Comment on Pendu et al, page 3746

Sticky business: von Willebrand factor in inflammation

José A. López  Puget Sound Blood Center

The molecular biology of inflammation takes a new turn with the report of Pendu and colleagues that von Willebrand factor binds leukocyte receptors mediating leukocyte rolling and firm adhesion.

The cardinal feature of inflammation is the migration of leukocytes from the blood into the tissue in response to chemical signals elaborated by extravascular cells or invading pathogens. These signals not only summon the leukocytes, they also prepare the endothelium to bind the leukocytes by inducing it to express adhesive molecules. Using these adhesion molecules, leukocytes decelerate by rolling; they then stop and migrate across the endothelial layer. Rolling is mediated by proteins of the selectin family that appear on the activated endothelium, either translocated immediately to the cell surface from storage granules (P-selectin) or synthesized de novo after several hours (E-selectin). The endothelial selectins bind a leukocyte counter-receptor known as P-selectin glycoprotein ligand-1 (PSGL-1). The rolling interaction slows the leukocytes and they become activated, partly through signals produced by ligation of PSGL-1. Activation changes the affinity of integrin αMβ2, which then binds endothelial counter-receptors, including ICAM-1, allowing the leukocytes to adhere firmly and exit the blood vessel. Activated platelets at sites of vessel injury also facilitate leukocyte emigration, binding both PSGL-1 and αMβ2 by virtue of high-density coatings of their respective counter-receptors, P-selectin and glycoprotein Ib.

This scenario now becomes even more complicated, with the findings of Pendu and colleagues that both PSGL-1 and αMβ2 can bind von Willebrand factor (VWF), as reported in this issue of the journal. PSGL-1 interacted weakly with VWF, accounting for transient contacts between unactivated leukocytes and VWF, whereas αMβ2 on activated leukocytes allowed them to adhere stably. Thus, one molecule, VWF, contains all of the determinants necessary to allow leukocytes to decelerate and stably adhere to a surface.

VWF is of particular interest because it is stored with P-selectin in endothelial Weibel-Palade bodies and is secreted in response to the same signals that externalize P-selectin. Earlier studies showed that VWF deficiency in mice lessened the inflammatory response in 3 diverse processes: wound healing, cytokine-induced meningitis, and atherosclerosis. These effects were interpreted as being due largely to the mispackaging and defective secretion of P-selectin associated with VWF deficiency. The new data indicate that VWF may contribute to inflammation by directly binding leukocytes.

The importance of this inflammatory mechanism is difficult to know. For one thing, VWF is quickly removed from the endothelial surface by the metalloproteinase ADAMTS13. Furthermore, even if VWF persists, leukocytes have to outcompete platelets, which outnumber them by up to 60-fold. The inflammatory role of VWF could thus be largely secondary, with the adherent, activated platelets providing a surface for leukocyte recruitment. In either case, VWF could recruit leukocytes when conditions favor the persistence of its hyperadhesive forms on the endothelial surface, as occurs under the influence of inflammatory cytokines, which not only stimulate VWF secretion but also inhibit its processing by ADAMTS13. It is of interest that VWF levels are elevated in both chronic and acute inflammation.

These interesting findings notwithstanding, the argument for whether VWF plays an active role in inflammation or merely serves as a nonspecific marker of its existence will ultimately be settled by astute clinical observation of patients with severe von Willebrand disease, with a particular emphasis on detecting defects in wound healing or enhanced susceptibility to infection.

The author declares no competing financial interests. The author is also affiliated with the University of Washington.

REFERENCES
Sticky business: von Willebrand factor in inflammation

José A. López