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CBWD GENE PRODUCTS AUGMENT MAMMALIAN ZINC HOMEOSTASIS

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We previously identified the CBWD genes (coding for COBW domain containing proteins) through an in silico search of the human genome for the presence of a zinc responsive element known as zinc transcriptional regulatory element (ZTRE). The human CBWD gene family consist of six isoforms with different chromosomal and cytogenetic locations and exhibit a remarkable nucleotide and amino acid sequence conservation. The prokaryotic homologues of CBWD proteins belonging to the GOG0523 family of proteins have been reported to have roles in zinc homeostasis; however, no known role has yet been documented for the mammalian types. The discovery that the zinc-sensitive element (ZTRE) occurred in multiple copies of the CBWD genes was intriguing and triggered further investigations into a likely role for this gene family in mammalian cellular zinc handling and/or trafficking. Moreover, we reported a protein that acts at the ZTRE site to mediate regulation of zinc homeostatic genes and found CBWD genes to be a prominent feature. Using Caco-2 cells as in vitro model of human enterocytes, we demonstrate the ability of CBWD genes to respond to changes in zinc content at both transcriptional and post-transcriptional levels evidenced by decreased transcript and overexpressed protein abundance in response to increased extracellular zinc concentration. We also show that increased expression of CBWD protein through a transgene extended cellular tolerance to extreme windows of zinc availability, demonstrating the potential of the human CBWD proteins to augment cellular zinc buffering. This potential buffering ability of CBWD gene products may be effected through cellular zinc redistribution evidenced by a less punctate zinc distribution in cells made to overexpress CBWD protein compared to control cells. Furthermore, overexpression of COBW protein attenuated the responsiveness of a zinc-sensitive metallothionein promoter, indicating an action consistent with a role in zinc trafficking or buffering. These findings give plausible evidence in support of the involvement of the mammalian CBWD gene products in cellular zinc homeostasis.

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