IZH1, IZH2, IZH3, and IZH4 encode a family of paralogous membrane proteins thought to affect zinc homeostasis either by altering membrane sterol content or by directly altering cellular zinc levels. The Izh proteins belong to a large and nearly ubiquitous family of proteins found in both prokaryotes and eukaryotes. This family is characterized by the presence of at least seven transmembrane domains and four highly conserved motifs rich in metal-binding amino acids. All of the conserved motifs are predicted to cluster on the cytoplasmic face of the membrane. Izh2p is located in the plasma membrane.All four IZH genes exhibit elevated expression in zinc-deficient cells. IZH1 and IZH2 are direct targets of the Zap1p transcription factor that senses zinc deficiency, whereas IZH4 is induced by excess zinc. IZH1 and IZH2 possess putative zinc responsive elementsin their promoter regions, located at -416and -225, respectively. IZH1, IZH2, and IZH4 are also induced by fatty acids via the Oaf1p/Pip2p complex that binds to oleate response elements. Putative OREs are present in the IZH1, IZH2, and IZH4promoters. The induction of IZH1 and IZH2 by Zap1p under zinc deficiency, as well as the specific decrease in Zap1p activity in cells overexpressing Izh proteins, suggests a connection between these genes, sterols, and zinc metabolism.No single IZH gene or combination of genes is essential for viability. Deletion of either IZH1 or IZH2 results in increased sensitivity to elevated zinc, whereas deletion of IZH3 or IZH4 results in reduced sensitivity. The izh2 mutation increases the length of the cell cycle in zinc-treated cells, whereas izh3 mutation decreases the lag phase under the same conditions. Overexpression of any of these four genes results in decreased activity of the Zap1p transcription factor when cells are grown in zinc-limiting medium.Three possible functions have been proposed for the Izh proteins. First, these proteins may function solely in sterol metabolism by influencing the permeability of the plasma membrane and, consequently, the homeostasis of cations such as zinc. It is also possible that the Izh proteins function as transporters for zinc used in a signaling capacity, a possibility that may explain their regulation by Zap1p and their effect on Zap1p activity. A third possibility is that the Izh proteins are involved in a signal transduction cascade that is independent of zinc, and that Zap1p is a downstream target of this pathway.