The pathogenesis of diabetic nephropathy is initiated and maintained by four causal factors, which can be classified broadly into metabolic, hemodynamic, growth, and proinflammatory or profibrotic factors (Figure 1).As examples, 1) in patients with type 1 diabetes, concentrations of MBL associate with progression of kidney disease from macroalbuminuria to ESRD (32); 2) in a prospective cohort study of 270 patients with newly diagnosed type 1 diabetes, H-ficolin was associated with an increased risk of worsening of albuminuria (33); and 3) MAC detected by antibodies directed against the C9 component of MAC localize it to the glomerular basement membrane (GBM), tubules, and Bowman capsule in patients with type 1 diabetes (34–36).A complex series of molecules, receptors, enzymes, and transcription factors participate in the process that drives the earliest stages of kidney disease to an enlarged kidney with hypertrophy, expanded extracellular matrix (ECM), glomerulosclerosis, vascular hyalinosis, interstitial fibrosis and tubular atrophy, and loss of function culminating in end-stage renal disease (ESRD).Table Icon TABLE 1 MR Blockade and Kidney Protection in Diabetes Innate Immunity, Complement Activation, and Diabetic Nephropathy Activation of the innate immune system through pattern recognition receptors such as membrane-bound toll-like receptors (TLR) and nucleotide-binding oligomerization domain (NOD)-like receptors may play an important role in the pathogenesis of diabetic nephropathy (30).Reduction in afferent arteriolar resistance can be provoked by reduction in NO oxide bioavailability; increased cyclooxygenase-2 (COX-2) prostanoids; activation of the kallikrein-kinin system, atrial natriuretic peptide, and angiotensin 1-7; and an increase in insulin (16).AGEs can produce cell injury by receptor and non-receptor (more...) Glycation of Tissues Hyperglycemia through a nonenzymatic mechanism can lead to production of advanced glycation end products (AGEs), which by glycation of various tissue constituents such as proteins, collagen, lipids, and ECM can provoke organ dysfunction.This depletes the cellular nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) concentration and alters the redox ratio, which can reduce NO bioavailability and alter enzyme function.An inhibitor of PKC-?--ruboxistaurin--has been tested in a phase 2 randomized clinical trial in patients with type 2 diabetes and persistent albuminuria (albumin-to-creatinine ratio [ACR] 200–2,000 mg/g creatinine) despite therapy with renin-angiotensin system inhibitors (15).Damage Induced by Products of Glucose Metabolism Glucose can induce damage in cells independent of glycation such as by the activation of the polyol pathway, hexosamine pathway, or protein kinase C (PKC) pathway or through the generation of ROS.Fibrosis at a molecular level is mediated in part because of activation of TGF?1, which has two synergistic effects: activation of connective tissue growth factor (CTGF) and a reduction in matrix metalloproteinases (MMPs).Table Icon TABLE 2 Pathological Classification of Diabetic Nephropathy Class I Diabetic Nephropathy On ultrastructural evaluation of the kidney histology, among the earliest change that occurs in the kidney is thickening of the GBM; light microscopy shows minimal, non-specific, or no changes.Glycation leads to activation of receptors on cells--the best characterized of which is the receptor of advanced glycation end products (RAGE)--that trigger the synthesis and release of nuclear factor ?B (NF?B) and the generation of reactive oxygen species (ROS).Histological manifestations of AGE accumulation include basement membrane thickening, reduced protein degradation that results in an increase in mesangial matrix, and an increase in interstitial extracellular volume.In the physiological state, receptor-mediated activation of PKC releases intracellular

calcium ions and diacylglycerol (DAG) and activates these enzymes.For example, compared to wild-type mice with streptozotocin-induced diabetes, MBL knockout mice have less kidney damage, less kidney hyper-trophy, lower urine albumin excretion, and less type IV collagen expression (31).Interrelations Among Pathogenic Factors in Diabetic Nephropathy The interplay of metabolic, hemodynamic, growth, and profibrotic factors is illustrated by consideration of the following preclinical experiments (37).Although the baseline production of CTGF by mesangial cells is low, exposure of mesangial cells to increased glucose concentration (a metabolic factor) or cyclic metabolic strain (a hemodynamic factor) increases the production of CTGF (a growth factor).These experiments demonstrate the interplay of all the pathogenic factors discussed above and underscore the complex interrelations of these factors, over time and at different locations in the kidney, in producing the histological manifestations of diabetic nephropathy.Polyol Pathway The polyol pathway involves the activation of the enzyme aldose reductase within cells when intracellular concentrations of glucose rise to hyperglycemic levels (11).The rate-limiting enzyme of the hexosamine pathway is glutamine:fructose-6-phosphate-amidotransferase (GFAT), which catalyzes the reaction between fructose-6-phosphate and the amine-donor glutamine to produce glucosamine-6-phosphate (14).In two different rodent models of AKI, bilateral ischemia reperfusion (IR) pretreatment with the nonsteroidal MR antagonist finerenone prevented the development of AKI (27).According to this classification system, diabetic nephropathy progresses from thickening of the GBM, to mesangial expansion, Kimmelstiel-Wilson lesions, and global glomerulosclerosis, which is reflected in the four classes, as discussed further below.These molecules, although transcription factors, initiate and maintain kidney damage by several processes (12), including cell growth and hypertrophy, inflammation, angiogenesis, endothelial dysfunction, and ECM production.In cultured mesangial cells, high glucose levels provoke production of transforming growth factor ?1 (TGF-?1); this effect is eliminated by inhibition of GFAT.Increase in efferent arteriolar resistance can result from an increase in the concentration of angiotensin II, thromboxane A2 (TxA2), endothelin 1 (ET-1), and ROS (16).The activation of glucose transporting pathways in the proximal tubule early in the course of diabetes stimulates the reabsorption of both glucose and sodium in the proximal nephron (12).Therefore, investigators have explored the relation between vascular proliferation and endothelial permeability--factors known to be important in the pathogenesis of diabetic eye disease--with the occurrence of diabetic nephropathy.In vivo studies in obese db/db diabetic mice demonstrate that CTGF transcription was increased 28-fold after ~3.5 months of diabetes (37).