Endothelial Dysfunction: The Secret Agent Driving Kidney Disease

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Endothelial dysfunction can be considered the heart of many kidney and metabolic diseases, including primary hypertension, diabetic nephropathy, and CKD. However, perhaps the conditions most associated with dysfunction or injury of the endothelium are thrombotic microangiopathies (TMAs), such as hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP). Specific types of these diseases have been associated with alterations in factors that alter angiogenesis, coagulation, and platelet activation and complement function. Although emphasis has tended to focus on one factor as causing one type of TMA, more recent studies suggest that TMAs often result from the synergism of multiple factors driving endothelial dysfunction. This emphasizes that general measures to improve endothelial health are likely the key for preventing and/or lessening the severity of many kidney and metabolic diseases. TMAs are diseases characterized by thrombocytopenia, microangiopathic hemolytic anemia, and renal injury, in which a common denominator seems to be endothelial dysfunction. Although the disease is generally dominated by renal manifestations in HUS, the dominant manifestation is more neurologic in TTP. Pregnancy-associated TMAs may manifest as a hemolysis, elevated liver enzymes, and low platelet count syndrome or preeclampsia. Other

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related conditions that are often separated from TMAs but in which intravascular blood coagulation also occurs include antiphospholipid syndrome, heparin-induced thrombocytopenia, and disseminated intravascular coagulation.

Over the last several decades, a series of breakthroughs has been reported for the various TMAs. These include the discoveries of the role of circulating antiangiogenic factors, such as soluble fms–like tyrosine kinase 1 (sFLT-1) and soluble endoglin, in preeclampsia; the role of Shiga toxin from enterotoxigenic Escherichia coli in epidemic HUS; the role of deficiency in complement regulatory proteins, such as factor H, in atypical HUS; and the functional absence of a disintegrin and metalloprotease with thrombospondin type 1 motif 13 (ADAMTS13) caused by genetic absence (in hereditary TTP or Upshaw–Schulman syndrome) or autoantibodies (in acquired TTP). The identification of specific etiologies associated with specific diseases feeds our natural inclination and that of medical school teaching to think that each disease has a specific cause and a specific treatment.

Although it is convenient to link a specific factor with a disease, it is becoming apparent that these factors are often not enough to cause the disease by themselves in the absence of other factors. For example, many subjects with a lack of factor H or a lack of ADAMTS13 are asymptomatic until some illness occurs that triggers the TMA. As another example, only a small fraction of subjects infected with Shiga toxin—expressing E. coli—develop HUS. This suggests that, for TMA to manifest, sufficient endothelial injury must be present, and this may require the presence of other factors that synergize together.

In this issue of JASN, Erpenbeck et al. investigate the role of ADAMTS13 deficiency as a synergistic factor with sFLT-1 in inducing a preeclampsia–like lesion. sFLT-1 is a circulating inhibitor for vascular endothelial growth factor and placental growth factor that is expressed at high levels in the circulation and placenta of subjects with preeclampsia. It is a prime candidate for causing preeclampsia on the basis of previous studies suggesting that a lack of vascular endothelial growth factor in glomeruli can lead to TMA; also, administration of sFLT-1 to pregnant rats can induce hypertension and proteinuria with a renal lesion of glomerular endotheliosis, similar to what is observed in preeclampsia. Although sFLT-1 is almost certainly one of the key factors driving preeclampsia, there are also reports that ADAMTS13 activity is commonly reduced in patients with preeclampsia. ADAMTS13 is a protease that cleaves large vWF multimers that are released from activated endothelial cells, thereby blocking local platelet aggregation and thrombosis. Erpenbeck et al. show that overexpression of sFLT-1 in control mice induced mild manifestations of TMAs, which has been previously reported, whereas a lack of ADAMTS13 resulted in no manifestations of TMAs. However, the combination resulted in a lesion that greatly resembled preeclampsia, with thrombocytopenia, hemolytic anemia, glomerular endotheliosis, and marked proteinuria and hypertension. Furthermore, the administration of recombinant ADAMTS13 could largely block the development of these lesions.

