The role of oxidative stress in apoptosis

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Abstract

Thymocytes undergo negative and positive selection during their development in the thymus. During this selection process, the majority of thymocytes are eliminated by apoptosis. In the first part of this dissertation, I examined the role of oxidative stress in thymocyte apoptosis. My initial observations show that thymocytes require molecular oxygen to undergo apoptosis, and treatment with N-acetyl-L-cysteine (NAC), a thiol antioxidant, inhibits thymocyte apoptosis *in vivo* as well as *ex vivo*. Various apoptosis-inducing stimuli increase intracellular hydrogen peroxide (H_2O_2) levels in thymocytes *ex vivo*, and treatment with NAC reduces the levels of intracellular H_2O_2 during apoptosis. The degree of reduction of H_2O_2 by NAC correlates well with the decrease of apoptosis, except in cells treated with γ-irradiation. These results indicate that the level of intracellular H_2O_2 influences a cell's vulnerability to undergo apoptosis under many conditions, but not all. I also show that cell death-related mitochondrial events are attenuated by NAC treatment in protected cells. By using various inhibitors of the mitochondrial electron transport chain, I identified the production site for H_2O_2 under all apoptosic conditions tested as complex III of the mitochondria. The results show that when the inhibitors decrease the production of H_2O_2 at the mitochondria, the mitochondrial cell death events are also significantly reduced under all conditions. I also show that the production of H_2O_2 and the mitochondrial cell death events are controlled by proteosomal activities during thymocyte apoptosis. ^ The second part of this dissertation focused on the role of hyperbaric oxygen (HBO) in enhancing apoptosis and/or suppressing cellular proliferation. This study provides evidence that HBO treatment increases intracellular H_2O_2, which is partly responsible for enhancing apoptosis in HL-60 cells, a granulocytic cell line. Since HBO is effective in treating chronic wounds, these results suggest HBO may exert its beneficial effect by inducing apoptosis in neutrophils, known to mediate chronic inflammation. I also provide a piece of evidence that exposure to HBO can stop the proliferation of breast cancer cells at various stages of the disease. This could be due to abrogated antioxidative defense mechanisms, which are commonly found in rapidly dividing cells. ^

Subject Area

Cellular biology|Immunology

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