Deciphering the Roles and Mechanism of Zn7MT3 in Abating Neuronal Cytotoxicity - Year Two

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Aggregation and cytotoxicity of amyloid-β (Aβ) with redox-active metals in neuronal cells have been implicated in the progression of Alzheimer's Disease (AD). Particularly, dysregulated interactions of copper and zinc in the brain plays a key role in heightening AD through intensified Aβ aggregation in senile plaques and production of reactive oxygen species (ROS) that impair cell function. Human metallothionein MT3, a naturally produced metalloprotein, is highly expressed in the normal human brain and is downregulated in Alzheimer disease. Zn7MT3 can protect against the neuronal toxicity of Aβ by preventing copper-mediated Aβ aggregation, abolishing the production of reactive oxygen species (ROS) and thereby abating the related cellular toxicity. In this study, we intend to decipher the biological roles and physical mechanism of Zn7MT3 in protecting against the neuronal cytotoxicity of Aβ1–42 with Cu2+ ions. In the presence/absence of Zn7MT3, the Aβ1–42–Cu2+-mediated aggregation, the production of ROS, and the cellular toxicity were investigated by transmission electron microscopy, ROS assay by means of a fluorescent probe, and SH-SY5Y cell viability. Herein, we show that Zn7MT3 relieves ROS production and related aggregate toxicity by characterized metal swap interactions between Zn7MT3 and Aβ1–42–Cu2+. Such metal homeostasis regulation and discovered, protective effects of Zn7MT3 from copper-induced Aβ1-42 aggregation toxicity may give rise to novel therapeutic approaches in treating AD and other related neurodegenerative disorders.