Molecular Aspects of Genetic Disorders of Copper Metabolism

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Copper is required for the catalytic activity of several important enzymes, but excess copper is toxic because it is a potent generator of free radicals. Copper homeostatic mechanisms have recently been identified. The lethal effects due to disruption of copper homeostasis are illustrated in two human genetic disorders, Menkes disease and Wilson disease. Both diseases are caused by mutations of two closely related copper-transporting ATPases (ATP7A and 7B) which transport copper from the cytosol to Gorgi apparatus in the cells, supply copper to secreted cuproenzymes in the transGlogi network, and then excrete copper from the cells. Menkes disease is caused by mutations in ATP7A gene and characterized by copper deficiency, including severe neurological degeneration, connective tissue abnormalities and hair abnormalities. In contrast, Wilson disease, caused by mutations in ATP7B gene, is characterized by copper toxicosis, including hepatitis and neurological disorders. The reason for the difference in the characteristic features of the both diseases is due to distinct pattern of tissue expression, that is, ATP7A is expressed in most tissues while ATP7B is mainly expressed in the liver. The treatment for Menkes disease accepted so far is parenteral administration of copper. The treatment is, however, ineffective for the neurological degeneration and connective tissue abnormalities, thus an alternative treatment should be investigated. Although Wilson disease can be treated with chelating agents, oral zinc administration has been noticed as an alternative therapy. Recently, ATP7B has also been noticed to be expressed in several types of carcinomas, and to be associated with cisplatin resistance.