Title:	ChaC2, an enzyme for slow turnover of cytosolic glutathione
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Abstract:	Glutathione degradation plays an important role in glutathione and redox homeostasis, and thus it is imperative to understand the enzymes and the mechanisms involved in glutathione degradation in detail. We describe here ChaC2, a member of the ChaC family of γ-glutamylcyclotransferases, as an enzyme that degrades glutathione in the cytosol of mammalian cells. ChaC2 is distinct from the previously described ChaC1, to which ChaC2 shows ∼50% sequence identity. Human and mouse ChaC2 proteins purified in vitro show 10–20-fold lower catalytic efficiency than ChaC1, although they showed comparable Km values (Km of 3.7 ± 0.4 mm and kcat of 15.9 ± 1.0 min−1 toward glutathione for human ChaC2; Km of 2.2 ± 0.4 mm and kcat of 225.2 ± 15 min−1 toward glutathione for human ChaC1). The ChaC1 and ChaC2 proteins also shared the same specificity for reduced glutathione, with no activity against either γ-glutamyl amino acids or oxidized glutathione. The ChaC2 proteins were found to be expressed constitutively in cells, unlike the tightly regulated ChaC1. Moreover, lower eukaryotes have a single member of the ChaC family that appears to be orthologous to ChaC2. In addition, we determined the crystal structure of yeast ChaC2 homologue, GCG1, at 1.34 Å resolution, which represents the first structure of the ChaC family of proteins. The catalytic site is defined by a fortuitous benzoic acid molecule bound to the crystal structure. The mechanism for binding and catalytic activity of this new enzyme of glutathione degradation, which is involved in continuous but basal turnover of cytosolic glutathione, is proposed.
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