Leukocyte Recruitment and Vascular Injury in Diabetic Nephropathy

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Different types of activated leukocytes play a crucial role in the pathogenesis of most kidney diseases from acute to chronic stages; however, diabetic nephropathy was not considered an inflammatory disease in the past. This view is changing now because there is a growing body of evidence implicating inflammatory cells at every stage of diabetic nephropathy. Renal tissue macrophages, T cells, and neutrophils produce various reactive oxygen species, proinflammatory cytokines, metalloproteinases, and growth factors, which modulate the local response and increase inflammation within the diabetic kidney. Although the precise mechanisms that direct leukocyte homing into renal tissues are not fully identified, it has been reported that intercellular adhesion molecule-1 and the chemokines CCL2 and CX3CL1 probably are involved in leukocyte migration in diabetic nephropathy. This review focuses on the molecular mechanisms of leukocyte recruitment into the diabetic kidney and the involvement of immigrated immune cells in the damage to renal tissues.

Diabetic Nephropathy

Diabetic nephropathy (DN) is the leading case of end-stage renal failure (review in reference [1]). The major features of DN include albuminuria, progressive reduction of GFR, and increased risk for cardiovascular diseases (1–3). DN is associated with the expansion of mesangial cells and development of characteristic features of renal injury, such as thickening of the glomerular basement membrane. In the end, glomerulosclerosis and tubulointerstitial fibrosis are observed in patients with diabetic pathology (4,5). Approximately 30% of patients with type 1 diabetes develop DN (6,7). Barkis *et al.* (8) reported that approximately 25 to 30% of patients with type 2 diabetes will develop overt DN. Recently, several murine models of DN were developed (review in reference [9]). The well-established streptozotocin (STZ)-induced (10–14) and nonobese diabetic (NOD) (15–18) mouse models are most commonly used to study type 1 diabetes. A few models of type 2 diabetes include db/db mice (19,20), ob/ob mice (21), agouti mice on different backgrounds (22,23), and C57BL/6 on high-fat diet (24). Although some features such as the absence of renal failure complicate the interpretations of the studies in murine models, several distinct stages of DN can be detected in murine models (9). Genetically deficient mice that lack different inflammatory molecules are expected to help dissect the molecular mechanisms of initiation and development of DN.

It is well known that hyperglycemia is a major factor risk for DN (25), but hyperglycemia does not account for all changes that are observed in renal tissues (26). It has been suggested that advanced glycation end products (AGE) (27–30), activation of protein kinase C (31), and overexpression of different growth factors (32) are associated with the pathogenesis of DN. Extracellular matrix accumulation is one of the hallmarks in the development of the disease that leads to the formation of glomerular and interstitial lesions (1,26). However, recent studies suggest that inflammatory processes and immune cells might be involved in the development and progression of DN. Infiltrated macrophages are found within renal diabetic tissues, and recent studies demonstrated that macrophage-derived products can induce further inflammation in the diabetic kidney (33–36). Furthermore, activated T lymphocytes have been associated with DN (37,38). One of the most striking features of leukocytes from patients with diabetes is the activated status of blood neutrophils (39,40). There is no doubt that immune cells participate in the vascular injury in the conditions of DN, and their migration into the kidney is a crucial step in the progression of this disease.

