Serial Review

Copper Biology in Health and Disease
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Introduction to serial reviews: Copper biology in health and disease

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Copper (Cu) is an essential trace element in the human body and utilized in various physiological processes, including antioxidant defense and neurotransmitter biosynthesis. The ability of Cu to cycle between the two oxidation states, namely Cu (I) and Cu (II), is important for its catalytic function as a cofactor for many enzymes such as superoxide dismutase (SOD), cytochrome c oxidase, and dopamine β-hydroxylase (DBH). In contrast, excess Cu is highly toxic to cells because it induces oxidative stress. Therefore, intracellular Cu levels are strictly regulated by Cu-transporters, including copper transporter 1 (CTR1) and copper-transporting P-type ATPase (ATP7A), and Cu-chaperons, including copper chaperone for superoxide dismutase (CCS) and antioxidant protein 1 (Atox1). These proteins play important roles in systemic Cu metabolism in the body. Mutation of the *ATP7A* gene is responsible for Menkes disease (MD), a genetically inherited Cu metabolism disorder.[1] In MD, defective Cu absorption in the intestine causes systemic Cu deficiency.

Growing evidence suggests that perturbation of cellular Cu homeostasis is closely related to neuronal injury detected in neurological disorders, such as Alzheimer's disease (AD), and cancer progression. For example, Cu facilitates the aggregation of amyloid-β peptide (Aβ), which is a risk factor for AD, to form Cu-Aβ complexes.[2] The complexes promote the production of reactive oxygen species (ROS) through Fenton-like reactions, resulting in neurotoxicity.[3] In addition, as Cu is required for the activity of cuproenzymes, such as SOD and DBH, dysregulation of Cu trafficking was reported to reduce their activity and result in cellular dysfunction.[4–6] On the other hand, the demand for Cu is higher in cancer cells than in normal cells. Cu depletion was reported to suppress the migration and metastasis of cancer cells; therefore, Cu deficiency using Cu chelators is considered to be a promising strategy for cancer therapy.[7]

In this serial review, the development of analytical methods for the measurement of Cu, involvement of the perturbation of Cu homeostasis in neurological disorders, and roles of Cu in cancer progression will be discussed.

References

1 de Bie P, Muller P, Wijmenga C, Klomp LW. Molecular pathogenesis of Wilson and Menkes disease: correlation of mutations with molecular defects and disease phenotypes. *J Med Genet* 2007; **44**: 673–688.
2 Kawahara M, Kato-Negishi M, Tanaka KI. Amyloids: regulators of metal homeostasis in the synapse. *Molecules* 2020; **25**: 1441.
3 Cheignon C, Tomas M, Bonnefont-Rousselot D, Faller P, Hureau C, Collin F. Oxidative stress and the amyloid beta peptide in Alzheimer's disease. *Redox Biol* 2018; **14**: 450–464.
4 Kondo M, Hara H, Kamijo F, Kamiya T, Adachi T. 6-Hydroxydopamine disrupts cellular copper homeostasis in human neuroblastoma SH-SY5Y cells. *Metallomics* 2021; **13**: mfab041.
5 Sudhahar V, Okur MN, Bagi Z, *et al*. Akt2 (protein kinase B beta) stabilizes ATP7A, a copper transporter for extracellular superoxide dismutase, in vascular smooth muscle: novel mechanism to limit endothelial dysfunction in type 2 diabetes mellitus. *Arterioscler Thromb Vasc Biol* 2018; **38**: 529–541.
6 Tokuda E, Furukawa Y. Copper homeostasis as a therapeutic target in amyotrophic lateral sclerosis with SOD1 mutations. *Int J Mol Sci* 2016; **17**: 636.
7 Shanbhag VC, Gudekar N, Jasmer K, Papageorgiou C, Singh K, Petris MJ. Copper metabolism as a unique vulnerability in cancer. *Biochim Biophys Acta Mol Cell Res* 2021; **1868**: 118893.

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