lactosylceramide levels are significantly elevated by 12-fold in urine of diabetic nephropathy patients compared with those of healthy individuals. Specific intracellular signaling mechanisms linking high extracellular glucose concentrations to enhanced glycosphingolipid production were determined in experiments conducted using mesangial cells cultured in hyperglycemic conditions in the presence...
and absence of inhibition of glucosylceramide synthase. The authors conclude that excessive glucose increases glycosphingolipid production by increasing the availability of the substrates ceramide and UDP-glucose under these disease conditions. The hypothesis that glycosphingolipids activate signaling through Smad3 and downregulate phosphorylated phosphatase and tensin homolog, which increases Akt phosphorylation and leads to hypertrophy and extracellular accumulation, in mesangial cells cultured in high-glucose media is supported by the present study. These data are further supported by the demonstration that pharmacological inhibition of glucosylceramide synthase reversed the mesangial cell pathology by inhibiting this fibrotic signaling pathway.

What is the evidence for a prominent role of dysregulated glycosphingolipids in kidney diseases? Excess glycosphingolipids have been documented to have a contributory function in disease initiation and the progression of metabolic syndrome, insulin resistance, and diabetes. Overexpression of glycosphingolipids in the kidney and urinary tract has been shown to contribute to the pathophysiological basis of several renal diseases, including Fabry’s disease, hemolytic uremic syndrome, and bacterial adhesion accompanying urinary tract infections (6). Activation of biosynthetic pathways for glycosphingolipid production plays a role in glomerulonephritis, acute kidney injury, kidney cancer, diabetic nephropathy, and polycystic kidney disease (2). Urinary and kidney glucosylceramide and lactosylceramide levels, but not serum levels, were significantly higher in patients with lupus nephritis, a finding that was replicated in MRL/lpr lupus mice (4). Importantly, lactosylceramide staining of renal biopsies from patients with lupus nephritis showed intense staining around the glomeruli in the mesangial region compared with biopsies from healthy control patients (4). Taken together, elevated urinary lipids seem to reflect renal-specific rather than systemic contributions to dysfunctional glycosphingolipid metabolism in disease. Because glucosylceramide and lactosylceramide are present in the urine, they represent potential noninvasive biomarkers for the diagnosis of severity of many forms of kidney disease.

The synthesis of most glycosphingolipids begins with glucosylceramide. Glucosylceramide synthase is the enzyme that reversibly converts ceramide and UDP-glucose under these disease conditions. The hypothesis that glucosylceramide synthase inhibitors may present a novel therapeutic strategy to ceramide and UDP-glucose under these disease conditions. The hypothesis that glucosylceramide synthase inhibitors may present a novel therapeutic strategy to reversing mesangial fibrosis in the type II diabetic mouse would provide the most valuable clinically relevant data to support inhibition of this system in humans with early stages of diabetic nephropathy. Pharmacological inhibitors of glucosylceramide synthase (eliglustat) are used in humans with Fabry’s and Gaucher’s diseases (5). For the reason that these inhibitors have been shown to be well tolerated for long-term use in patients, glucosylceramide synthase inhibitors may present a novel therapeutic treatment of diabetic kidney disease. Subathra et al. (7) may have provided the renal clinical and research community with a missing link—glycosphingolipids—between glomerular fibrosis and early diabetic renal disease.

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