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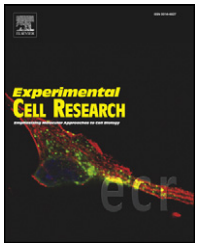

Review Article

Hepatic response to aluminum toxicity: Dyslipidemia and liver diseases

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ABSTRACT

Aluminum (Al) is a metal toxin that has been implicated in the etiology of a number of diseases including Alzheimer's, Parkinson's, dialysis encephalopathy, and osteomalacia. Al has been shown to exert its effects by disrupting lipid membrane fluidity, perturbing iron (Fe), magnesium, and calcium homeostasis, and causing oxidative stress. However, the exact molecular targets of aluminum's toxicity have remained elusive. In the present review, we describe how the use of a systems biology approach in cultured hepatoblastoma cells (HepG2) allowed the identification of the molecular targets of Al toxicity. Mitochondrial metabolism is the main site of the toxicological action of Al. Fe-dependent and redox sensitive enzymes in the tricarboxylic acid (TCA) cycle and oxidative phosphorylation (OXPHOS) are dramatically decreased by Al exposure. In an effort to compensate for diminished mitochondrial function, Al-treated cells stabilize hypoxia inducible factor-1α (HIF-1α) to increase ATP production by glycolysis. Additionally, Al toxicity leads to an increase in intracellular lipid accumulation due to enhanced lipogenesis and a decrease in the β-oxidation of fatty acids. Central to these effects is the alteration of α-ketoglutarate (KG) homeostasis. In Al-exposed cells, KG is preferentially used to quench ROS leading to succinate accumulation and HIF-1α stabilization. Moreover, the channeling of KG to combat oxidative stress leads to a reduction of L-carnitine biosynthesis and a concomitant decrease in fatty acid oxidation. The fluidity and interaction of these metabolic modules and the implications of these findings in liver-related disorders are discussed herein.

Contents

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Introduction

Environmental pollutants, such as heavy metals and organic molecules, are known to participate in the pathogenesis of various diseases in humans. While, heavy metals like mercury (Hg), lead (Pb), and cadmium (Cd) have been shown to induce neurodegeneration, carcinogenesis, and anemia [1–3], organic pollutants, such as phthalates, have also been implicated in numerous disorders including type 2 diabetes and obesity [4,5]. Aluminum (Al) toxicity has also garnered considerable interest due to its bioavailability and adverse effects on human health and persistence in the environment. Indeed, Al toxicity is associated with various pathological conditions including Alzheimer's, Parkinson's, osteomalacia, anemia, and obesity [6–12]. The toxicity of Al has been attributed to its ubiquity in the environment and the frequency of exposure. Dietary sources of Al, such as foods, cookware, and drinking water, are important contributors to Al exposure and uptake [8] (Fig. 1). Owing to aluminum's hard acid properties, valency, and pro-oxidant capabilities, this trivalent metal readily perturbs Fe homeostasis, disrupts biological membranes, enhances ROS formation, and damages DNA [6,8,9,13,14]. Exposure of neurons and astrocytes to Al is known to activate apoptotic cascades, provoke cell cycle arrest, and interfere with cell signaling pathways [14–18] (Fig. 1). Al uptake in the human body can occur via a number of routes. However, dietary absorption is a common route for Al accumulation in the body. Following the dietary exposure to Al, it is subsequently distributed throughout the human body. Various tissues have been shown to accumulate Al however, the highest levels of Al are found in the bone and liver and to a certain extent the brain [19–21] (Fig. 1).

Hepatocytes are the functional units of the liver and rely on a series of complex metabolic networks in order to maintain energy homeostasis in the human body. Various environmental toxins have been shown to perturb liver physiology. However, the influences of pollutants, such as Al, on the molecular networks, which govern the physiological functions of hepatocytes, remain poorly resolved. The response of cellular systems to stimuli is complex with numerous functionally diverse networks interacting to manifest an appropriate response. Investigating individual pathways has successfully uncovered the various components involved in the adjustment of cell behavior to different conditions. Systems biology has been employed to decipher the transport and distribution of systemic Al [22,23]. However, to our knowledge this experimental paradigm has never been employed to investigate the effects of Al on cell physiology and function. In this review, we discuss how we used systems biology to identify the impact of Al toxicity on the metabolic networks in HepG2 cells. Al toxicity induced mitochondrial dysfunction in HepG2 cells leading to enhanced anaerobiosis and lipid accumulation. The role of α-ketoglutarate (KG) in mitigating Al-induced abnormalities is also explained.

Mitochondrial dysfunction: Al toxicity perturbs hepatic energy metabolism

Al disrupts the tricarboxylic acid (TCA) cycle and aerobic respiration

Mitochondrial metabolism and aerobic respiration are central to the physiological function of hepatocytes. The mitochondria in

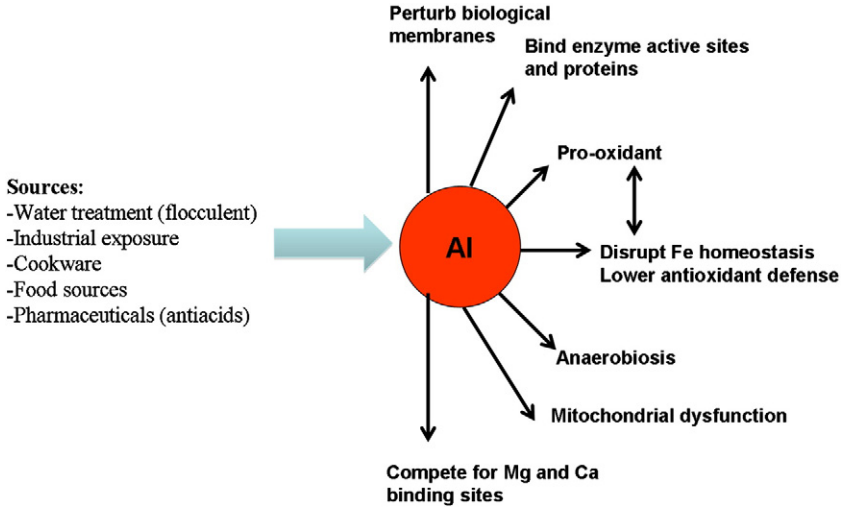

Fig. 1 – Exposure to Al and its toxicological impacts. Dietary uptake represents the major route of Al uptake. Due to the chemical properties of Al, this trivalent metal disrupts multiple cellular processes. The ability of Al to exert these negative effects on cells has been linked to a number of pathologies.