Title:	Glutathione degradation by the alternative pathway (DUG pathway) in Saccharomyces cerevisiae is initiated by (Dug2p-Dug3p)2 complex, a novel glutamine amidotransferase (GATase) enzyme acting on glutathione
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Keywords:	Gel-filtration chromatography Glutathiones Homodimerize
Issue Date:	2012
Publisher:	The American Society for Biochemistry and Molecular Biology, Inc
Citation:	Journal of Biological Chemistry, 287 (12), pp. 8920-8931.
Abstract:	The recently identified, fungi-specific alternative pathway of glutathione degradation requires the participation of three genes, DUG1, DUG2, and DUG3. Dug1p has earlier been shown to function as a Cys-Gly-specific dipeptidase. In the present study, we describe the characterization of Dug2p and Dug3p. Dug3p has a functional glutamine amidotransferase (GATase) II domain that is catalytically important for glutathione degradation as demonstrated through mutational analysis.Dug2p,whichhasan N-terminal WD40 and a C-terminal M20A peptidase domain, has no peptidase activity. The previously demonstrated Dug2p-Dug3p interaction was found to be mediated through the WD40 domain of Dug2p. Dug2p was also shown to be able to homodimerize, and this was mediated by itsM20Apeptidase domain. In vitro reconstitution assays revealed that Dug2p and Dug3p were required together for the cleavage of glutathione into glutamate and Cys-Gly. Purification through gel filtration chromatography confirmed the formation of aDug2p-Dug3pcomplex.Thefunctionalcomplex had a molecular weight that corresponded to (Dug2p-Dug3p) 2 in addition to higher molecular weight oligomers and displayed Michaelis-Menten kinetics.(Dug2p-Dug3p) 2hadaK mfor glutathione of 1.2 mM, suggesting a novel GATase enzyme that acted on glutathione. Dug1p activity in glutathione degradation was found to be restricted to its Cys-Gly peptidase activity, which functioned downstream of the (Dug2p-Dug3p) 2 GATase. The DUG2 and DUG3genes, but notDUG1, were derepressed by sulfur limitation. Based on these studies and the functioning of GATases, a mechanism is proposed for the functioning of the Dug proteins in the degradation of glutathione.
Description:	Only IISERM authors are available in the record.
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