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Mechanistic Insights into the Regulation of Mitochondrial Fission by Cyclin C

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Mechanistic insights into the regulation of mitochondrial fission by cyclin C.

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Cyclin C is a component of the mediator complex of RNA polymerase II that localizes to the nucleus under normal conditions. In response to stress, cyclin C translocates to the cytosol and mitochondria and mediates stress-induced mitochondrial fission and apoptosis. The molecular mechanisms by which cyclin C induces mitochondrial fission are unknown. Using in vitro experimental approaches, we sought to investigate the mechanistic basis of cyclin C mediated mitochondrial fission. We found that recombinant cyclin C and Drp1, the dynamic-like GTPase that produces mitochondrial scission, directly interact with each other without the requirement of any accessory proteins. This interaction requires the C-terminal 120 amino acids of cyclin C independent of the cyclin Box motif that directs Cdk binding. Upon heterologous expression, the GFP tagged carboxyl terminal domain localized to mitochondria and induced mitochondrial fission in cyclin C null MEF cells even in the absence of stress. On the contrary, the N-terminal 250 amino acid cyclin box domain is responsible for the nuclear retention of cyclin C under normal conditions and cannot induce stress-induced mitochondrial fission. The GTPase domain of Drp1 is an important site of interaction between Drp1 and cyclin C. Using size-exclusion chromatography and native-PAGE, we found that cyclin C reduces the oligomerization of Drp1 in solution. This is accompanied by a concomitant decrease in Drp1 GTPase activity in the presence of lipids. The ability of cyclin C to depolymerize Drp1 is enhanced by GTP and GTP analogs. We hypothesize that cyclin C

depolymerizes inactive multimeric Drp1 in solution enabling the interaction of Drp1 with the mitochondrial fission machinery to facilitate mitochondrial fission.