Acrodermatitis enteropathica and an overview of zinc metabolism

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Acrodermatitis enteropathica is a rare autosomal recessive disorder of zinc deficiency. The genetic defect has been mapped to 8q24 and the defective gene identified as SLC39A4, which encodes the zinc transporter Zip4. The diagnosis is made by way of clinical presentation together with histopathology and laboratory tests. Here we provide an overview of zinc metabolism and a description of inherited and acquired zinc deficiency. (J Am Acad Dermatol 2007;56:116-24.)

OVERVIEW OF ZINC METABOLISM

Three functions of zinc

The functions of zinc have been organized into 3 categories: catalytic, structural, and regulatory.[1,2] Zinc is an essential component of the catalytic site of hundreds of different metalloenzymes where it functions as a Lewis acid. Keilin and Mann[3,4] described the first zinc-dependent metalloenzyme in 1939 when they characterized zinc's association with carbonic anhydrase, an enzyme essential for the metabolism of carbon dioxide in plant and animal cells. Other well-studied zinc metalloenzymes include alkaline phosphatase, RNA polymerases, and alcohol dehydrogenase.

In the mid-1980s zinc was characterized as an important structural component of gene regulatory proteins.[5] Hanas et al[5] reported that zinc ions were required for the site-specific DNA binding activity of the *Xenopus* transcription factor IIIA. Since then hundreds of "zinc finger" sequences have been found occurring at all levels of the evolutionary tree including: viruses, bacteria, yeast, insects, and mammals. The structure of these proteins is dependent on zinc chelation centers, which contain histidine and cysteine residues. At these sites, zinc facilitates appropriate protein folding. Zinc finger proteins play a key role in the formation and maintenance of all tissues including the skin. ZAC, for example, is a zinc finger transcription factor that is highly expressed in basal keratinocytes. Interestingly, basal cell carcinomas lose expression of ZAC, whose normal function includes tumor suppressor activity; specifically, it can induce apoptosis and G1 cell cycle arrest.[6] In contrast to ZAC, the hedgehog signaling pathway drives proliferation and differentiation by activating the Gli family of zinc finger transcription factors. Mutations that result in constitutive sonic hedgehog activity and, thus, increased expression of Gli1 and Gli2, are associated with basal cell carcinomas. For example, a genetic defect resulting in the inactivation of the Ptch 1 tumor suppressor, an inhibitor of sonic hedgehog, results in the nevoid basal cell carcinoma syndrome. Other well-characterized zinc finger proteins include the retinoic acid receptors and vitamin D receptors. Zinc is also an important structural component of other types of proteins; it is required for the intracellular binding of tyrosine kinase to T-cell receptors, and the CD4 and CD8α coreceptors.[7]

The third function of zinc is regulation. For example, it has been discovered that zinc acts as an ionic signal in cells moving through gated membrane channels and, like calcium, excess amounts are toxic. Zinc is selectively stored and released from neurons in the cerebral cortex, which have been termed "gluzinergic" because they also release glutamate.[8] Once inside the cell, zinc can modify cellular

Abbreviations used:

AE: acrodermatitis enteropathica
lm: lethal milk
SLC: solute-linked carrier

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Funding sources: None.
Conflicts of interest: None identified.
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Published online November 6, 2006.
0190-9622/$32.00

doi:10.1016/j.jaad.2006.08.015

function by binding to and detaching from zinc-dependent proteins.[8] One specific example is zinc's ability to regulate gene expression by binding to the metal response element transcription factor. The importance of this biologic pathway is highlighted by the fact that a null mutation of the metal response element transcription factor is lethal.[9] Expression of some zinc transporter proteins is regulated by the metal response element transcription factor as is the expression of metallothionein, which functions in zinc trafficking.

