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Translocation of Cyclin C During Oxidative Stress Is Regulated by Interactions with Multiple Trafficking Proteins

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Translocation of cyclin C during oxidative stress is regulated by interactions with multiple trafficking proteins.

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Eukaryotic cells take cues from their environment and interpret them to enact a response. External stresses can produce a decision between adjusting to behaviors which promote surviving the stress, or enacting a cell death program. The decision to undergo programmed cell death (PCD) is controlled by a complex interaction between nuclear and mitochondrial signals. The mitochondria are highly dynamic organelles that constantly undergo fission and fusion. However, a dramatic shift in mitochondrial morphology toward fission occurs early in the PCD process. We have identified the transcription factor cyclin C as the biochemical trigger for stress-induced mitochondrial hyper-fragmentation in yeast (Cooper et al., 2014 Dev. Cell) and mammalian (Wang et al., 2015, MCB) cells. In response to PCD stimuli such as oxidative stress, cyclin C is released from the nucleus and associates with the mitochondrial fission machinery. Loss of cyclin C prevents mitochondrial fission while its ectopic introduction into the cytoplasm induces complete fragmentation in the absence of stress. Many of the details of the control of cyclin C localization within the cell have not been elucidated.
To initially investigate the regulation of cyclin C translocation events in S. cerevisiae, a two hybrid screen was used. We have identified multiple conserved trafficking proteins which interact with cyclin C. These

include Gea1/2 and multiple components of the TRAPPII complex, both of which act as guanosine exchange factors (GEFs) for small GTPase regulators of vesicle traffic (Arf1/2 and Ypt31/32 respectively). Arf1 and its homolog Arf2 also mediate mitochondrial dynamics and contact with the ER. Gea2 interaction with cyclin C was confirmed by co-immunoprecipitation, and fluorescence microscopy data also indicates that the two proteins can colocalise. The use of conditional mutants has revealed that upon loss of functional Gea1/2 or Arf1/2, cyclin C is translocated to the cytosol without stress. Following from this we propose a model in which the protein trafficking machinery acts to keep cyclin C in the nucleus during healthy cell maintenance.