The study by Erpenbeck et al. thus, suggests that a reduction in ADAMTS13 activity might be a synergistic factor to the pathogenesis of preeclampsia. Although exciting, the study would have been stronger if Erpenbeck et al. had shown this synergy in pregnant mice. In addition, Erpenbeck et al. showed the synergy in mice that were null for the ADAMTS13 gene, thereby having no ADAMTS13 activity at all. Although this is clinically relevant to subjects with hereditary TTP who also have <10% ADAMTS13 activity, it may or may not be relevant to subjects with preeclampsia who have partial reductions (20%–40%) in ADAMTS13 activity. Thus, it will be important to evaluate whether the ability of sFLT-1 to induce TMAs is enhanced in the setting of partial reduction in ADAMTS13 activity (such as might occur with heterozygote mice). Nevertheless, the study emphasizes the potential importance of synergistic factors in causing preeclampsia and raises the possibility that measures, such as the administration of recombinant ADAMTS13, might potentially be beneficial in treating preeclampsia.

Other studies also have found that a lack of ADAMTS13 can augment the effect of Shiga toxin to induce HUS in animals. Indeed, Shiga toxin seems to increase the risk for HUS by blocking both ADAMTS13 activity and factor H activity on the endothelium.

The concept of synergy explains why pregnancy is so susceptible to endothelial injury. During pregnancy, the uterus and placenta undergo marked angiogenesis to generate the blood vessels that will help nurture the fetus, but at term, this process has to be reversed. Not only are antiangiogenic factors, such as sFLT-1 and endoglin, produced, but also, there is a marked increased production of coagulations factors (creating a hypercoagulable state). This is likely why hereditary diseases, such as factor H deficiency, may clinically manifest during pregnancy with either atypical HUS or fetal loss and why the effect of endotoxin to induce shock and disseminated intravascular coagulation (the Shwartzman reaction) is amplified in pregnancy.

Two take–home messages come out of this work. First, although we like to categorize TMAs into either clinical categories (such as HUS and TTP) or entities with specific etiologies, the actual disease may involve a variety of factors that alter endothelial function or integrity, and perhaps, this may explain why we frequently see overlap in presentations. Thus, distinction between various entities of TMAs may be lost depending on the relative contribution of the various factors involved. Treatments may, therefore, need to focus on the specific factors involved more than simply treating a disease category.

Second, it is important to maintain a healthy endothelium, because the healthier that it is, the better it can fend off endothelial insults. This may not carry over simply to preventing TMAs but also, many metabolic and kidney diseases. For example, endothelial dysfunction associated with reduce endothelial nitric oxide production may play a key role in the development of primary hypertension, metabolic syndrome, diabetic nephropathy, and even progression of CKD. Thus, more focus needs to be placed on improving endothelial cell health. One important
aspect is improving the diet, because some foods, particularly those with fructose from added sugars, such as sucrose and high-fructose corn syrup, can impair endothelial function, partly by their ability to induce uric acid.15 Soft drink intake is known to be a risk factor for preeclampsia.16 Thus, one needs to think about how one might improve endothelial function as a general measure for reducing TMAEs and other kidney diseases.17 For example, endothelial protectants, such as dextran sulfate, have been reported to provide protection in an animal model of HUS.18

The last decade can be rightfully claimed as the era of the podocyte. The large numbers of scientific contributions on the nature of the slit diaphragm and how alterations in these proteins can lead to proteinuria have represented some of the greatest breakthroughs in nephrology. However, it is increasingly evident that the health of the vascular endothelium is also key to both the prevention and the treatment of kidney diseases. Activation of the endothelium is key to initiating innate immunity and inflammation, complement activation, coagulation, platelet dysfunction, and vasoconstriction. Capillary loss, which is also induced by endothelial injury, can lead to downstream ischemia, which can cause fibrosis and inflammation and impair function. Thus, the secret agent driving many kidney diseases may be endothelial dysfunction, which is defined broadly as alteration in any mechanism leading to impaired endothelial function and integrity. Finding ways to improve endothelial health may be a stealth way for both preventing and slowing kidney diseases.

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