Rtg2p determinants residues of longevity in *Saccharomyces cerevisiae*

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INTRODUCTION: Rtg2p is a protein involved in the retrograde signaling, a communication pathway between mitochondria and nucleus in *Saccharomyces cerevisiae.* This protein has been associated with longevity in *S. cerevisiae* acting independently of its role in retrograde response, probably by suppression of extrachromosomal rDNA circles and also improvement of mitophagy. Rtg2p has a N-terminal domain very important for its role in retrograde signaling, yet the importance of this domain on longevity was not reported. **OBJECTIVE:** The objective of this study was to identify the structural determinants of Rtg2p, controlling the function of this protein in aging and retrograde response. **METHODS:** Thirteen point mutants were produced (*RTG2*-L56G, *RTG2*-E106A, *RTG2*-E106H, *RTG2*-R109E, *RTG2*-N113A, *RTG2*-E137A, *RTG2*-D158A, *RTG2*-T138A, *RTG2*-A160G, *RTG2*-G161A, *RTG2*-S163A, *RTG2*-Q165E, *RTG2*-Q165A) by site-directed mutagenesis, using rational design by decomposition of residues correlation networks (DRCN). The strains obtained for analysis of retrograde response were grown in both solid and liquid medium, in the presence or absence of glutamate, and *CIT2* gene expression was measured. To analyze longevity, replicative life span assays were performed in all strains. **RESULTS AND DISCUSSION:** Most mutations showed glutamate auxotrophy and presented a low expression of *CIT2*, with exception of strains *RTG2*-N113A, *RTG2*-G161A and *RTG2*-Q165A that showed a higher expression than *rtg2Δ* strain. Regarding replicative longevity of mutants, one can highlight the mutations *RTG2*-R109E, *RTG2*-E106A, *RTG2*-E106H and *RTG2*-E137A, even with a single amino acid change have a very similar replicative longevity phenotype as observed in *rtg2Δ* strain. Conversely, the *RTG2*-L56G mutant showed an increase in the minimum and maximum longevity compared to WT strain. **CONCLUSIONS:** In conclusion, our results demonstrate that the N-terminal domain is very important to the function of Rtg2p, both in longevity as well as in the retrograde response. They also show there are structural determinants in Rtg2p that control longevity in both dependent or independent manner of the communication between mitochondria and nucleus.

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