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Cytochrome *c*: An old protein controlling life and death since the dawn of time

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Cytochrome *c* (C*c*), a small soluble hemeprotein, is highly conserved along evolution. In mammals, C*c* plays a dual role in cell life and death: Under homeostatic conditions, C*c* is retained inside the mitochondria and acts as an electron shuttle in the electron transfer respiratory chain. Upon apoptotic stimuli, however, C*c* is released into the cytoplasm so as to serve as an essential key factor by binding to Apaf-1 and further assemblying the apoptosome, the machinery responsible for activation of caspases[1]. The mitochondria-to-cytoplasm C*c* translocation has been long considered as a random event, although it is an evolutionarily conserved process even in organisms in which the apoptosome assembly is independent of C*c* or in which the apoptosome is missing. These findings, along with the fact that apoptosis remains active in Apaf-1 knockout mutants but not in C*c* knockout mutants[2,3], lead one to wonder if cytoplasmic C*c* could play other putative signaling functions.

To better understand the role of C*c* in the onset of apoptosis and to harmonize the different phenotypes of Apaf-1 and C*c* knockout mutants, we have developed a proteomic approach based on affinity chromatography with human C*c* as bait. A total of 24 C*c* partners in human cell extracts, respectively, have been identified. Their *in vivo* interaction with C*c* and cellular localization were further analyzed by BiFC and further corroborated by *in vitro* NMR and SPR assays. Altogether, our results open a new way to understand the C*c*-dependent activation and progression of programmed cell death in human cells.

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