The Role of Endozepine (t-ACBP) in Ceramide-induced Apoptosis

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Ceramide is a key component of the sphingolipid signalling pathway. Intermediary metabolites of ceramide catabolism are thought to play a role in cellular responses such as cell cycle arrest, cell differentiation and apoptosis. Using promoter-trap retroviral mutagenesis we have generated somatic cell mutants that are resistant to ceramide-induced apoptosis.

Characterisation of one of these mutants demonstrated that a gene coding for 10 kD acyl CoA binding protein called endozepine was inactivated by retroviral integration, resulting in the loss of expression of this gene. Recent studies implicated endozepine in apoptosis since this protein was co-released together with known pro-apoptotic proteins from mitochondria during the opening of the permeability transition pore. Here we demonstrate that loss of expression of this protein leads to resistance to apoptosis whereas the introduction of this protein into cells, using protein transduction methods, activates apoptosis. An investigation into mitochondrial membrane potential (MMP) changes in this mutant, following induction of apoptosis with ceramide and shows a decreased reduction of MMP, which may result from reduced endozepine levels. Data also show that resistance to apoptosis coincides with reduced caspase-3 activity. Studies on the binding capacity of endozepine for palmitoyl-CoA and ceramide have been undertaken using heteronuclear NMR to determine the role of endozepine in ceramide signalling, and these results lead to the alternative hypothesis, that endozepine is required for the ceramide biosynthetic pathway, perhaps as an amplification step during apoptosis.