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Poster Abstract – D.69

INTERACTIONS BETWEEN YEAST MITOCHONDRIAL AND NUCLEAR GENOMES: THE LYCORINE RESISTANCE IN THE RETROGRADE REGULATION

MADDALUNO L.*, PONTIERI P.*, MASSARDO D.R.*, SANSONE C.*, ESPOSITO B.*, ALIFANO P.**, DEL GIUDICE L.*

*) IGB "ABT" – CNR, Via P. Castellino 111, 80131 Naples (Italy)
**) DiSteBa, University of Salento, Via Monteroni, 73100 Lecce (Italy)

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Mitochondrial (mt) genomes of the yeast *Saccharomyces cerevisiae* can exist in different states: rho^+ (wild-type), mit^- (mt point mutations), rho^- (partial deletions of mtDNA), and rho^0 (entirely lacking mtDNA). Cells are able to monitor and to respond to the different functional states of their organelles. Yeast cells respond to mitochondrial dysfunction by altering the expression of a subset of nuclear genes. This response, called retrograde regulation, functions to better adapt cells to mitochondrial defects (Butow and Avadhani, 2004). In derepressed, respiratory-deficient cells, the expression of genes involved in anaplerotic pathways, transport of small molecules, peroxisomal activities, and stress response are up-regulated. Expression of these genes is activated in cells lacking mitochondrial function by involvement of *RTG1*, *RTG2*, and *RTG3* genes whose protein products bind to "R-boxes" in the promoter region. Rtg2p plays a pivotal role in the retrograde pathway because it is both a sensor of the functional state of mitochondria and is required for the activation of RTG-dependent gene expression by promoting the cytoplasmic-to-nuclear translocation of Rtg1p and Rtg3p.

Previously we have demonstrated that the lycorine, an alkaloid of the family of Amaryllidaceae, is able to differentiate between cells devoid of mtDNA (rho^0) and cells with mtDNA, either rho^+ or mit^- or rho^-. Wild-type rho^+ cells, rho^- cells, and mit^- cells are all sensitive to lycorine; rho^0 cells, however, are resistant to high concentrations of the drug. Since rho^0 strains, lacking the entire mitochondrial genome, are in the higher dysfunctional mitochondrial status, we have analysed a retrograde regulation process by lycorine resistance in rho^0 cells. To this aim, we have analyzed the growth of rho^0 *Δrtg* strains, deleted in *RTG* genes, in presence of lycorine. We found that rho^0 *Δrtg* mutants, lacking of the RTG retrograde regular products, were sensitive to lycorine as well as rho^+ yeast strains. Our data on lycorine point to a signalling of mitochondria to nucleus. Since the growth of rho^+ cells is inhibited in presence of lycorine both in glucose and glycerol medium, it could be hypothesized that in rho^0 cells the dysfunctional mitochondrial status stimulates overexpression of nuclear genes very likely involved in both nuclear and mtDNA replication.

A principal candidate among the latter nuclear genes is the mtDNA poly γ gene. It has been hypothesized an additional role of mtDNA poli γ protein besides mtDNA replication since it is stable in the absence of the entire mtDNA in rho^0 cells. In our case, the presence or the absence of mtDNA influences the expression of this gene(s) and it is mediated by the retrograde response, in

fact, we have shown that the lycorine-resistant phenotype is expressed in rho^0 strains only in the presence of RTG nuclear background (Del Giudice et al., 2005).

- Butow RA, Avadhani NG (2004). Mitochondrial Signaling: The Retrograde Response. Mol. Cell. 14: 1-15
- Del Giudice L. et al. (2005). Gene 354: 9-14

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