Endothelial cell-surface tissue transglutaminase inhibits neutrophil adhesion by binding and releasing nitric oxide

Nitric oxide (NO) produced by endothelial cells in response to cytokines displays anti-inflammatory activity by preventing the adherence, migration and activation of neutrophils. The molecular mechanism by which NO operates at the blood-endothelium interface to exert anti-inflammatory properties is largely unknown. Here we show that on endothelial surfaces, NO is associated with the sulfhydryl-rich protein tissue transglutaminase (TG2), thereby endowing the membrane surfaces with anti-inflammatory properties. We find that tumor necrosis factor-α-stimulated neutrophil adherence is opposed by TG2 molecules that are bound to the endothelial surface. Alkylation of cysteine residues in TG2 or inhibition of endothelial NO synthesis renders the surface-bound TG2 inactive, whereas specific, high affinity binding of S-nitrosylated TG2 (SNO-TG2) to endothelial surfaces restores the anti-inflammatory properties of the endothelium, and reconstitutes the activity of endothelial-derived NO. We also show that SNO-TG2 is present in healthy tissues and that it forms on the membranes of shear-activated endothelial cells. Thus, the anti-inflammatory mechanism that prevents neutrophils from adhering to endothelial cells is identified with TG2 S-nitrosylation at the endothelial cell-blood interface.