It has been 30 years since the first description of antineutrophil cytoplasmic antibodies (ANCA).1 Elucidation of their role in systemic vasculitis has revolutionized our understanding of these diseases, and the resultant attention on the neutrophil has made it the central cell in the investigation of small vessel vasculitis.2 However, even given the developing consensus that ANCA are pathogenic,3–5 there is clearly much more to the story. In this issue of JASN, Le Roux et al.6 report that elevated circulating levels of soluble fms-like tyrosine kinase 1 (sFlt1), an endogenous antiangiogenic protein, are associated with ANCA-associated vasculitis (AAV) and may contribute to microvascular endothelial cell injury.

It has been evident for some time that ANCA titers correlate poorly (in both directions) with disease activity.7,8 Furthermore, there are many broader issues that remain unclear. For example, why are the lesions of a systemic process found only in particular regions of the vascular system? Renal pathologists have long recognized that the early glomerular lesion of ANCA disease, segmental necrosis, is primarily accompanied by neutrophil margination and accumulation. However, within a short time, mononuclear leukocytes come to predominate, a progression that may suggest a stepwise nature to the pathogenesis of these lesions. Interestingly, monocytes, a prominent cell of these later stages, also possess the ANCA autoantigens and may contribute to the pathogenesis of these lesions. Interestingly, monocytes, a prominent cell of these later stages, also possess the ANCA autoantigens and may contribute to the pathogenesis of these lesions. These results further support the notion that ANCA activate monocytes in a manner similar to the way they prime monocytes in vitro.

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interactions. Fortunately, recent studies have begun to examine the endothelium beyond that initial injury, focusing on the subsequent detachment and circulation of these mainly necrotic/apoptotic endothelial cells. Although this process is likely relevant for a variety of vascular diseases, and technical issues of how to best measure it remain, several studies showed that the number of circulating endothelial cells (CECs) correlates with ANCA disease activity. There is also increasing recognition of the importance of endothelial repair and its mechanisms.

The ability of native endothelium to directly proliferate at a site of injury may be limited, and bone marrow–derived endothelial progenitor cells (EPCs) may play a pivotal role in vascular repair. Immunosuppression and ANCA disease remission have been associated with an increase in circulating EPCs. Their functionality can be influenced by the administration of agents such as erythropoietin, statins, and, notably, vascular endothelial growth factor (VEGF). Furthermore, reduced numbers of circulating EPCs associate with increased risk of relapse of ANCA disease. CECs may themselves impair EPCs in vasculitis patients. Studies in this field have been somewhat hampered by the lack of standard assay methodology. Nevertheless, there is a growing consensus that endothelial health is a function of the balance between injury and repair, with the CEC/EPC ratio as a potential biomarker in diverse vascular diseases including AAV.

Recognition of the endothelium as an independent determinant in ANCA disease raises the question of the role of angiogenic factors that play a role not only during vascular repair but also in maintaining blood vessel homeostasis. The endothelial-specific angiopoietin (Ang)-Tie ligand receptor system is likely to play a large role in general vascular inflammation. Angiopoietin-2 (Ang-2) overexpression causes glomerular endothelial apoptosis and capillary leakage. Circulating Ang-2 is elevated and closely correlates with clinical scores of disease activity and numbers of CECs in AAV. However, VEGF is a more potent endothelial growth factor. Its two major receptors are Flt1 (or VEGFR1) and VEGFR2. Alternative splicing, as well as cleavage of membrane-bound VEGFR1, leads to a secreted isoform—sFlt1 (or sVEGFR1)—that has been identified in the circulation of women with preeclampsia. Circulating levels of sFlt1 are both proportional to the severity of the disease and precede clinical manifestations. Elevated levels of sFlt1, through VEGF inhibition, induce a systemic antiangiogenic state and contribute to glomerular damage, hypertension, and proteinuria of preeclampsia. Side effects of VEGF inhibition in patients undergoing antiangiogenic cancer therapy include glomerular endothelial injury, which is consistent with the homeostatic role of VEGF in the mature vasculature.

Consequently, the work by Le Roux et al. is most welcome. The authors demonstrate that circulating levels of sFlt1 are significantly increased during acute AAV and that this increase is most marked in patients with PR3-ANCA. Levels of sFlt1 in the acute phase of AAV correlate with the degree of proteinuria but do not correlate with the percentage of crescents in renal biopsies. However, the levels noted are significantly lower than those seen during active preeclampsia.

The mechanism of injury, sFlt1-mediated VEGF depletion, was demonstrated through the use of the well established chicken chorioallantoic membrane in vitro angiogenesis assay. Sera from patients with acute PR3-AAV (but not anti-MPO) led to the near-complete disruption of the microvasculature in the treated area, an effect that was completely reversed by the addition of human VEGF. These data also suggest a biologic difference between anti-PR3 and anti-MPO AAV that requires further investigation. The major sources of sFlt1 (in the absence of a placenta) are endothelial cells and monocytes. Interestingly, the current work suggests that monocytes are most relevant, as serum from patients with acute PR3-AAV induce the release of sFlt1 by human monocytes but not by human umbilical vein endothelial cells. This issue is not entirely settled, because it is far from clear how representative of other endothelial phenotypes, especially glomerular, human umbilical vein endothelial cells really are.

Recent years have also seen increased attention to the role of complement in ANCA disease and thus the convergence between innate immunity and angiogenesis. This is a complex field that is only in its earliest stages. Using mouse models, Langer et al. have shown the complement system to be a negative regulator of neovascularization, with C3 and C5 deficiencies promoting angiogenesis. Most notably, their proangiogenic effect is not direct, with monocytes playing a mediating role, particularly with regard to C5a, which induces secretion of sFlt1 by monocytes in vitro. Our authors documented elevated serum levels of C5a during the acute phase of AAV, which correlated with serum sFlt1 levels. However, in their hands, C5a failed to induce sFlt1 release by monocytes. In contrast, they did show that anti-PR3 antibodies, and to a much lesser extent anti-MPO antibodies, induced sFlt1 release by monocytes, independently of C5a. What accounts for the difference between these two autoantibodies remains unclear, as does the role of membrane cleavage in the liberation of sFlt1.

The notion that ANCA is acting through monocytes, perhaps independently of the neutrophil–endothelial axis, to impair vascular recovery opens up a new avenue of AAV investigation, with many potential targets for future investigation, biomarker development, and therapeutic intervention. The authors are to be congratulated for documenting what might have been thought to be obvious, but apparently was not—that vasculitis is an antiangiogenic state. In so doing, they have also reminded us of the distinctions between, and complex interplay of, vascular injury and repair.

DISCLOSURES
S.A.K. is a co-inventor of multiple patents related to angiogenic proteins for the diagnosis and therapy of preeclampsia. These patents have been licensed to multiple companies. S.A.K. reports having served as a consultant to Roche and
Beckman Coulter and has financial interest in Aggamin LLC. I.E.S. reports no conflicts.

REFERENCES


See related article, “Elevated Soluble Flt1 Inhibits Endothelial Repair in PR3-ANCA–Associated Vasculitis,” on pages 155–164.

Sodium Intake, ACE Inhibition, and Progression to ESRD

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