Title:	The glutathione degrading enzyme, Chac1, is required for calcium signaling in developing zebrafish: redox as an upstream activator of calcium
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Abstract:	Calcium signaling is essential for embryonic development but the signals upstream of calcium are only partially understood. Here, we investigate the role of the intracellular glutathione redox potential in calcium signaling using the Chac1 protein of zebrafish. A member of the γ-glutamylcyclotransferase family of enzymes, the zebrafish Chac1 is a glutathione-degrading enzyme that acts only on reduced glutathione. The zebrafish chac1 expression was seen early in development, and in the latter stages, in the developing muscles, brain and heart. The chac1 knockdown was embryonic lethal, and the developmental defects were seen primarily in the myotome, brain and heart where chac1 was maximally expressed. The phenotypes could be rescued by the WT Chac1 but not by the catalytically inactive Chac1 that was incapable of degrading glutathione. The ability of chac1 to alter the intracellular glutathione redox potential in the live animals was examined using Grx1-roGFP2. The chac1 morphants lacked the increased degree of cellular oxidation seen in the WT zebrafish. As calcium is also known to be critical for the developing myotomes, brain and heart, we further investigated if the chac1 knockdown phenotypes were a consequence of the lack of calcium signals. We observed using GCaMP6s, that calcium transients normally seen in the developing embryos were strongly attenuated in these knockdowns. The study thus identifies Chac1 and the consequent change in intracellular glutathione redox potential as important upstream activators of calcium signaling during development.
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