Zn^{2+}, a dynamic signaling molecule

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Abstract

Zinc is essential for cell proliferation thereby promoting growth and development, yet a rise of intracellular zinc is a leading cause of neuronal cell death in excitotoxic syndromes. While pervious studies have addressed mostly the structural role of zinc as a cofactor of numerous enzymes and zinc finger proteins, recent data suggest that zinc is acting as a signaling molecule. Despite the accumulating knowledge on the transporters, which are shown to maintain cellular and subcellular zinc homeostasis, the mechanisms by which they function are much less understood. Changes in extracellular or intracellular zinc trigger the activation of major signaling pathways, partially mediated by a specific zinc sensing receptor, which are linked to either cell growth or cell death. These proteins, which are regulated by zinc, will be the subject of this review. The major challenges in future studies will be to reveal the cellular network of zinc signaling and their links to cellular zinc homeostasis.

1 Zinc in health and disease

Zinc, is an essential trace element for cell growth and development and its deficiency leads to abnormal growth (Evans 1986; Vallee and Falchuk 1993; Sandstead et al. 1998; MacDonald 2000). Among the most well known syndromes associated with zinc deficiency is growth arrest, improper development of the brain, loss of taste and smell, attenuated wound healing, and impaired immune response (Prasad 1998; Hambidge 2000; Komai et al. 2000; MacDonald 2000; Sandstead 2000; Scott and Koski 2000; Wapnir 2000; Bhatnagar and Taneja 2001). Zinc deficiency has been also linked to retarded development of the male reproductive system (El-Tawil 2003). The most severe manifestation of zinc deficiency is Acrodermatitis enteropathica that is a genetic disorder linked to improper zinc uptake leading to severe skin lesions, diarrhea, and subsequently brain damage (Perafan-Riveros et al. 2002). While this disorder was described many years ago, it has been only recently that the genes and cellular mechanisms underlying this disorder were identified (Wang et al. 2002, 2004b).

While earlier works focused on pathophysiological aspects of zinc deficiency, during the past three decades it has been repeatedly demonstrated that excessive rise in cellular zinc, particularly in brain cells, may also be harmful (Assaf and Chung 1984; Sloviter 1985; Danscher et al. 1997; Suh et al. 2000; Weiss et al.

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2000; Takeda 2001; Frederickson 2003; Sensi and Jeng 2004). Zinc, endogenously released, has been shown to induce neuronal cell death following its permeation into neurons. Such neuronal cell death is associated with ischemia, where certain brain regions such as the CA1 and CA3 regions of the hippocampus and neocortical layers 3, 5, and 6 are considered particularly vulnerable (Choi 1996; Choi and Koh 1998; Suh et al. 1999; Wei et al. 2004). The role of zinc in cytotoxicity has been first implied by the depletion of presynaptic zinc from the mossy fibers of the hippocampus followed by its appearance in post synaptic neurons destined to death (Frederickson et al. 1988, 1989; Lee et al. 2002a). Neurons could be rescued by the application of extracellular zinc chelators such as Ca-EDTA prior to the insult or by blocking the Ca/kainite AMPA channels, a major zinc permeation pathway to neurons (Koh et al. 1996; Sensi et al. 1999; Yin et al. 2002; Wei et al. 2004). Recent data suggest that not only the "free" synaptic zinc is linked to neuronal cell death but suggest a role for zinc that is released from intracellular pools (Lee et al. 2003; Sensi and Jeng 2004). Studies employing a zinc transporter knockout model in which synaptic zinc is depleted have also shown zinc-dependent neuronal death, highlighting the role of intracellular zinc pools in zinc dependent cell death (Cole et al. 2000; Lee et al. 2000). Zinc linked neuronal cell death is also occurring in epilepsy and traumatic brain injury (Buhl et al. 1996; Nagatomo et al. 1998; Suh et al. 2000). Finally, zinc has been recently linked to the formation of β-amyloid senile plaques and its chelation using clioquinol resulted in reduction of the number and size of the senile plaques (Cuajungco et al. 2000; Cherny et al. 2001). Indeed, using the same chelator decreased the synaptic and vesicular zinc pools in the brain and pancreas respectively (Nitzan et al. 2003).

In pancreatic islets of Langerhans zinc is co-released with insulin in concentrations similar to the synaptic zinc in the brain (Gee et al. 2002). Although zinc deficiency may increase β-cells apoptosis and its presence enhances proliferation (Kato et al. 1997; Schott-Ohly et al. 2004) intracellular accumulation of zinc has been suggested to affect β-cell death, in models of diabetes type 1, and contribute to the destruction of the islet (Apostolova et al. 1997; Kim et al. 2000b).

The importance of zinc in development and the pathophysiologies linked to its excess are well documented (Table 1), however, the cellular mechanisms linking the changes in zinc to cell fate are much less understood. In recent years, genes and proteins linked to zinc homeostasis were identified. Lethal milk syndrome in mice, for example, has been associated with a mutation of the zinc transporter, ZnT-4. In this syndrome, maternal milk does not contain adequate zinc levels and the pups die of zinc deficiency unless supplemented with zinc (Huang and Gitschier 1997). In humans, the ZIP4 gene, a zinc transporter involved in epithelial zinc absorption, has been linked to the human acrodermatitis enteropathica (Kury et al. 2002; Wang et al. 2002). This review will, therefore, focus on advances of our understanding of zinc transport and signaling mechanisms, which are linked to the physiology and pathophysiology of zinc homeostasis.