Glomerular Endothelial Dysfunction,
Altered Hemorheology and Hemodynamic Maladjustment in Nephrosis with Focal Segmental Glomerulosclerosis

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Oxidative stress and a defective immunocirculatory balance induce glomerular endothelial cell (GEC) dysfunction, which is expressed as proteinuria and altered hemorheology, namely blood hypercoagulability, blood hyperviscosity, and local intravascular coagulation in severe nephrosis. In addition, defective release of endothelium-dependent vasodilators in conjunction with enhanced production of vasoconstrictors induces hemodynamic maladjustment by preferential constriction at the efferent arteriole. Such constriction has three significant hemodynamic impacts. Proximal to the efferent arteriolar constriction, it induces an overestimated glomerular filtration rate due to hyperfiltration, and an elevated intraglomerular hydrostatic pressure. Distal to the efferent arteriolar constriction, it exaggeratedly reduces the peritubular capillary flow. Such hemodynamic maladjustment causes over-distension of the glomerular capillary, detaching the podocyte from the basement membrane. Podocyte injury decreases the production of vascular endothelial growth factor, thereby aggravating the GEC injury. Increased GEC injury further aggravates the hemodynamic maladjustment, the podocyte injury, and eventually the GEC injury, in a vicious cycle. Sustained ischemic injury activates the profibrogenic pathway and eventually culminates in tubulointerstitial fibrosis. In accordance with this concept, correction of hemodynamic maladjustment with vasodilators and of altered hemorheology with antplatelet drugs and anticoagulation will improve renal hemodynamics and function, and prevent the progression of renal disease.

Key words: immunocirculatory disturbance, glomerular endothelial dysfunction, hemodynamic maladjustment, renal perfusion, vasodilators

INTRODUCTION

Two crucial issues that need to be addressed in nephrosis associated with focal segmental glomerulosclerosis (FSGS) are the proteinuria, which is mainly steroid resistant, and the mechanism of nephronal damage, namely tubulointerstitial fibrosis (TIF) and glomerulosclerosis. There is much evidence that ab-
normal T cell function induces proteinuria in both the human clinical setting and in animal models. Plasma from nephrotic patients contains a vascular permeability factor derived from T cells. Within this context, there is increased Th1 proinflammatory cytokine activity, namely tumor necrosis factor alpha, interleukin (IL)-2, IL-8, IL-12, IL-15, and IL-18 [1–6]. In minimal-change disease or mesangial proliferative nephrosis, the anti-inflammatory cytokine (IL-10) of the Th2 pathway is also usually elevated. However, in nephrosis with FSGS, there is defective release of anti-inflammatory cytokines [3,4].

Experimental studies indicate that during relapse of minimal-change nephrosis, nuclear extracts from peripheral blood mononuclear cells display high levels of nuclear factor kappa B (NF-κB) DNA-binding activity, consisting primarily of p50/Rel A (p65) complexes [7]. The lack of expression of I-κB alpha protein is associated with down-regulation of I-κB alpha mRNA, and increases in the levels of mRNA encoding the preprooese alpha 2 subunit in the proteolytic pathway. Stimulation of the NF-κB pathway is believed to be triggered by infection, toxin, lipid, or reactive oxygen species. Enhanced reactive oxygen species in conjunction with defective antioxidants have been demonstrated in both mild and severe forms of nephrosis [8].

**Glomerular Endothelial Dysfunction**

Injury to the glomerular endothelial cell (GEC) induces loss of negative surface charge, which enhances proteinuria and procoagulant activity [9]. Procoagulant activity is characterized by the presence of blood hypercoagulability, shortened platelet half-life and fibrinogen half-life, blood hyperviscosity, fibrin deposit in the kidney, elevated levels of fibrin degradation products in the serum and urine, and altered hemorheology of erythrocytes during active proteinuria [10–19]. In addition, there is defective release of vasodilators in the dysfunctional GEC and, at the same time, enhanced release of vasoconstrictors, namely angiotensin II, endothelin, and thromboxane A₂. A mild degree of such a provasoconstrictive state is observed in nephrosis associated with mesangial proliferation (MesP), which is reflected by a mild reduction in renal plasma flow (RPF) and a mild elevation in arteriolar resistance [20]. However, in severe nephrosis such as FSGS, a greater magnitude of intrarenal hemodynamic abnormality is observed, which is characterized by a greater reduction in RPF and peritubular capillary flow (PTCF), a greater increase in afferent and efferent arteriolar resistance, and elevated intraglomerular hydrostatic pressure (PG) [21,22]. An in vitro study has recently demonstrated that sera from nephrotic patients can induce endothelial cell cytotoxicity [23]. Sera from patients with MesP nephrosis increased endothelial cell cytotoxicity to 18 ± 9%, compared with 1.8 ± 0.8% with control sera, whereas sera from patients with nephrosis associated with FSGS increased endothelial cell cytotoxicity to 40 ± 9%. Such an endothelial cell cytotoxicity test in vitro correlates with GEC dysfunction in vivo, as determined by intrarenal hemodynamic study [23].

**Hemodynamic Maladjustment**

In severe nephrosis such as FSGS and MesP nephrosis associated with TIF, elevated vasoconstrictors induces hemodynamic maladjustment by preferentially constricting the efferent arteriole. Such a constriction has three significant hemodynamic impacts. First, proximal to the efferent arteriolar constriction, it induces an overestimated glomerular filtration rate due to hyperfiltration. Second, it causes an elevated PG due to the higher blood inflow and lower blood outflow. Intraglomerular hypertension in conjunction with defective blood quality, altered hemorheology, enhanced proinflammatory activity, and renal hypoperfusion culminates in the development of glomerulosclerosis. Third, distal to the efferent arteriolar constriction, it exaggeratedly reduces the PTCF supplying the tubulointerstitium (Figure 1).

