

Protective role of human recombinant p-selectin glycoprotein ligand-1 immunoglobulin chimera (rPSGL-Ig) on amelioration of intestinal ischemia/reperfusion-induced intestinal hyperpermeability and lung injury

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All three selectin family members (P, E and L) have been implicated as mediators of leukosequestration caused local or distant ischemia/reperfusion (I/R) injury. We hypothesized that treatment with recombinant P-selectin glycoprotein-Ig chimera (rPSGL-Ig), a homodimeric mucin which can bind P selectin, would ameliorate intestinal mucosal hyperpermeability in a rat model of superior mesenteric artery (SMA) occlusion and reperfusion. Four groups of animals were studied (n=6/group): (1) sham; (2) I/R (60 min I/60 min R); (3) I/R with rPSGL-Ig (0.4 mg/kg i.v. bolus) administered 5 min prior to I and 1 min prior to R (Protocol 1); and (4) I/R with rPSGL-Ig (0.4 mg/kg i.v. bolus) administered 5 min prior to I and 1 min prior to R plus a continuous infusion of rPSGL-Ig (0.4 mg/kg/h) (Protocol 2). Intestinal permeability was assessed using an everted gut sac technique

by measuring the mucosal-to-serosal clearance of FITC-dextran (M.W.=4 kDa). Both protocols provided early protection of ischemia- and I/R-induced mucosal barrier dysfunction, but only Protocol 2 provided durable protection. Mucosal (but not serosal) blood flow of rats treated with Protocol 2 was higher than that of control rats and Protocol 1-treated rats. Polymorphonuclear leukocytes (PMN) influx into the intestinal tissue was prevented by both Protocols. To evaluate remote lung injury, FITC-albumin (M.W.=70 kDa; 5 mg/kg, i.v. bolus) was employed as a marker of pulmonary capillary permeability (n=6/group). Bronchoalveolar lavage (BAL) of the right lung was obtained at the end of R. Peripheral blood leukocytosis was found in control and Protocol 1 groups. Although pulmonary capillary hyperpermeability was not detected in any of the groups,

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intralveolar sequestration of PMNs was prevented by Protocol 2. These data indicate that; 1) selectins play a role of pathogenesis of I/R-induced gut mucosal hyperpermeability, 2) intra-alveolar influx PMNs may be the earliest sign of I/R-induced lung injury.