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The Role of Endothelial Cell Injury in Thrombotic Microangiopathy

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Abstract

Thrombotic microangiopathy (TMA) refers to a clinical and pathological syndrome in which endothelial injury results in the manifestations of thrombocytopenia, microangiopathic hemolytic anemia, and renal injury. A host of etiologies may induce endothelial injury and TMA, including enteric bacterial toxins, deficiency or dysfunction of complement regulatory proteins, deficiency or inhibition of von Willebrand factor cleaving proteases, and factors that inhibit endothelial cell proliferation and turnover. This has led specialists to concentrate on these specific inciting factors in terms of designing treatment and management. However, a key and less recognized factor is the underlying level of endothelial health. Indeed, many subjects with hereditary etiologies may remain disease free for years, and may never develop disease. Others with acute inciting events such as E coli O157 enteritis never manifest TMA. Experimental studies document the importance of specific factors such as endothelial nitric oxide levels in helping to protect animals from TMA. This suggests that one might approach the management of TMA not simply with specific treatments aimed at the underlying hereditary cause or inciting event, but rather also at general measures that may improve overall endothelial health. We propose studies to determine if interventions known to improve endothelial health, such as the administration of ACE inhibitors, statins, vitamin C, allopurinol, or nitric oxide-producing drugs may be able to prevent TMA even in subjects with underlying hereditary conditions that would otherwise predispose them to these diseases.

Keywords

hemolytic uremic syndrome; nitric oxide; endothelial cell; vascular endothelial growth factor

Background

Thrombotic microangiopathy refers to a clinical and pathological syndrome characterized by thrombocytopenia, mechanical hemolytic anemia, and renal injury. The underlying pathogenesis of thrombotic microangiopathy is considered to be *endothelial cell injury*, resulting in the renal lesion of arteriolar injury, endothelial swelling of the glomerular and peritubular capillaries, and intracapillary platelet and fibrin rich thrombi formation. The two

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Ryan J. Goldberg-none
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Richard J. Johnson has patents on the use of VEGF to treat thrombotic microangiopathy and also to treat preeclampsia.
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most common types of thrombotic microangiopathies are the hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP). HUS is a condition in which the renal manifestations are most manifest, and TTP presents more as a systemic disorder in which renal involvement is classically mild.

Case Vignette

A 37-year-old woman presents to the emergency room with epistaxis. She has a history of atypical hemolytic uremic syndrome (aHUS). Her first diagnosis of aHUS was made during the post-partum period of her first and only pregnancy 15 years ago. She responded to multiple rounds of plasma exchange. Her second episode of aHUS occurred 10 years ago around the time of an upper respiratory infection and again responded to multiple rounds of plasma exchange. She maintains that she has been asymptomatic since her last presentation. Her only other medical problem is hypertension for which she takes metoprolol 25 mg twice daily. She has been feeling fatigued and chilled for two days prior to the epistaxis. In the emergency room, serum hematocrit was 25.4%, hemoglobin was 8.5 g/dL, and platelets were 55. LDH level was 1019 and haptoglobin was undetectable. Serum creatinine was 2.5 and BUN was 45. Plasma exchange is initiated and the patient responds after 18 treatments. Serum creatinine and the time of hospital discharge is 1.4. Recurrent aHUS in an uncommon disorder and presents a challenge to the treating physician. Currently there are no direct therapeutic agents that have been shown to prevent recurrent episodes of aHUS. We hypothesize that agents known to improve endothelial health may have a role in preventing aHUS relapses.

Pathogenesis

Over the last decades a variety of etiologies of the thrombotic microangiopathies have been identified (Table 1). The best established diagnoses are TMAs associated with infection due to *E Coli* 0157:H7, the ADAMTS13 deficiency, or with genetic or acquired deficiencies in complement regulatory proteins. Treatments for these conditions are often tailored for the underlying etiology. For example, TMA caused by *E Coli*, generally responds to supportive care alone [1], whereas plasma exchange is preferred for patients with ADAMTS13 related disease to either replace the deficient protease or to remove anti-protease antibodies[2]. Patients with TMA secondary to complement regulatory protein deficiencies or mutations are usually treated with plasma exchange to replace the deficient complement protein. However, long term outcomes in patients with Factor H, Factor I, or C3 mutations remains poor[3].