Increased PG distends the glomerular capillary loop, thereby detaching the podocyte from the basement membrane. Increased podocyte injury in this manner, in conjunction with toxic injury from reactive oxygen species and proinflammatory cytokines, decreases the production of vascular endothelial growth factor (VEGF), which is essential to the survival and regeneration of the endothelial cell. Both Kriz and associates [24] and Rennke [25] have elegantly demonstrated podocyte injury by detachment from the basement membrane secondary to ballooning of the capillary loop in nephrosis with FSGS. Mild reduction in the level of VEGF mRNA and its receptor (flk-1) mRNA was transiently documented in the first week following injection of puromycin aminonucleoside to induce nephrosis [26]. However, permanent loss of podocyte function, with impaired production and release of VEGF, is likely in nephrosis with FSGS. Defective release of VEGF, leading to impaired angiogenesis, is correlated with progressive renal disease [27,28]. A decrease in VEGF and flk-1 renders the endothelial cell apoptotic or cytotoxic. Histochemical staining for glomerular endothelial factor VIII and postglomerular endothelial factor VIII has demonstrated a greater loss of endothelial cells in the renal microcirculation in nephrosis with FSGS than in MesP.
Nephrosis with focal segmental glomerulosclerosis

Thus, injury to the GEC is enhanced and aggravates hemodynamic maladjustment and injury to the podocyte, eventually causing further injury to the GEC and post GEC in the renal microcirculation, in a vicious cycle. Finally, sustained ischemic injury to the PTCF, which activates the profibrogenic pathway, culminates in the development of TIF [30–35]. The significance of reductions in PTCF in relation to the development of TIF has been demonstrated by multiple regression analysis, which revealed that reductions in PTCF correlate inversely with the development of TIF. This means that the lower the reduction in PTCF, the greater the magnitude of TIF. Furthermore, reduction in PTCF precedes the development of TIF, which supports this cause-and-effect relationship [36].

In accordance with the preceding concept of GEC dysfunction induced by oxidative stress and immunocirculatory disturbance, such toxic triggers affect the podocyte and induce podocyte dysfunction or injury. Podocyte injury with structural damage such as podocytopenia and nephrin loss is believed to be associated with proteinuria [37]. A synergistic interaction between injury to the glomerular endothelium and podocyte amplifies the vicious cycle that eventually leads to progressive reduction in renal perfusion and increase in the magnitude of proteinuria (Figure 1).

**Therapeutic Strategy to Prevent Renal Disease Progression**

The magnitude of GEC dysfunction and its effect on hemodynamic maladjustment is likely to determine the severity of disease and the magnitude of TIF in severe nephrosis. A therapeutic intervention to correct the hemodynamic maladjustment and restore GEC function would be welcome. Indeed, treatment with vasodilators, including angiotensin converting enzyme inhibitors (ACEIs), angiotensin II type 1 receptor antagonists (AIIRAs), and calcium-channel blockers, can improve renal perfusion and decrease PG to normal (Figure 2) [38–42]. In practice, a combination of vasodilators is recommended, and the doses needed to correct hemodynamic maladjustment are more than those needed for blood-pressure reduction. Blood-pressure reduction is usually achieved much earlier than conversion of renal arteriolar resistance to normal. Altered hemorheology can be corrected by antiplatelet and anticoagulant therapy [10,11,44,45]. Antioxidant therapy with high doses of vitamin C (1,000–3,000 mg/day) and vitamin E (800 units/day) restores GEC function and suppresses endothelial cell cytotoxicity [8,45–48].

If persistent proteinuria is encountered in nephrosis with FSGS following vasodilator treatment, treatment with *Ganoderma lucidum* (750 mg/day) can suppress steroid-resistant proteinuria [49].

These therapeutic strategies have resulted in improvements in renal hemodynamics and renal function. There is substantial increase in creatinine clearance.

**Figure 1.** Pathogenetic mechanism of renal disease progression in severe nephrosis. AII = angiotensin II; ET = endothelin; LIC = local intravascular coagulation; MMPI = matrix metalloproteinase inhibitor; PAI = plasminogen activator inhibitor; PTCF = peritubular capillary flow; RA = afferent arteriolar resistance; RE = efferent arteriolar resistance; ROS = reactive oxygen species; RPF = renal plasma flow; TGFB = transforming growth factor beta; Th = T helper; TXA2 = thromboxane A2; VEGF = vascular endothelial growth factor.

**Figure 2.** Correction of hemodynamic maladjustment with vasodilators: pre- and post-treatment intrarenal hemodynamic study in nephrotic patients with focal segmental glomerulosclerosis treated with angiotensin converting-enzyme inhibitor, angiotensin II receptor antagonist, calcium-channel blocker, and antiplatelet agent in accordance with the dose described previously [43]. RA = afferent arteriolar resistance; RE = efferent arteriolar resistance; PG = intraglomerular hydrostatic pressure; RPF = renal plasma flow; PTCF = peritubular capillary flow; GFR = glomerular filtration rate.
ance and a decline in the fractional excretion of magnesium (FE Mg) in severe nephrosis with FSGS [8, 49]. Inasmuch as the FE Mg correlates directly with the magnitude of TIF [50] and inversely with the reduction in PTCF [51], improvement in FE Mg following treatment implies that the inflammatory process in the tubulointerstitium is likely to be suppressed. In this regard, it has recently been demonstrated that a combination of an ACEI and an AIIRA can diminish kidney tissue angiotensin II levels, and that regression of kidney disease can be accomplished in animal models [52,53].

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