Leukocyte Adhesion Cascade

In most organs, leukocyte recruitment is a well-organized cascade-like process that consists of three major steps: (*1*) Selectin-dependent leukocyte rolling on the endothelial layer, (*2*) chemokine-dependent integrin activation with subsequent leukocyte adhesion, and (*3*) diapedesis (41) (Figure 1). The initial capture and rolling is mediated by a family of three type-I cell-surface glycoproteins: L-, P-, and E-selectins (42). L-selectin is expressed on monocytes, granulocytes, and lymphocytes,
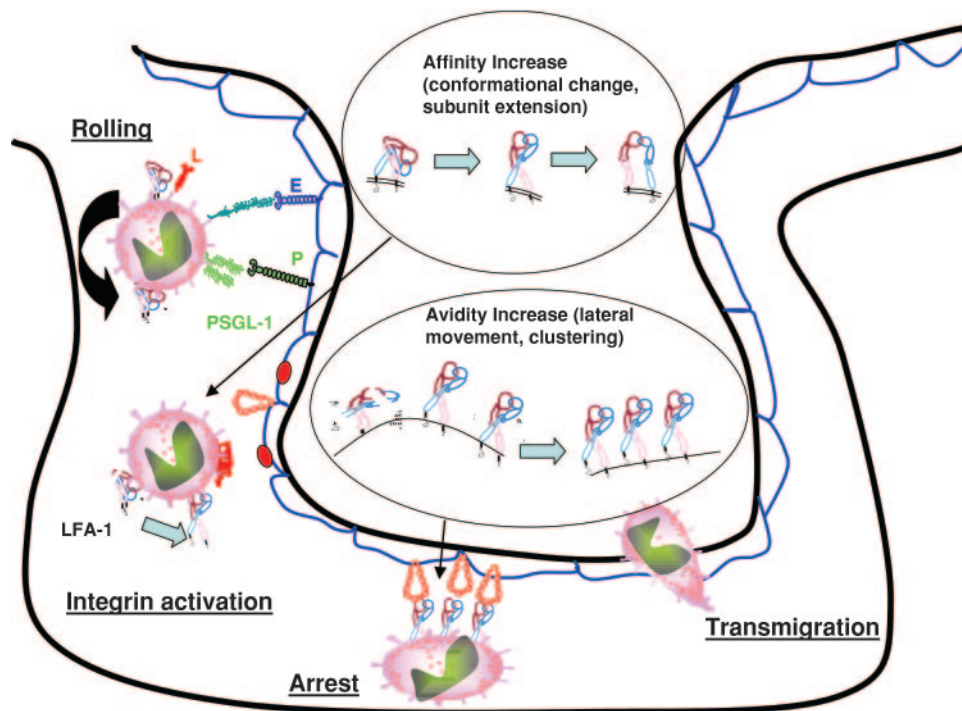
Figure 1. Leukocyte adhesion cascade in a glomerular capillary. Monocytes (and other leukocytes; data not shown) are rolling on endothelial cells (blue) *via* E-selectin (blue) and/or P-selectin (green) interacting with P-selectin glycoprotein ligand-1 (PSGL-1) and other ligands. Integrins such as LFA-1 are in the off position (bent conformation). Upon encountering an arrest chemokine (red ellipse on endothelium), signaling through chemokine receptors (red receptor on monocyte) causes conformational activation of LFA-1 and probably other integrins, associated with a more extended conformation (top insert). This enables binding to intercellular adhesion molecule-1 (orange homodimer), upon which integrins cluster by lateral movement in the leukocyte membrane (bottom insert). Stable firm adhesion precedes transmigration (adhesion molecules not shown).

where it plays a crucial role in directing T and B lymphocyte homing into peripheral lymph nodes (43). L-selectin ligands are expressed in high endothelial venules of lymph nodes and collectively are known as peripheral node addressins (44). P-selectin is detected intracellular in α-granules of platelets and in Weibel-Palade bodies of endothelial cells and is released to the plasma membrane upon activation (45). P-selectin binds fucosylated and sialylated O-glycans that are present on a single glycoprotein, P-selectin glycoprotein ligand-1 (PSGL-1). All neutrophils, monocytes, and lymphocytes express PSGL-1, but its functionality as a P-selectin ligand depends on a highly regulated set of glycosylation steps (46). E-selectin expression is not found in most vessels in normal/noninflamed conditions; however, E-selectin expression is rapidly upregulated under inflammatory conditions (47). Recently, PSGL-1 (48) and CD44 (49) were proposed to be ligands for E-selectin, and other ligands may exist. Importantly, the engagement of L-selectin (50), PSGL-1 (51), and E-selectin (52) might lead to leukocyte activation and stabilize arrest under flow. For neutrophils, the successful transition from rolling to adhesion depends on the time the rolling leukocyte interacts with the endothelium (53). Slower rolling velocity provides prolonged time of the leukocyte interaction with endothelial cells that leads to proper activation of leukocytes and successful arrest. Other important factors that will orchestrate the adhesion of rolling leukocytes are arrest chemokines (54).

