Learning from Yeast: *Saccharomyces cerevisiae* as a Model of Study for Cancer as a Mitochondrial Metabolic Disease

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INTRODUCTION: Emerging evidence indicates that cancer is primarily a mitochondrial metabolic disease. Mitochondria can control nuclear gene expression trough the retrograde signaling pathway (RTG). Due to genetic ('humanization' of yeast) and metabolic (Crabtree X Warburg) similarities between *Saccharomyces cerevisiae* and cancer cells, this microorganism has been often used for cancer research. **OBJECTIVES:** Our goals are to evaluate: (i) whether the disruption of respiratory metabolism in *S. cerevisiae* could trigger irreversible respiratory-deficient *petite* mutagenesis with participation of RTG; (ii) the inhibitory effect of trehalose-6-phosphate (T6P) over the phosphorylation capacity of yeast hexokinases. **MATERIAL AND METHODS:** WT or *rtg2*Δ cells were grown in glucose (fermentative) or glycerol media (oxidative metabolism) and treated with oxidative phosphorylation inhibitors. Percentage of *petite* was evaluated using the tetrazolium (TTC) agar overlay technique. The inhibitory effect of T6P was assessed by measuring hexokinase activity in the presence or absence of T6P in cell extracts of mutant *S. cerevisiae* that lacks HXK1, HXK2 or GLK1. **RESULTS AND DISCUSSION:** Antimycin A, which inhibits complex III, was able to generate *petites* even though irreversibility of the phenotype on the population has not yet been assessed. HXK2 deficiency decreased the specific growth rate during growth on glucose, showing that HXK2 plays an essential role in metabolic adaptation under glucose-repression conditions. T6P at 0.2 mM was found to inhibit phosphorylation capacity of yeast hexokinases in similar percentage under respiratory or fermentative conditions, even though the percentage was different in each mutant. **CONCLUSIONS:** Partial results indicate a link between oxidative phosphorylation impairment and irreversible glucose repression shown by *petites*, which resemble cancer cells. T6P might act a differential inhibitor of yeast hexokinases, raising the possibility that it might also inhibit human hexokinases in a similar way. We aim to inhibit selectively human hexokinase II, overexpressed in cancer cells and related to metabolic adaptation towards fermentation.

Keywords: *Saccharomyces cerevisiae*, Cancer, *Petites*, Trehalose-6-phosphate, Warburg effect
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