Importantly, there is a notion that there could be a missing factor in TMA, and this is supported by a variety of findings. For example, patients with deficient complement regulation leading to atypical hemolytic uremic syndrome (aHUS) may be asymptomatic for decades prior to the development of disease[3, 4] while disease flares in these patients are often initiated by an inciting event such as an infection. There are also case reports of patients with combined ADAMTS13 deficiency and complement protein mutations who had more severe disease[5]. Some subjects with severe hemorrhagic colitis due to *E coli* O157 develop HUS whereas others do not. While there is much focus on the mechanisms by which E coli O157 toxins or lack of key complement regulatory proteins may cause TMA, less emphasis has been placed on the underlying health of the endothelium (Figure 1). Thus, it is the contention in this paper that initiating measures to improve endothelial health could provide an ancillary approach to the management of these disorders.

The endothelium is a highly active tissue responsible in part for regulating vascular tone, coagulation, and inflammation. Why the glomerular endothelium is the main target of TMAs is, unfortunately, still unknown. Some have postulated that the fenestrated nature of the

glomerular endothelial cell (GEC) leaves it more susceptible to complement activation since the glomerular basement membrane is without its own complement regulators[3]. Also, the GEC has been shown to be dependent on podocyte produced vascular endothelial growth factor to maintain its health so a process negatively impacting the podocyte may then lead to a weakened endothelial cell[6]. While direct injury of the endothelium is known to cause TMA, alterations in underlying endothelial function may also have a key predisposing role. We discuss specific functions of the endothelium and how it may modulate TMA. If our notion is true, an important insight will emerge, which is that general measures to maintain a healthy endothelium could be an alternative strategy for both preventing and managing TMA regardless of the underlying etiology.

Recent Advances

Protective Factors for the Endothelium

Endothelial cells express endothelial nitric oxide synthase (eNOS), which produces low levels of nitric oxide (NO) that has a key function in maintaining local vasodilation, protecting endothelial cells from toxicity of circulating cytokines such as tumor necrosis factor-alpha (TNF-α), and reducing the risk for local thrombosis. Endothelial NO, for example, inhibits the exocytosis of endothelial cell vacuoles (Weibel Palade bodies) to release P selectins and von Willebrand factor (vWF), both of which can initiate local inflammation and thrombosis[7]. Control of endothelial NO levels is governed in part by vascular endothelial growth factor (VEGF), and VEGF also has important roles in maintaining endothelial cell integrity.

The importance of endothelial NO in TMA is becoming increasingly recognized. For example, mice deficient in endothelial NO develop a TMA-like lesion with aging that is associated with glomerular capillary deposition of vWF and elevated circulating P selectin levels consistent with unimpaired release of endothelial –derived Weibel Palade bodies[8]. Preeclampsia, which is another form of TMA, has also been associated with low circulating nitric oxide levels even following recovery of disease[9]. Compatibly, recent evidence documented that soluble endoglin, which can inactivate eNOS by inhibiting TGF-beta signaling[10], increases the risk for preeclampsia[11, 12]. Finally, hemolysis, such as occurs in TMA, may further lower NO levels due to the ability of free hemoglobin to consume NO[13].

A reduction in local VEGF in the podocyte can also induce a TMA-like lesion in the kidney[14]. Since VEGF is a major factor to regulate endothelial NO production, a potential mechanisms for this TMA could be low NO level due to a lack of VEGF stimulation. Likewise, inhibition of circulating VEGF due to the production of a soluble VEGF receptor (sFLlt-1) has been shown to have a role in preeclampsia[11]. Similarly, inhibition of VEGF with the monoclonal VEGF inhibitor bevacizumab may cause a TMA-like lesion with proteinuria and hypertension in patients[6].

Recently, it has been found that approximately 5% of patients with atypical HUS may carry mutations in the gene for thrombomodulin, a glycoprotein that may help regulate both clotting and complement activation on the endothelial cell surface [15]. When thrombomodulin activity is altered, the endothelial cell surface is at further risk for injury.

