

Mitochondrial active Ras2 protein promotes apoptosis and regulated cell death in a cAMP/PKA pathway-dependent manner in budding yeast.

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Abstract:

In previous papers, using the eGFP-RBD3 probe, which binds Ras-GTP with high affinity, we showed that activated Ras proteins are localized to the plasma membrane and in the nucleus in wild-type *Saccharomyces cerevisiae* cells growing exponentially on glucose, while an aberrant accumulation of activated Ras in mitochondria correlates to mitochondrial dysfunction, accumulation of ROS and an increase of apoptosis. Now we show that lack of *TPS1*, known to trigger apoptosis in *S. cerevisiae*, induces localization of active Ras proteins in mitochondria, confirming the above-mentioned correlation. Next, by characterizing the *ras1Δ* and *ras2Δ* mutants, we show that active Ras2 proteins, which accumulate in the mitochondria following addition of acetic acid (a pro-apoptotic stimulus), are likely the GTPase involved in regulated cell death, while active Ras1 proteins, constitutively localized in mitochondria, might be involved in a pro-survival molecular machinery. Finally, by characterizing the *gpa2Δ* and *cyr1Δ* mutants, we show that active mitochondrial Ras proteins promote apoptosis through the cAMP/PKA pathway.