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Molecular and Cell Biology of Zinc Metabolism and Function

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The search to understand the biochemical function(s) of zinc has spanned over half a century. Most of the initial effort involved a description of zinc metalloenzymes. It is now recognized that zinc has functions that can be divided into three categories: catalytic (metalloenzymes); structural (zinc finger and related protein domains); and regulatory (transcription factors and other intracellular, zinc-dependent mediators). The extent to which zinc nutrition can influence each of these functions has received attention. Recently, research has been directed primarily at the latter two functions.

It is not clear how much influence the dietary zinc supply has on maintaining the occupancy of zinc finger domains and thus their biochemical function. Evidence is accumulating that the CCCC, CCHH, CCHC configurations are not equivalent in zinc binding affinity and interaction with the intracellular free zinc pool. The differential activation of zinc finger domains for DNA binding directed by this pool could have a major consequence on gene expression. Of equal importance is the transcriptional regulation of genes by zinc through interaction with the

metal transcription factor 1 (MTF-1) or other zinc-responsive transcription factors. It is believed that MTF-1 senses the dietary zinc supply available to cells and regulates metallothionein synthesis. It may also regulate other zinc-responsive genes by a similar mechanism.

We have used differential hybridization and, more recently, differential mRNA display to search for genes that are directly or indirectly regulated by the level of zinc in the diet. Thus far, a number of intestinal genes that increase or decrease in expression during low zinc intake have been identified. Notable among these are uroguanylin, an intestinal polypeptide that regulates fluid secretion into the intestine, and cholecystokinin, which acts to regulate food intake (through receptors in the brain) and stimulate pancreatic secretion. These genes are upregulated in zinc deficiency and could explain, in part, the zinc sensitive diarrhea, anorexia, and increased pancreatic zinc loss associated with this nutritional condition. Regulation of these genes may be direct via a MTF-1 dependent mechanism or indirect through a variety of physiologic mediators. Of equal importance is the dietary regulation of the zinc transporters which are responsible for maintaining intracellular zinc concentrations and, hence, body zinc homeostasis. ZnT-1, the first of the four transporters to be examined thus far, is responsive to the dietary zinc supply under some nutritional situations. Collectively, recent research shows that dietary zinc and intracellular zinc are in direct communication to execute important functions for this micronutrient.

References

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