

inflamed blood vascular endothelium, although simultaneously, it may also impede lymphocyte egress from SLOs. Equally intriguing is that CLEVER-1 mediates adhesion of tumor cells to vascular and lymphatic endothelial cells,⁴ and thus may be a target for interfering with metastasis formation.

The work of Salmi et al raises several questions: How does CLEVER-1 “know” when to help lymphocytes move from abluminal to luminal and vice-versa? What factors contribute to CLEVER-1’s functional expression? Does CLEVER-1 distinguish trafficking of lymphocyte subsets? CLEVER-1 reportedly is a scavenger receptor for bacteria and advanced glycation end products. How does this function integrate into its role in lymphocyte trafficking?

● ● ● CLINICAL OBSERVATIONS / HEMOSTASIS

Comment on Nick et al, page 3878, and comment on Liaw et al, page 3958

APC: braking neutrophils to benefit patients?

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Higher plasma concentrations of activated protein C (APC) associate with improved survival during sepsis, and exogenous APC decreases neutrophil chemotaxis and recruitment, suggesting that the actions of APC on neutrophils may be a critical determinant of outcome during severe sepsis.

The observation that recombinant human activated protein C (rhAPC) improves survival among patients with severe sepsis¹ has intensified interest in the biology of APC in infection. Previous studies of endogenous APC were limited by the resolution of available assays. In the present issue, Liaw and colleagues used a more sensitive antibody capture assay system to accurately quantify APC concentrations in plasma samples from patients with severe sepsis. Circulating APC was detected in all patients. Liaw et al postulated that the variability in plasma APC concentrations may be due to differences in the ability to activate protein C and may be functionally significant. Consistent with this, APC concentrations were higher in plasma from patients who survived sepsis compared with those who did not. Alongside evidence that exogenous APC improves survival,¹ these results suggest that endogenous APC serves protective functions, and more is better, during severe sepsis.

While questions remain, means to regulate lymphocyte trafficking will lead to new therapies for many disabling diseases, and the findings of Salmi et al provide a solid foundation toward that end. ■

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trophils in a dose-response fashion. Therefore, rhAPC decreases the ability of human neutrophils to migrate toward chemokines in vitro and to an inflammatory site in vivo.

Excessive sequestration and emigration of neutrophils can contribute to tissue injury and the pathophysiology of sepsis. Is the ability of APC to decrease neutrophil recruitment responsible for the beneficial effects of endogenous and exogenous¹ APC during sepsis? Several facts bear consideration. First, it cannot be determined from these studies whether neutrophil recruitment is indeed diminished by APC during sepsis. A single instillation of lipopolysaccharide in the lungs differs meaningfully from severe systemic infection. Second, decreasing neutrophil recruitment may or may not benefit patients with severe sepsis. While neutrophils can damage tissue, they also kill bacteria. More than half of the patients in the study by Liaw et al were diagnosed with primary infections in the lung. Decreased neutrophil recruitment in the lungs, as in the study by Nick et al, could adversely affect pulmonary host defenses. Thus, the influence of APC on neutrophil recruitment may be beneficial or detrimental during infection, determined by the degree to which neutrophils are effecting tissue injury and bacterial killing, and by the degree to which tissue injury or bacterial burden is pathogenetic. Third, APC is more than just an inhibitor of neutrophil chemotaxis. Effects of APC on cells other than neutrophils (such as endothelial cells or monocytes) or on processes other than chemotaxis (such as coagulation, fibrinolysis, apoptosis, or gene expression) may significantly contribute to protection during infection. The studies in this issue of *Blood* demonstrate that APC associates with improved survival during severe sepsis and diminishes neutrophil recruitment. These important findings raise the question of whether endogenous and exogenous APC benefits patients with severe sepsis by limiting neutrophil recruitment. ■

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