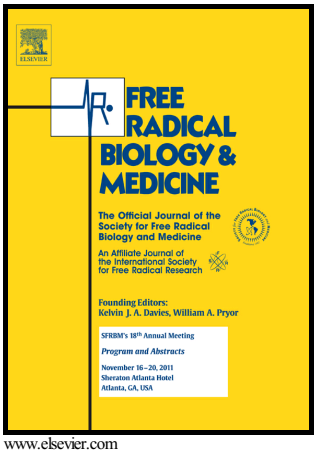
Physical interaction between the MAPK Slt2 of the PKC1-MAPK pathway and Grx3/Grx4 glutaredoxins is required for the oxidative stress response in budding yeast

Nuria Pujol-Carrion, Maria Angeles de la Torre-Ruiz



www.elsevier.com

PII: S0891-5849(16)31123-6
DOI: http://dx.doi.org/10.1016/j.freeradbiomed.2016.12.023
Reference: FRB13129

To appear in: *Free Radical Biology and Medicine*

Received date: 4 August 2016
Revised date: 2 December 2016
Accepted date: 18 December 2016

Cite this article as: Nuria Pujol-Carrion and Maria Angeles de la Torre-Ruiz Physical interaction between the MAPK Slt2 of the PKC1-MAPK pathway an Grx3/Grx4 glutaredoxins is required for the oxidative stress response in buddin y e a s t , *Free Radical Biology and Medicine* http://dx.doi.org/10.1016/j.freeradbiomed.2016.12.023

Physical interaction between the MAPK Slt2 of the PKC1-MAPK pathway and Grx3/Grx4 glutaredoxins is required for the oxidative stress response in budding yeast

Nuria Pujol-Carrion and Maria Angeles de la Torre-Ruiz*

Department of Basic Medical Sciences, IRB-Lleida. University of Lleida. Av. Alcalde Rovira Roure nº 80. 25198-Lleida

*Corresponding author: M. Angeles de la Torre-Ruiz. madelatorre@cmb.udl.cat

ABSTRACT

This study demonstrates that both monothiol glutaredoxins Grx3 and Grx4 physically interact with the MAPK Slt2 forming a complex involved in the cellular response to oxidative stress. The simultaneous absence of Grx3 and Grx4 provokes a serious impairment in cell viability, Slt2 activation and Rlm1 transcription in response to oxidative stress. Both *in vivo* and *in vitro* results clearly show that Slt2 can independently bind either Grx3 or Grx4 proteins. Our results suggest that Slt2 form iron/sulphur bridged clusters with Grx3 and Grx4. For the assembly of this complex, cysteines of the active site of each Grx3/4 glutaredoxins, glutathione and specific cysteine residues from Slt2 provide the ligands. One of the ligands of Slt2 is required for its dimerisation upon oxidative treatment and iron repletion. These interactions are relevant for the oxidative response, given that mutants in the cysteine ligands identified in the complex show a severe impairment of both cell viability and Slt2 phosphorylation upon oxidative stress. Grx4 is the relevant glutaredoxin that regulates Slt2 phosphorylation under oxidative conditions precluding cell survival. Our studies contribute to extend the functions of both monothiol glutaredoxins to the regulation of a MAPK in the context of the oxidative stress response.

Keywords: Signalling; glutaredoxins; MAPK; oxidative stress; PKC1 pathway; budding yeast; iron; cell survival