



Intracellular Zinc: A mediator of Vascular Aging and Disease?

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Editorial

Aging is a major risk factor in the development of cardiovascular diseases. Accumulation of waste materials like damaged mitochondria and decline in stress response mechanisms contribute to increased oxidative stress over time. The free radical theory of aging postulates that increased levels of reactive oxygen species [ROS] cause genomic and mitochondrial DNA damage leading to sustained oxidative stress that promotes tissue dysfunction and aging. In the cardiovascular system, NADPH oxidases produce ROS that are involved in normal function; however, overproduction of ROS by these enzymes, as well as decreased expression of antioxidant enzymes are associated with vascular dysfunction and disease [1].

Cellular senescence, a hallmark of mammalian aging, is a process of permanent cell cycle arrest [2] that has been linked to the development of age-related diseases, including atherosclerosis [3-5]. A causative role for senescence in disease development was reported as the selective removal of senescent cells in vivo showed a delay in age-related diseases [6]. Although senescent cells have lost their replicative capability, they possess a secretory and pro-oxidative/inflammatory phenotype [7] that likely contributes to organ dysfunction during aging.

It is well known that nutritional status plays an important role in disease development. Over-consumption of high calorie foods is a risk factor for diseases like metabolic syndrome, atherosclerosis and diabetes; however less is known about the consequences of micronutrient deficiencies in cardiovascular disease progression.

Zinc deficiency, which has a prevalence of 31% worldwide [8], has been linked to increased risk of cardiovascular diseases such as atherosclerosis by undefined mechanisms [9,10]. Beattie et al. reported that low dietary zinc intake promoted atherosclerosis in ApoE knockout mice, which was associated with increased inflammation. Using LDL receptor knockout mice, Shen et al. showed that zinc deficiency increased the expression of inflammatory markers and that zinc was required for the protective anti-inflammatory function of PPAR [11]. Moreover, maternal zinc deficiency in rats was correlated with increased susceptibility to cardiovascular diseases in adult life of the offspring [12,13].

The fact that zinc deficiency develops during aging suggests a possible link between zinc and senescence. However, a causative role for zinc deficiency in promoting vascular senescence that may accelerate atherosclerosis has not been established. In vitro experiments from our laboratory support the notion that altered zinc homeostasis accelerates cellular senescence by a ROS-dependent mechanism in vascular smooth muscle cells [VSMCs] [14]. Addition of exogenous zinc activates a NADPH oxidase leading to increased levels of ROS that cause senescence in these cells. In addition to the increased production of ROS, zinc also decreased the antioxidant

capacity by down regulating catalase expression [14]. Thus, intracellular zinc not buffered by zinc regulatory mechanisms creates a vicious cycle that promotes oxidative damage and senescence in VSMCs. A role for intracellular zinc in aging has been also shown in other systems. Unbalanced intracellular zinc is a well-established mediator of oxidative damage and neuronal cell death in neurological diseases like Alzheimer's disease [15,16]. In the brain excess zinc, such as the one released after cellular injury, alters mitochondrial membrane potential, activates cytoplasmic ROS generating enzymes, such as 12-lipoxygenase [12-LOX], and stimulates signal transduction pathways that contribute to neuronal cell death. Thus, increased intracellular zinc in vitro and zinc deficiency in vivo lead to oxidative stress that may mediate vascular disease. How could these observations be explained? One possibility is that zinc deficiency may induce changes in the expression of zinc regulators such as zinc transporters causing a redistribution of intracellular zinc. For example, down regulation of the zinc transporters ZnT3 and ZnT10 [exporters that decrease intracellular zinc] induces senescence of VSMCs by decreasing catalase and increasing ROS levels [14]. Down regulation of these transporters reduces zinc accumulation in intracellular compartments [14], likely causing a rise in cytosolic zinc. Furthermore, zinc deficiency increases Zip6 [importer that increases intracellular zinc] and decreases ZnT1 expression to increase zinc uptake in the brain [17]. Thus, it is possible that this could also be the case in the cardiovascular system.

To fully understand the role of zinc in vascular aging and disease, intracellular zinc level and its distribution as well as expression of zinc transporters in response to zinc deficiency in the cardiovascular system should be addressed. Since zinc deficiency is not only associated with lower zinc intake but also with chronic diseases, development of this emerging area of research is urgently needed.

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