Phosphatidylinositol 3-Kinase and Xanthine Oxidase Regulate Nitric Oxide and Reactive Oxygen Species Productions by Apoptotic Lymphocyte Microparticles in Endothelial Cells

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Résumé en anglais	Microparticles (MPs) are membrane vesicles released during cell activation and apoptosis. We have previously shown that MPs from apoptotic T cells induce endothelial dysfunction, but the mechanisms implicated are not completely elucidated. In this study, we dissect the pathways involved in endothelial cells with respect to both NO and reactive oxygen species (ROS). Incubation of endothelial cells with MPs decreased NO production that was associated with overexpression and phosphorylation of endothelial NO synthase (eNOS). Also, MPs enhanced expression of caveolin-1 and decreased its phosphorylation. Microparticles enhanced ROS by a mechanism sensitive to xanthine oxidase and P-IκBα inhibitors. PI3K inhibition reduced the effects of MPs on eNOS, but not on caveolin-1, whereas it enhanced the effects of MPs on ROS production. Microparticles stimulated ERK1/2 phosphorylation via a PI3K-depedent mechanism. Inhibition of MEK reversed eNOS phosphorylation but had no effect on ROS production induced by MPs. In vivo injection of MPs in mice impaired endothelial function. In summary, MPs activate pathways related to NO and ROS productions through PI3K, xanthine oxidase, and NF-κB pathways. These data underscore the pleiotropic effects of MPs on NO and ROS, leading to an increase oxidative stress that may account for the deleterious effects of MPs on endothelial function.
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