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Old yellow enzyme2 (OYE2), a key mediator of oxidative stress and programme cell death in yeast

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Abstract

Programmed cell death (PCD) has been documented not only in higher organisms but also bacteria and yeast. Proteins of the Bcl-2 family are important regulators of mammalian cell life and death, with some functioning to prevent (Bcl-2) and others to promote (Bax) apoptosis. Old yellow enzymes (OYE) group of FMN- oxidoreductases has been extensively characterized with regard to biochemical catalysis but little information exists on the biological functions of these proteins. In a genetic screen to identify modifiers of Bax dependent lethality in yeast, the C-terminus of OYE2 was isolated based on its capacity to restore sensitivity to a Bax-resistant yeast mutant strains.

Overexpression of full length OYE2 suppresses Bax lethality in yeast, lowers endogenous reactive oxygen species (ROS), increases resistance to H2O2-induced programmed cell death (PCD) and significantly lowers ROS levels generated by organic prooxidants. Reciprocally, Δoye2 yeast strains are sensitive to prooxidant-induced PCD. Overexpression and knockout analysis indicates these OYE2 antioxidant activities are opposed by OYE3, a highly homologous heterodimerizing protein, which functions as a prooxidant promoting H2O2-induced PCD in wild type yeast. OYE3 requires the presence of OYE2 to promote cell death, since the deletion of the 12 C-terminal amino acids and catalytic inactivation of OYE2 by a Y197F mutation enhance significantly survival upon H2O2- induced PCD in wild type cells, but accelerate PCD in Δoye3 cells, implicating the oye2p-oye3p heterodimer for promoting cell death upon oxidative stress. Unexpectedly, a strain with a double knockout of these genes (Δoye2 oye3) is highly resistant to H2O2-induced PCD, exhibits increased respiratory capacity, and undergoes less cell death during the adaptive response in chronological aging. Simultaneous deletion of OYE2 and other antioxidant genes hyperinduces endogenous levels of ROS, promoting H2O2-induced cell death and sensitize towards αβ-unsaturated aldehydes (acrolein and methylvinyl ketone: in Δoye2 glr1 yeast high levels of oxidized glutathione (6 fold than wild type) elicited gross morphological aberrations involving the actin cytoskeleton, and defects in organelle partitioning. OYE cooperate in enhancing the survival with knockouts of mitochondrial apoptoic remarks regulators (Δaif1, Δcyc1) but not cytoplasmic and nuclear (Δyca1, Δnma111).

Based on this work, OYE proteins are firmly placed in the signaling network connecting ROS generation, PCD modulation and cytoskeletal dynamics in yeast.