Arrest chemokines are present on the endothelial surface under physiologic or pathologic conditions, and their interaction with appropriate chemokine receptors on leukocytes will lead to the activation of integrins on rolling cells. From *in vitro* studies, a broad spectrum of chemokines have been suggested to initiate activation of integrins and subsequent leukocyte arrest, but only a few chemokines were identified as arrest chemokines *in vivo*. Secondary lymphoid chemokine (SLC; CCL21) on high endothelial venules induces arrest of naïve and memory T lymphocytes (55). Keratinocyte-derived chemokine (KC; mouse Gro-α, CXCL1), monocyte chemoattractant protein-1 (MCP-1; CCL2), and regulated on activation, normal T cell exposed and secreted (RANTES; CCL5) trigger arrest of rolling monocytes (56–59). There are several reports that demonstrate Gro-α and IL-8 as functional arrest chemokines for neutrophils *in vitro* (60–62), and their receptor CXCR2 is necessary for chemokine-induced neutrophil arrest *in vivo* (63). It also has been recently reported that fractalkine (CX3CL1) induces arrest of CD16^{+} monocytes under flow conditions (64).

When rolling leukocytes receive activation signals through selectin and/or chemokine receptor engagements, integrin activation is initiated (65). Integrins are heterodimeric receptors that consist of α and β subunits that form a ligand-binding head and play a crucial role in leukocyte adhesion (66). *In vitro*, arrest of rolling granulocytes has been shown to be through α_4 integrins (67), $\alpha_L\beta_2$ (LFA-1) (68), and $\alpha_M\beta_2$-(Mac-1) (69). Two mod-

els of integrin activation have been demonstrated: (*1*) Conformational changes of integrins that lead to increased receptor affinity and (2) the formation of clusters of heterodimers with increased avidity (70). The best understanding of molecular events comes from analysis of LFA-1/ICAM-1 interactions on lymphocytes. Constantin *et al.* (71) demonstrated that chemokine triggers affinity changes and clustering through distinct signaling pathways. To elucidate the conformational changes during integrin activation, Kim *et al.* applied the method of fluorescence resonance energy transfer (66). In the resting state, α and β subunits of LFA-1 are arranged close to each other; however, upon intracellular activation of integrin adhesiveness (inside-out signaling), this complex undergoes significant spatial separation with opening of the binding site (66). In addition, chemokine-triggered lymphocyte activation induces an extended state that primes LFA-1 for ligand binding and firm adhesion (72,73).

Much has been learned regarding the last step of leukocyte recruitment into inflamed tissues, the process of transmigration (74,75). Several adhesion molecules, such as platelet cells adhesion molecule (76), junctional adhesion molecule-1 (77), and CD99 (78), are involved in the direction of leukocyte transmigration, and β_1-integrins are involved in leukocyte locomotion in tissues (79).

Immune Cell Recruitment in DN

Little is known about the migration patterns of different types of immune cells into renal tissues in DN. There are two major limitations to studying the impact of immune cells on renal vascular endothelial injury: The limited methods to characterize leukocyte trafficking during inflammation and the limited techniques (80) to estimate the impact of inflammatory mediators that are released by immune cells within the diabetic renal tissues (81). Homing of neutrophils is thought to be a hallmark of acute kidney inflammation, and recruitment of macrophages and T cells indicates chronic inflammatory processes. Although the detailed mechanisms of leukocyte migration to renal tissues are not completely understood, there is evidence that selectins, integrins, and chemokines participate in this recruitment.

Macrophage Recruitment

Macrophages are one of the central mediators of renal vascular inflammation, and their accumulation is a characteristic feature of DN (33–36). Adoptive transfer studies show that macrophages can induce proteinuria and mesangial proliferation in a model of experimental glomerulonephritis (82). Therefore, it is possible that infiltrating macrophages might induce or accelerate the mesangial cell proliferation during the development of DN. Detailed molecular mechanisms that direct macrophage migration are not fully characterized, but chemokines/chemokine receptors as well as integrins are involved in this process. Increased expression of intercellular adhesion molecule (ICAM-1) that serves as a ligand for LFA-1 was detected in models of type 1 (83) and type 2 DN (84,85). ICAM-1 expression can also be induced by factors such as hyperglycemia (31), AGE (86), oxidative stress (87), hyperlipidemia (88),

and hyperinsulinemia (89). The crucial role of ICAM-1 in a model of type 1 diabetes that was induced by a single dose of STZ was shown using ICAM-1–deficient mice (90). Diminished infiltration of macrophages, reduced expression of TGF-β and collagen IV in glomeruli, reduced urinary albumin excretion, glomerular hypertrophy, and mesangial matrix expansion were associated with reduced renal injury in diabetic ICAM-1–deficient mice (90). In a model of type 2 diabetes, Chow *et al.* (91) used ICAM-1–deficient db/db mice and showed significant reduction in albuminuria and a decrease in the number of glomerular and interstitial macrophages that was associated with reduced glomerular hypertrophy, hypercellularity, and tubular damage.

