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Basic Science Aspects

Mitochondrial Complex III Is Involved in Proapoptotic Bak-Induced Microvascular Endothelial Cell Hyperpermeability

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Abstract

It has been shown that the intrinsic mitochondrial apoptotic cascade is activated in vascular hyperpermeability after conditions such as hemorrhagic shock. Studies from our laboratory demonstrated mitochondrial reactive oxygen species (ROS) formation in endothelial cells during vascular hyperpermeability. We hypothesized that the participation of mitochondrial ROS in the intrinsic apoptotic cascade results in microvascular endothelial cell hyperpermeability. The purpose of this study was to identify the site(s) of ROS formation in the mitochondrial complex(es) that leads to hyperpermeability. Rat lung microvascular endothelial cell monolayers were pretreated with inhibitors of the complex(es) (I-V) before the activation of the mitochondrial apoptotic cascade using the proapoptotic peptide BAK (BH3). Inhibitors of the xanthine oxidase, nicotinamide adenine dinucleotide phosphate (reduced form) oxidase, NOS, and cytochrome P-450 monooxygenase were also studied. The hyperpermeability was determined by the fluorescence of fluorescein isothiocyanate-albumin that leaked across endothelial cells and ROS production by 2',7'-dichlorofluorescein diacetate. Cytochrome *c* levels were also measured. BAK (BH3)-transfected cells showed increased ROS, cytosolic cytochrome *c*, and hyperpermeability ($P < 0.05$). Complex III inhibitors antimycin A (10 μM) and stigmatellin (10 μM) attenuated BAK (BH3)-mediated ROS formation and hyperpermeability ($P < 0.05$). The complex III inhibition decreased BAK (BH3)-mediated cytochrome *c* release. The results suggest that mitochondrial ROS formation, particularly at respiratory chain complex III, is involved in BAK-induced monolayer hyperpermeability.

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