PL-3

THE CYTOTOXIC ACTIVITY OF ANTHRAX LETH TOXIN IS INHIBITED BY PHOSPHOLIPASE A_2 INHIBITORS

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The molecular mechanism of cytotoxic effect exerted by the lethal toxin (LeTx) of *Bacillus anthracis* is not well understood. In the present study, using primary culture of mouse peritoneal macrophage, we have investigated possible cytotoxic mechanisms. LeTx was not found to induce high-level of nitric oxide (NO) production for NO-mediated toxicity. Fragmentation of DNA, a biochemical marker of apoptosis, was not observed in LeTx treated cells. Pretreatment of cells with antioxidants such as melatonin and dehydroepiandrosterone (DHEA) did not protect the LeTx-induced cytotoxicity. However, addition of phospholipase A_2 (PLA_2) inhibitors (quinacrine, bromophenacyl bromide, manoalide, butacaine) to the culture medium resulted in the inhibition of cytotoxicity of LeTx in a dose-dependent manner. LeTx-induced cytotoxicity was also inhibited by the tyrosine-specific protein kinase inhibitor genistein, but not by the protein kinase C inhibitor staurosporine or H-7. The results of these studies indicate a role for PLA_2 and protein kinase in the cytotoxic mechanism of macrophages by anthrax lethal toxin.