Urinary levels of MCP-1 (CCL2) are significantly increased in patients with DN and are correlated with the number of CD68-positive infiltrating macrophages in the interstitium (92). In addition, both immunohistochemical and *in situ* hybridization analyses revealed MCP-1–positive cells within the tubulointerstitial lesions of human DN (92). MCP-1 is considered to be specifically activated by the transcriptional factor NF-κB (93), especially in the presence of high glucose (94). Renal expression of MCP-1 is also induced by elevated glucose levels and possibly AGE (95). Inhibition of the renin-angiotensin system improves DN in patients with type 1 and type 2 diabetes through the suppression of renal MCP-1 (96). These results suggest that renal MCP-1 is involved in the direction of macrophage migration into diabetic kidney. Although experiments that evaluate the possible regulation of inflammatory cell influx under conditions of diabetes are not completed yet, there is a promising study indicating that administration of anti–MCP-1 antibodies prevents glomerular sclerosis and interstitial fibrosis (97).

Fractalkine (CX3CL1) is one of the few chemokines that exist in membrane and soluble forms (98), and its expression was detected in human coronary arteries with atherosclerosis and diabetes (99) and in STZ-induced diabetic kidneys along the glomerular capillary lumen and peritubular capillaries (100). Human and murine monocytes express CX3CR1, which is the receptor for fractalkine (101). Increased CX3CR1 mRNA expression was detected in an early stage of diabetic kidney, and some CX3CR1-positive cells seem to be activated macrophages (100). It has been shown that fractalkine induces arrest of CD16$^+$ monocytes under flow conditions (64); therefore, it might be possible that within renal tissues, fractalkine functions as an arrest chemokine and serves as one of the factors that induce monocyte adhesion preceding migration into diabetic kidney. The expression of CX3CR1 by T lymphocytes under different inflammatory conditions was reported recently (102,103), and further studies will be necessary to determine the role of this receptor in the T lymphocyte recruitment into the different sites of inflammation. At the present time, it is unclear how macrophage accumulation in interstitium or glomeruli induces major damage in the diabetic kidney. Some studies of other kidney diseases suggest that inflammatory cells accumulating around peritubular capillaries are important sites of cytokine and chemokine production, including IL-1, TNF-α, MCP-1, macrophage-colony stimulating factor, macrophage inflammatory protein-1β (MIP-1β; CCL4), and MIP-2 (CXCL2) in the injured

kidney (104–108). It is interesting that *in vitro* studies have shown that IL-1β, TNF-α, IFN-γ, and other inflammatory stimuli can induce the production of a broad spectrum of chemokines such as IL-8 (CXCL8), MCP-1, IFN-γ inducible protein (CXCL10), MIP-1α (CCL3), and RANTES (CCL5) by resident renal cells (109). It is likely that these chemokines might direct the migration of different leukocyte types into renal tissues and induce further inflammation.

T Lymphocyte Recruitment

Although trafficking of naïve, effector, and memory T cells into peripheral lymph nodes, spleen, skin, gut, and liver has been the subject of extensive studies, the mechanisms of T cell homing into the kidney under different pathologic conditions are not fully identified. The fundamental appreciation of the importance of the leukocyte recruitment in the induction of endothelial dysfunction has changed significantly the view of the pathogenesis of DN. Because naïve as well as effector T cells constitutively express LFA-1, and ICAM-1 expression is found on renal endothelial, epithelial, and mesangial cells (83–85), it is likely that this interaction will play a significant role during T cell migration into kidney. Indeed, homing of CD4$^+$ T cells into glomeruli of diabetic kidney was decreased in ICAM-1–deficient-db/db mice compared with db/db mice (91). It should be noted that the activation of CD4$^+$ and CD8$^+$ T cells by AGE can initiate IFN-γ secretion by T cells (110), which will induce further inflammation and oxidative stress within renal tissues.

