Mycophenolate acid inhibits endothelial NAD(P)H oxidase activity and superoxide formation by a Rac1-dependent mechanism.

Endothelial dysfunction precedes hypertension and atherosclerosis and predicts cardiac allograft vasculopathy and death in heart transplant recipients. Endothelial overproduction of reactive oxygen species, such as superoxide anions produced by NAD(P)H oxidase, induces endothelial dysfunction. Because immunosuppressive drugs have been associated with increased reactive oxygen species production and endothelial dysfunction, we sought to elucidate the underlying mechanisms. Reactive oxygen species, release of superoxide anions, and NAD(P)H oxidase activity were studied in human umbilical vein endothelial cells and in polymorphonuclear neutrophils. Gp91ds-tat was used to specifically block NAD(P)H oxidase. Transcriptional activation of different subunits of NAD(P)H oxidase was assessed by real-time RT-PCR. Rac1 subunit translocation and activation were studied by membrane fractionation and pull-down assays. Calcineurin inhibitors significantly increased endothelial superoxide anions production because of NAD(P)H oxidase, whereas mycophenolate acid (MPA) blocked it. MPA also attenuated the respiratory burst induced by neutrophil NAD(P)H oxidase. Because transcriptional activation of NAD(P)H oxidase was not affected, but addition of guanosine...
restored endothelial superoxide anions formation after MPA treatment, we speculate that the inhibitory effect of MPA was mediated by depletion of cellular guanosine triphosphate content. This prevented activation of Rac1 and, thus, of endothelial NAD(P)H oxidase. Because all heart transplant recipients are at risk for cardiac allograft vasculopathy development, these differential effects of immunosuppressants on endothelial oxidative stress should be considered in the choice of immunosuppressive drugs.

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