While a lack of these factors may predispose to TMA, there is also evidence that replacing these factors may confer benefit in TMA. For example, NO has been shown to be protective in animal models of HUS suggesting a role for vasodilation and platelet inhibition[16]. Administration of VEGF can also rescue or protect renal injury in animal models of TMA [17, 18]. This suggests that stimulation or maintenance of endothelial NO or VEGF could be protective from pathogenic mechanisms driving TMA.

Factors Disrupting Endothelial Function

Malignant hypertension may cause TMA via injury to the vascular endothelium. van den Born et al demonstrated increased amounts of VWF and reduced levels of ADAMTS13 in a group of patients with malignant hypertension and TMA[19]. Endothelial NO levels are also low in this condition, likely due to consumption by local oxidative stress[20]. Indeed, Vaziri et al have reported that the injection of an inhibitor of the intracellular glutathione antioxidant pathway results in acute oxidative stress, a loss of nitric oxide, and the development of malignant hypertension in rats[21].

Conditions that disrupt the normal anticoagulant function of the endothelium can increase the risk for TMA. For example, pregnancy is a well-known hypercoagulable state, especially for subjects at term and post-delivery. The coagulation factors I, II, VII, VIII, IX, and X all increase along with a decrease in protein S levels and an increase in acquired resistance to activated protein C (APC) [22, 23]. Interestingly, increases in plasma thrombomodulin, plasminogen activator inhibitor-1, and von Willebrand factor with a corresponding decrease in ADAMTS13 levels[24], all of which occur in pregnancy, indicate the possibility of loss of endothelial cell membrane integrity and decreased fibrinolytic activity, respectively[25]. It is thus not surprising that approximately 10% of cases of TMA occur with pregnancy or in the post-partum period[24, 26]. Pregnancy has also been reported to precipitate TMA in subjects with hereditary TTP-HUS[24].

Estrogen in OCPs also have prothrombotic effects including inducing APC resistance, increasing the plasma levels of Protein C and protein C inhibitors, and decreasing APC independent anticoagulation activity of protein S and the plasma levels of total Protein S and C4b binding protein[27]. Similarly, subjects on birth control pills (OCPs) have been reported to be at increased risk for developing idiopathic HUS[28, 29]. In turn, estrogen is able to protect endothelial cell by stimulating endothelial NO production[30]. Hence, it is possible that the prothrombotic effects of estrogen could be blocked by a concomitant increase in endothelial NO in the presence of healthy endothelium whereas it might be unmasked in the setting where endothelial NO levels are reduced (such as in subjects with obesity or metabolic syndrome).

The production of complement regulatory proteins by the endothelium may help to prevent activation of the coagulation cascade. The membrane attack complex attracts and activates platelets and causes the release of VWF from endothelial cells while the complement fragment proteins C3a and C5a induce platelet activation and aggregation, up regulate plasminogen activator inhibitor-1, and trigger the release of cytokines[31]. C5a also has been shown to cause the release of the anticoagulant molecule heparan sulfate from endothelial cells further increasing the thrombogenic potential on the endothelial cell surface[32]. C4b binding protein also complexes with Protein S, thereby decreasing its anticoagulant effects. Thus in areas of endothelial cell inflammation local complement activation could increase the risk for local clot formation. This likely explains the relationship of HUS to hereditary conditions in which complement regulatory protein mutations occur, but also suggests that any condition that leads to local intravascular complement activation could predispose to the development of an HUS like syndrome.

Direct Endothelial Toxins

The calcineurin inhibitors (CNI) cyclosporine and tacrolimus are also associated with TMA in both renal transplant and non-renal transplant patients. In renal transplantation, a multiple hit etiology is easily implicated as a number of additional factors have been linked to post-transplant de novo TMA, including marginal kidneys, viral infections, other medications, and malignancy[33]. CNIs directly injure endothelial cells, decrease the production of

prostacyclin and NO while increasing thromboxane A2 and endothelin synthesis, and reduce the formation of activated protein C [34–37]. Dysregulation of complement regulatory proteins by CNI may contribute to cyclosporine-induced TMA [38]. Agents that block mTOR, such as sirolimus, may increase the risk of TMA in subjects receiving CNI also in part by delaying repair of injured endothelium and by causing a local down regulation of VEGF[39]

Chemotherapy agents may also increase the risk for TMA by inducing endothelial injury. Examples include mitomycin-C, gemcitabine and quinine [40, 41, 42] The mechanism of injury is not well understood but in part may relate to the development of antibodies to tumors [43], and with quinine to the development of autoantibodies to normal cells such as platelets, granulocytes, and endothelial cells[42].