The role of RANTES in directing of T lymphocyte homing into the diabetic kidney is not clear yet; however, a study of a murine lupus nephritis model identified an important role of RANTES in this disease (111). Moore *et al.* (111) elegantly showed that genetically modified tubular epithelial cells secreting RANTES under the renal capsule increase interstitial nephritis in MRL-*Fas^{lpr}* mice. Moreover, constitutive RANTES expression directs subset-specific homing of CD4$^+$ T cells in kidney. T cell accumulation is also found in the juxtaglomerular apparatus of patients with type 1 diabetes (38). The functional role of T cells within this compartment is not clear yet, but this T cell influx is common among young patients with type 1 diabetes, especially those with accelerated duration of diabetes, and correlates with glomerular filtration surface and albumin excretion rate (38).

A T helper-1 (Th1) response precedes and accompanies type 1 diabetes (112); therefore, it is possible that accumulation of Th1 cells will be prevalent in diabetic kidney. Little is known about the homing of Th1 cells during the development and progression of kidney diseases. It has been reported that the homing of effector Th1 cells in glomeruli is P-selectin and ICAM-1 dependent and associated with increased levels of IFN-γ and MIF in crescentic Th-1–mediated glomerulonephritis (113). Although the mechanisms of Th1 cell migration in models of DN have not been reported yet, elevated levels of ICAM-1 and P-selectin within the diabetic kidney were found. Further studies will elucidate the possible role of these adhesion molecules in the migration into the diabetic kidney.

Neutrophil Recruitment

Neutrophil influx is associated with the acute response to inflammation or injury. Neutrophils secrete enzymes and products of oxidation that can harm the local microenvironment and induce tissue damage. The role of neutrophils in the development of DN is not well understood; however, there is some evidence that neutrophils might be involved in this pathologic process. Abnormal activation of blood neutrophils has been reported in patients with type 1 and type 2 diabetes (39,40). DN neutrophils failed to remove CD11b (α-subunit of Mac-1) from the cell membrane, and CD11b expression persisted at elevated levels even after a 90-min incubation (39). This elevated expression of CD11b could play a role in the directing of neutrophil migration in the renal inflamed tissues expressing upregulated levels of ICAM-1. In agreement with these data, Tasuji *et al.* (40) showed that spontaneous adhesion of neutrophils from patients with diabetes is increased significantly compared with adhesion of neutrophils from patients with normoalbuminuria as well as healthy control subjects. The precise molecular mechanisms that orchestrate trafficking of neutrophils in diabetic kidney are not yet defined, but studies with other models of kidney pathology suggest that integrins might participate in this process. In an inflammatory model of anti–glomerular basement membrane (GBM) nephritis in rats blocking antibodies for CD18 have revealed an important role of this family of four integrins in the neutrophil homing (114).

A possible role of selectins in the development of DN was suggested by increased expression of selectins in kidneys of patients with diabetes (115). Expressions of E- and P-selectin both were increased in the glomeruli and interstitial capillaries of human diabetic kidneys compared with kidneys of other glomerular diseases (115). E-selectin expression correlated with the influx of CD14$^+$ monocytes/macrophages into the interstitium. Several studies have shown elevated selectin expression is associated with high glucose levels (116). AGE likely influence E-selectin expression through AGE receptors expressed by macrophages and endothelial and mesangial cells (117). CD44, a family of type I transmembrane glycoproteins expressed on leukocytes and epithelial and endothelial cells, has been reported to be involved in the neutrophil homing in a model of renal ischemia/reperfusion injury (118). It is interesting that CD44 was proposed recently to be a neutrophil ligand for endothelial E-selectin (49). The impact of this novel mechanism of leukocyte homing in diabetic nephropathy has not been investigated yet.

Role of Immune Cells in Endothelial Dysfunction

Endothelial dysfunction is associated with most forms of cardiovascular diseases, such as coronary artery diseases, chronic renal failure, and diabetes (119,120). There is an increasing body of evidence that immigrated blood leukocytes might significantly alter the phenotype of endothelial cells and increase inflammation of the vascular bed (Table 1).

