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Endothelial nitric oxide synthase protects aortic allografts from the development of transplant arteriosclerosis.

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BACKGROUND: Inducible nitric oxide synthase (iNOS) is up-regulated in rejecting allografts and is protective against allograft arteriosclerosis; it suppresses neointimal smooth muscle cell accumulation and inhibits adhesion of platelets and leukocytes to the endothelium. However, the functional importance of endothelial NOS (eNOS) in the rejecting allografts remains unclear.

METHODS: We examined the effects of selective eNOS deficiency in aortic allografts in a murine chronic rejection model using grafts from eNOS knockout (KO) mice (C57BL/6 background; H2b) and normal C3H (H2K) as recipients. Grafts from wild-type C57BL/6 mice served as controls. Grafts from iNOS KO mice served as a second group of controls where the contribution from iNOS was eliminated but eNOS was preserved. Aortic grafts were harvested and analyzed at days 10-14, 18-22, and 26-30 after transplantation. **RESULTS:** Endothelial NOS-deficient grafts showed significantly increased intima/media ratios at days 26-30 compared to controls. Immunostaining demonstrated that in eNOS KO grafts, eNOS was not detectable whereas iNOS was expressed prominently in infiltrating recipient mononuclear cells. In control grafts, eNOS expression was preserved in the endothelium even by day 30, and associated with a decrease in intimal thickening. We further demonstrated that early overexpression of iNOS by ex vivo gene transfer completely prevented the development of arteriosclerosis associated with eNOS deficiency. **CONCLUSIONS:** We found that eNOS plays a protective role in allografts, and that in eNOS-deficient allografts, early overexpression of iNOS is capable of preventing the development of allograft

arteriosclerosis. In allografts with dysfunctional vascular endothelium and impaired eNOS activity as a result of ischemia or native arteriosclerotic disease, iNOS gene therapy may serve to improve their long-term survival and function.

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