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Regulation of Apoptosis by a Novel Factor, CIA

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Various apoptotic stimuli activate cytoplasmic signaling cascades that eventually lead to nuclear DNA fragmentation, a biochemical characteristic of apoptosis. In the present study, we identified an anti-apoptotic CAD inhibitor interacting with ASK1 (CIA), which inhibits both cytoplasmic JNK/SAPK signaling cascades activated by apoptosis signal-regulating kinase 1 (ASK1) and nuclear DNA fragmentation mediated by caspase-acitvated DNase (CAD/DFF40/CPAN). The CIA transcript is expressed in a variety of mouse tissues including heart, brain, liver, kidney, and testis. CIA directly interacted with ASK1 and suppressed ASK1 activation *in vitro* and in cultured cells. Interestingly, CIA also physically associated with CAD, and inhibited an nuclease activity of CAD. Furthermore, overexpressed CIA inhibited the caspase-3-activated DNA fragmentation in human embryonic kidney 293 cells. 293 cells stably expressing CIA were resistant to apoptosis induced by various cellular stresses. The association of CIA to ASK1 occurred in the cytoplasm while CIA interacted with CAD in the nuclei. In addition, CIA translocated into nuclei in response to tumor necrosis factor (TNF) while sequestered in cytoplasm in cells undergoing apoptosis induced by TNF and actinomycin D. Collectively, our data suggest that CIA blocks both the cytoplasmic ASK1 activation and nuclear DNA fragmentation during apoptosis.