Macrophages can produce a broad spectrum of potential inducers of renal injury; however, the precise cascade that leads

Table 1. Possible mechanisms of leukocyte recruitment and involvement in the process of diabetic nephropathy[a]

Cell Type	Adhesion Molecules, Chemokines	Products	Proposed Role	References
Monocytes, macrophages	ICAM-1, MCP-1	Nitric oxide, reactive oxygen species, IL-1, TNF-α, complement factors, metalloproteinases, PDGF, TGF-β	Endothelial damage, induction of fibroblast and mesangial cell proliferation	(90,91,96,97,128–130, 132–134)
T lymphocytes	LFA-1/ICAM-1, RANTES	IFN-γ, TNF-α	Activation of endothelial cells and macrophages	(91,110)
Neutrophils	Mac-1	Superoxide anion, hydrogen peroxide	Endothelial damage	(40,137)

[a]ICAM-1, intercellular adhesion molecule-1; MCP, monocyte chemoattractant protein-1; RANTES, regulated on activation, normal T cell exposed and secreted.

to renal injury has yet to be determined. The expression of IL-1, TNF-α, and macrophage MIF is markedly upregulated in the injured kidney (36,109,120–122). Podocytes are considered the major source of IL-1α and IL-1β, and at high glucose levels, they may also produce MCP-1 (123,124). These molecules promote inflammation and induce further expression of macrophage colony-stimulating factor and ICAM-1 in renal cells (125–127). Once activated, macrophages release nitric oxide, reactive oxygen species, IL-1, TNF-α, complement factors, and metalloproteinases (128), all of which promote renal injury. Moreover, activated macrophages secrete factors such as PDGF that promote fibroblast proliferation (129). Increased secretion of TGF-β by peripheral blood mononuclear cells was reported in patients with type 1 DN (130). With respect to the interaction between macrophages and mesangial cells, it has been shown that the culture supernatant of macrophages can stimulate mesangial cells to produce fibronectin *in vitro* (131). It should be noted that macrophage-derived factors such as PDGF and IL-1 also can induce mesangial cell proliferation (132,133). Macrophage-derived IL-1β induces the synthesis of TGF-β that seems to be at least partially responsible for fibrogenic and proliferative effects of IL-1β on fibroblasts (134). It is interesting that renal fibrosis as measured by TGF-β1 expression, collagen IV, and interstitial α-smooth muscle actin was dramatically reduced in ICAM-1–deficient mice (91). This is a key event in disease progression, as mice that are deficient in ICAM-1 and, therefore, defective in macrophage homing into renal tissues have shown significant reduction in renal injury (91).

T lymphocytes from patients with diabetes have an activated phenotype (37) and TNF-α–expressing Th1 cells are prevalently detected (112,121). In addition, AGE induce synthesis of IFN-γ that further accelerates the inflammation by the activation of macrophages and vascular cells with the renal tissues.

Usually, neutrophils are the first defense against bacterial infections, because these leukocytes have a broad arsenal of immediate action weapons. However, neutrophils also can induce endothelial dysfunction by production of elevated levels of reactive oxygen species and release of cytotoxic proteinases. NADPH oxidase is a membrane-associated enzyme that generates a family of reactive oxygen species (reviewed in reference [135]). Upon neutrophil activation, specific granules that contain microbial peptides, proteins, and proteolytic enzymes are released (136). It has been reported that neutrophils from patients with diabetes show increased release of oxygen radicals, such as superoxide anion (40) and hydrogen peroxide (137), that might damage endothelial cells and accelerate the progression of diabetic nephropathy (138,139). There is an increasing body of evidence suggesting that neutrophils from patients with diabetes display an activated phenotype, which is reflected by elevated spontaneous adhesion, TNF-α–stimulated production of superoxide and N-formyl-methionyl-leucyl-phenylalanine–stimulated aggregation in patients with type 2 (140) and type 1 (141) diabetes.

Future Directions

One of the possibilities to reduce diabetic kidney damage may be diminishing T cell and macrophage trafficking. Anti–ICAM-1 antibodies or interventions aimed at reducing levels of oxidative stress, hyperglycemia, and advanced glycation end products may be promising approaches in reducing renal disease in patients with diabetes. Interactions of the chemokine or chemokine receptor levels may provide specific therapies that can curb the development of DN. A better understanding of neutrophil, monocyte, and lymphocyte recruitment in DN is likely to result from mechanistic studies in animal models of DN. Promising mouse models (9) that facilitate this endeavor now are available.

Acknowledgments

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