The pathophysiology of multiple disease states, including sepsis,2,3 hypertension,4 atherosclerosis,5-5 and ischemia-reperfusion injury,6 is characterized by loss of the endothelial barrier function leading to the accumulation of plasma-borne proteins, tissue edema, and cell death. Importantly therapeutic strategies that inhibit loss of endothelial barrier function have typically focused on preventing endothelial activation,7 inhibiting endothelial cell free radical generation,8 and targeting intracellular kinases.9 Many studies demonstrate that upregulation or prevention of Rac1 inhibition during endothelial cell activation leads to preserved endothelial barrier function.11

In addition to edema, sepsis is characterized by endothelial activation, and the generation of microemboli attributed to the upregulation of the tissue factor–mediated clotting cascade further complicates the clinical course of sepsis.12 Preclinical studies have demonstrated that the cytokine cascade induced by sepsis adversely affects endothelial and intimal barrier functions.3 In addition to decreasing endothelial barrier function, the cytokine cascades have been shown to activate the clotting cascade through endothelial cell tissue factor expression.10 This upregulation of tissue factor can lead activation of the extrinsic coagulation cascade and, because of the generation of factors Xa and Va, the generation of thrombin (Figure). The potential therapeutic benefit of downregulating endothelial activation and thrombin generation has been demonstrated through the early use of activated protein C (Xigris) in patients with evidence of worsening sepsis.13

In this issue of Circulation, Aman et al14 further our understanding of the molecular mechanisms regulating the Rho family GTPase Rac1 and endothelial barrier function through their studies on the molecular effects of imatinib mesylate (Gleevec). Imatinib was first approved in 2001 and has shown clinical efficacy in the treatment of chronic myelogenous leukemia and gastrointestinal stromal tumors.15 It was designed to inhibit tyrosine kinases, including c-abl kinase, platelet-derived growth factor receptors, c-KIT, and discoid domain receptors 1 and 2.16 In an excellent example of translation medicine, Aman et al14 initiated their studies on the effects of imatinib and endothelial barrier function based on the observations of Overbeek et al,17 who reported observing resolution of interstitial edema after the administration of imatinib in a patient with suspected pulmonary veno-occlusive disease.

In their studies, Aman et al14 investigated through in vitro and in vivo models the effects of imatinib on microvascular perfusion, extravasation of fluid, and vascular leakage, concluding that imatinib has a direct protective effect on the endothelial barrier through its previously unrecognized effect of imatinib, inhibition of the abl-related gene (Arg) kinase, and the subsequent preservation of Rac1.14 In vitro studies using human umbilical vein endothelial cells demonstrated that imatinib inhibited endothelial leakage in response to vascular endothelial growth factor in a dose-dependent manner attributed to the preservation of cell-cell junctions and prevention of gap formation. Their studies identified a novel molecular effect of imatinib on endothelial cells, because the observed effects were mediated through inhibition of Arg kinase and preservation of Rac1 activity and endothelial barrier function. Small-interfering RNA knockdowns of known tyrosine kinases, platelet-derived growth factor receptor-α and -β, c-Abl, and discoid domain receptor 1, did not mimic the effects of imatinib on thrombin-induced endothelial barrier dysfunction, whereas knockdown of Arg did.

Murine models were used to demonstrate the protective effect of imatinib in vivo. Extravasation of fluid was evaluated with Evan blue. Of note, however, vascular leakage and pulmonary edema were compared between mice pretreated with imatinib or saline. Although significant benefits were noted in these experiments in mice pretreated with imatinib, the potential clinical relevance of this finding for patients with ongoing sepsis remained unclear. To address the clinical relevance, the investigators assessed the effects of imatinib treatment in animals with ongoing sepsis induced by cecal ligation and puncture. In this model, imatinib was administered 6 and 18 hours after induction of sepsis with assessment of vascular leakage by Evan blue dye extravasation. The study results demonstrated a significant attenuation of vascular leakage in the kidneys and the lungs 24 hours after the induction of sepsis.14

Editorial

Novel Mechanisms for Maintaining Endothelial Barrier Function in Sepsis

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The data from this study further define the molecular mechanisms associated with loss of endothelial barrier function in sepsis and the potential for imatinib inhibition of endothelial dysfunction through preservation of rac1 (Figure). The data further demonstrate a novel role for Arg kinase in inducing endothelial barrier dysfunction in sepsis. Beyond the specific effects of imatinib, these data further define the therapeutic potential of inhibiting thrombin in sepsis. The inhibition can either be through inhibition of thrombin generation (eg, with activated protein C) or specific downstream effects of thrombin, such as Arg kinase, as seen in the study by Aman et al.\textsuperscript{14} with imatinib (Figure).

The improvements observed in response to imatinib are in contrast to those obtained with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors. 3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors are known to aid in the maintenance of endothelial barrier function, yet the inhibition of 3-hydroxy-3-methylglutaryl coenzyme A reductase blocks geranylgeranylation and downstream translocation of RhoA and Rac1 to the cell membrane. Despite the downregulation of Rac1 activity, 3-hydroxy-3-methylglutaryl coenzyme A reductase has been shown to inhibit thrombin-mediated decreases in endothelial barrier function in vitro\textsuperscript{5,18} and in vivo.\textsuperscript{5} Whether this implies an as yet to be identified off-target effect of statin therapy or the inhibition of superoxide through the parallel inhibition of reduced nicotinamide-adenine dinucleotide phosphate oxidase remains to be determined.

On a cellular level, imatinib protects the endothelial barrier and may prevent edema formation in the setting of thrombin generation; however, it is interesting to note that periportal and pedal edemas are 2 of the most common adverse effects of chronic imatinib treatment.\textsuperscript{19,20} Clearly whether these and other adverse effects represent confounding or problematic consequences of off-target effects of imatinib on preservation of endothelial barrier function awaits further investigation. The authors hypothesize that duration of treatment and specific inhibition of Arg and c-abl in individual vascular beds may account for these findings. Given that treatment of sepsis with imatinib could be achieved with short-term use, it may lessen the potential for significant adverse effects attributed to inhibition of off-target kinases. Given the limited treatments options and the devastating consequences of significant loss of endothelial barrier function in sepsis, it would appear that further investigation may be warranted to determine whether this interesting preclinical study has identified real clinical potential.

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References


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