Zinc transporters

With such important physiologic functions, it is not surprising that zinc levels are highly regulated. Zinc transporters are transmembrane proteins encoded by two solute-linked carrier (SLC) gene families, ZnT (SLC30) and Zip (SLC39). Human transporters are designated SLC30A or SLC39A followed by a number to represent the family member in order of discovery. For example, SCL39A4 encodes the fourth Zip zinc transporter discovered, Zip4. The two gene families, ZnT and Zip, have opposite roles in cellular zinc homeostasis. ZnT transporters reduce intracellular zinc by either promoting zinc efflux from cells or zinc transport into intracellular vesicles. In contrast, Zip transporters increase intracellular zinc concentrations by promoting zinc influx into cells or zinc release from intracellular vesicles.[10] In human beings there are 9 known ZnT transporters and 15 Zip transporters. The small intestine seems to be the main site of zinc homeostasis with transporter expression responsive to dietary zinc intake such that low dietary zinc increases intestinal zinc absorption and decreases intestinal zinc losses.[10-15]

The ZnT family members have 6 transmembrane domains, with a long histidine loop between transmembrane domains IV and V. This histidine loop is likely a zinc-binding domain. In addition, there is evidence to suggest that the ZnT family members act as dimers or trimers.[16,17] The first zinc transporter discovered was ZnT1. This protein is highly expressed in small intestine, renal tubular epithelium, and placenta.[18] It functions to transfer zinc from enterocytes into the circulation. In support of this role, in growing rats, ZnT1 is concentrated along the basolateral membranes of enterocytes.[19,20]

ZnT4 is highly expressed in the mammary gland, where it is associated with milk-containing vesicles, evidence to support its role of zinc transport in milk. It is also highly expressed in the brain and small intestines in rodents.[18,21]

Zip proteins are characterized by 8 transmembrane domains organized into two blocks of 3 and 5, which are separated by a histidine-rich cytoplasmic metal-binding site.[22,23] The function of Zip4 has been well characterized.[12,24-27] This tissue-specific zinc-regulated zinc transporter is abundantly expressed in enterocytes and functions to absorb dietary zinc from the small intestine. Zinc deficiency causes increased expression of Zip4 whereas zinc supplementation causes decreased expression.

Mutations of zinc metabolism

Given that there are multiple genes encoding zinc transporters, it is surprising that there are only a few inherited diseases known to involve zinc metabolism. The lethal milk (lm) mouse has an autosomal recessive defect resulting in low breast milk levels of zinc.[28,29] Pups of any genotype who suckle an lm/lm female die before weaning. The defective gene in lm mice is ZnT4.[21] This is the only known spontaneous defect in murine zinc metabolism. After it was discovered that the lm mouse had a defect in ZnT4, mothers of infants with acquired zinc deficiency were screened for expression of ZnT4. It was concluded that a defect in ZnT4 was not responsible for acquired zinc deficiency in human beings.[30]

In human beings, acrodermatitis enteropathica (AE) was probably first described in 1936 by Brandt,[31] who reported a "dermatitis in children with disturbances of the general condition and the absorption of food elements." Neils Danbolt[32-34] together with Karl Closs[32] extensively characterized AE and they are generally credited for establishing AE as a unique disease entity. Initially the cause of AE was unknown and the disease was often fatal. In 1951, a 3-year-old child was presented to the Chicago Dermatological Society and it was suggested by Dr Herman Pinkus[34] that the clinical picture closely resembled that of the cases described by Danbolt and Closs.[32] Dillaha et al[35-37] reported the fortuitous observation that this child was essentially cured after treatment with diiodoquinoline. Other groups confirmed the therapeutic effect of diiodoquinoline as well.[38,39] However, enthusiasm for the use of this antimalarial was tempered by the subsequent recognition that irreversible retinopathy was a predictable complication of diiodoquinoline therapy. The link between zinc deficiency and AE was formally hypothesized by Moynahan[40-42] and zinc supplementation quickly became the therapy of choice for AE.[39-42]

Individuals with AE have severe zinc deficiency derived from a defect of zinc absorption in the duodenum and jejunum.[43,44] Danbolt[34] recognized a familial pattern of AE. Homozygosity mapping of consanguineous Jordanian and Egyptian kindreds