E coli associated HUS

Shiga toxin, released by *E Coli* O157:H7, is the primary cause of diarrhea associated HUS. Shiga toxin acts in part by inducing endothelial cells to secrete ultra large VWF, by impairing the activity of ADAMTS13, and by increasing the expression of P-selectin and platelet endothelial cell adhesion molecule 1[44]. Shiga toxin also binds and prevents the activity of the complement regulatory protein, Factor H[45], and may explain why activation of systemic complement occurs in cases of HUS induced by E coli O157[46].

Despite the significant toxicity of Shiga toxin to the endothelium, during outbreaks of HUS caused by *E Coli* only a small percentage of exposed individuals end of developing HUS. This may be partially explained by virulence factors such as inoculum size, or host factors such as age, gastric acidity, immune status, antibiotic use and immune response[47]. However, the underlying health of the endothelium likely has a major role. This could explain why subjects with underlying defects in complement regulation who develop TMA after exposure to Shiga toxin appear to develop particularly severe disease[48] It may also explain why mice deficient in ADAMTS13 do not develop TMA unless they are stimulated to do so with shiga toxin, epinephrine, or collagen [49, 50].

Summary

We therefore propose that the underlying health of the endothelium may have a large role in governing the manifestations of disease following insult to the endothelium (Figure 2). When considered this way, treatments aimed at improving endothelial function might be useful in protecting individuals from developing TMA from both exogenous and hereditary mechanisms.

Table 2 shows agents that are known to improve endothelial function and theoretically could have a role in preventing TMA. For example, statins, in addition to their lipid lowering qualities, increase the expression of endothelial NO and decrease the inflammatory and thrombogenic potential of endothelial cells[51–53]. Angiotensin converting enzyme inhibitors and to a lesser extent, angiotensin receptor blockers, also increase endothelial NO. Xanthine oxidase inhibitors have also been shown to improve endothelial function in a number of clinical trials[54,55]. We propose future studies, particularly in subjects with hereditary causes of TMA, to see if the use of these agents may be able to reduce the episodes of TMA.

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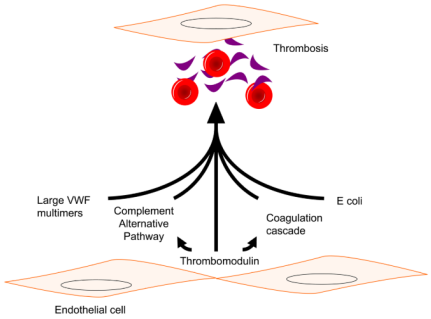

Figure 1.
Pathogenesis of thrombotic microangiopathy. Abbreviation: vWF, von Willebrand factor.

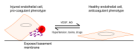

Figure 2.
Pathways to endothelial cell injury. Abbreviations: NO, nitric oxide; VEGF, vascular endothelial growth factor

Table 1

Etiologies of Thrombotic Microangiopathy

E Coli O157:H7 or other shiga toxin producing organisms
ADAMTS13 deficiency
Complement regulatory protein deficiencies or mutations
Drugs (Calcineurin inhibitors, oral contraceptives, chemotherapeutic agents, ticlodopine, clopidogrel, quinine)
Pregnancy related
Neuraminidase producing organisms leading to T antigen recognition and possible endothelial cell injury
Hemodynamic factors including malignant hypertension
Idiopathic

Table 2

Factors thought to be supportive of endothelial cell health or those thought to trigger endothelial cell dysfunction and thrombosis

Factors associated with anticoagulation and endothelial cell health	Factors associated with procoagulation and endothelial cell dysfunction
Statins[51–53]	Complement mutations
Angiotensin converting enzyme inhibitors, angiotensin receptor blockers[56, 57]	ADAMTS13 related
Polyphenols[58, 59]	Pregnancy, increased estrogen
Ascorbic acid[60]	Decreased NO
Allopurinol[61–63]	Drugs, toxins