Editorial

For leukocytes to participate in control of local infection or repair of injured tissue they must leave the vasculature and emigrate to the affected tissue site. Abnormal accumulation of leukocytes in a variety of tissues contributes to inflammatory and autoimmune diseases. The widely accepted paradigm for leukocyte migration includes initial rolling of the leukocyte along the vessel wall, then firm adhesion to the wall, and finally emigration through the endothelial cell layer in a process known as diapedesis (1, 2). Rolling of PMNs is mediated by the interaction of a member of the selectin family of proteins with a specific carbohydrate ligand. Firm adhesion of PMNs is established by activation of a member of the β_2 (CD18) integrin family of proteins which then binds to a counterligand on the surface of the endothelial cell. Pathophysiologic accumulation of PMNs has been determined from animal models to play a role in a number of settings including ischemia/reperfusion injury, acute lung injury, meningitis and glomerulonephritis. In this issue of the *Journal*, Takada and colleagues report that in a rat model the early changes of kidney ischemia/reperfusion injury can be inhibited by infusion of soluble P-selectin glycoprotein ligand-1 (PSGL-1) (3).

The selectin family of cell adhesion molecules has three members. L-selectin is expressed constitutively on PMNs, monocytes, eosinophils, and some subsets of B and T cells. P-selectin is constitutively present in the α-granules of platelets and the Weibel Palade bodies of endothelial cells and is rapidly translocated to the cell surface when release of these storage granules is induced by thrombogenic or inflammatory stimuli. P-selectin surface expression is generally short lived although P-selectin expression can be upregulated in endothelial cells by transcription of mRNA in response to TNFα or IL-3 resulting in more chronic exposure. E-selectin expression is limited to endothelial cells. It is expressed in response to inflammatory stimuli, for example IL-1β, TNFα, and IFN-γ, and requires new protein synthesis for expression. The selectins share a common domain structure composed of an amino-terminal calcium-dependent lectin domain, an epidermal growth factor–like domain, two to nine domains with homology to domains in complement binding proteins, a transmembrane domain, and a carboxy-terminal cytoplasmic tail. This structural homology is reflected in the specific carbohydrate ligands to which they bind. While all of the selectins recognize the tetrasaccharides sialyl-Lewis^x and sialyl-Lewis^a, definitive identification of true, biologically relevant ligands for selectins has been difficult. Of the putative selectin ligands thus far identified, PSGL-1, a membrane-bound glycoconjugate, best fits the criteria for a specific ligand (4). Although PSGL-1 binds with relative selectivity to P-selectin, it is also recognized by the other members of the selectin family, L-selectin and E-selectin. The requirements for P- and L-selectin binding to PSGL-1 are more stringent than those for E-selectin binding. PSGL-1 bearing sialyl-Lewis^x will bind to E-selectin. Binding to P- or L-selectin requires that PSGL-1 be further posttranslationally modified by tyrosine sulfation in the amino terminus of the protein.

The role of P-selectin in ischemia/reperfusion injury has been explored previously in rabbit ear and feline myocardium models. These earlier studies used infiltration of PMNs into the affected tissue, extent of tissue necrosis, and loss of tissue function as indicators of ischemia/reperfusion injury. In their elegant study of ischemia/reperfusion injury in the rat kidney, the investigators have developed a richer description of the cellular and molecular sequelae in the early hours and up to 7 d after injury (3). Upregulation of E-selectin and rapid migration of PMNs into the organ, upregulation of ICAM-1 and complement component C3 mRNA, lymphocyte and macrophage infiltration, infiltration of $CD4^+$ lymphocytes and MHC class II expression, and the appearance of T cell–derived cytokines, chemoattractants, and macrophage-derived products are all features of the response to this injury.

In this study, soluble PSGL-1 was used to inhibit selectin-mediated events. Administration of soluble PSGL-1 during ischemia and 3 h after reperfusion diminished all of the cellular and molecular responses, some to control levels. Morphologic examination showed decreased renal damage, and renal function was also preserved. Soluble PSGL-1 truncated by removal of an amino-terminal decapeptide containing the site of PSGL-1 tyrosine sulfation (5) was ineffective in blocking PMN influx and induction of E-selectin upregulation in response to ischemia/reperfusion injury (3). E-selectin, but not L- or P-selectin, binds to this truncated form of PSGL-1. These data are used to suggest that inhibition by soluble PSGL-1 of the early phases of ischemia/reperfusion injury in the kidney is mediated through its binding to P-selectin (3). A role for E-selectin may be excluded by these results. A role for L-selectin cannot be rejected based upon the data presented. L-selectin may increase PMN recruitment to the affected site through binding of PMN-associated PSGL-1 to PMN-associated L-selectin. Secondary PMN recruitment through PSGL-1–L-selectin interaction will be abrogated by agents that interfere with the prerequisite PMN recruitment through PSGL-1–P-selectin interaction.

In other models of ischemia/reperfusion injury, antibodies directed against CD18 or against ICAM-1, an endothelial cell surface ligand for CD18, significantly inhibit tissue injury. These results fit the paradigm for PMN extravasation described above. Pharmacologic intervention in one of the steps of PMN extravasation may prove to be a useful strategy to ameliorate the transient dysfunction that follows ischemia/reperfusion in the setting of kidney or other organ transplant. Will it be preferable to target P-selectin– or CD18-mediated events? Ultimately the answer to this question must be experimentally determined but several factors argue on the side of intervention in selectin-mediated events. Treatment with anti-CD18 antibodies has been shown in some animal models to lead to increased risk of infection. Mice lacking a single member of the selectin family have not shown increased risk of infection but

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mice lacking both E- and P-selectin do demonstrate a susceptibility to opportunistic infections (6). Thus, intervention which targets only P-selectin may prove advantageous. Selectin expression is restricted to the vasculature; intervention in selectin-mediated events may have fewer side effects. Finally, prevention of leukocyte rolling interferes with what is believed to be the first event in the inflammatory cascade after ischemia/reperfusion and may thus be most effective in preventing tissue injury.

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