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Linking copper, tyrosines and protein aggregation in Alzheimer's disease

The prevalence of Alzheimer's disease (AD), the most common cause of dementia nowadays, is expected to increase within the coming years, representing a serious threat for society and the healthcare system. For this reason, a lot of research is being devoted to unraveling the root physiological processes that ultimately lead to the onset of AD.

A**β** is a self-assembling peptide (peptide is a generic term for an amino acid chain, while large peptides are usually called proteins) that forms deposits, also called amyloid plaques, in the synaptic cleft. Such plaques have been observed in AD brains and are thought to interfere with neurological activity; however, they have also been detected in healthy brains. Intermediate A**β** aggregates called oligomers, comprised of a few A**β** molecules, are seemingly more toxic and better correlate with the disease.

Metal ions play crucial roles in the human body; nevertheless, they can cause serious damage to biomolecules and cells (such as DNA and neurons) when not submitted to tight regulation. Misbalanced levels of copper, which is involved in neurotransmission, have been found in AD brains where it generates oxidative stress, eventually leading to neuron dysfunction and death. Moreover, copper coenriches with A**β** peptide in the synaptic cleft, where it is believed to stabilize oligomers and enhance their toxicity.

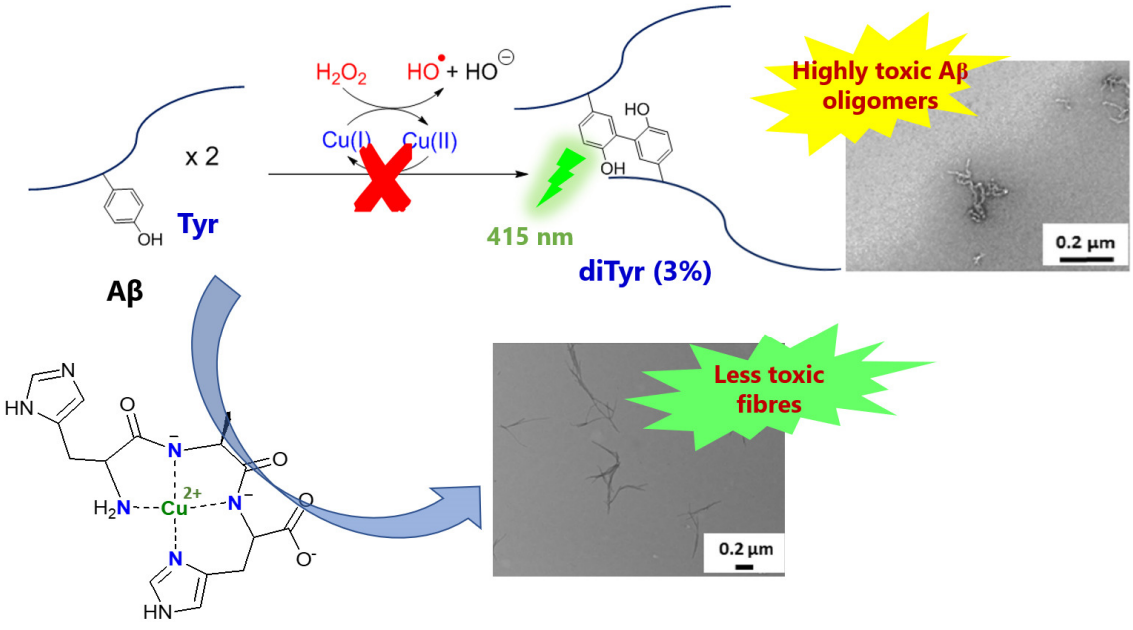

Fig. 1.

Copper can induce changes to A**β** itself; for instance, two A**β** molecules can undergo irreversible binding through the amino acid tyrosine, resulting in A**β** dimers with increased stability. These dimers have been detected in AD patients, whereas they are rarely found in healthy individuals.

Hence, copper-capturing drugs represent a promising tool against AD as they may restore natural A**β** aggregation into (less toxic) amyloid plaques and prevent copper-mediated generation of oxidative stress. In this context, we have used short (3 amino acids) peptides of sequence HXH, where H is histidine (an effective copper binder) and X is a varying amino acid, which effectively displaced A**β**-bound copper ions and prevented the production of oxidizing species.

Also, we have studied the role of A**β** dimers in the aggregation of the peptide, which remains unclear. For this reason, we have prepared dityrosine, a fluorescent model of the dimers made of two tyrosine residues. This model allowed us to detect and quantify the amount of A**β** dimers generated under different representative conditions and to evaluate their impact on amyloid formation. Upon incubation of A**β** with physiological concentrations of copper and hydrogen peroxide (H_2O_2, an oxidizing species abundant in AD dysfunctional mitochondria), up to 3% of A**β** dimers were detected, while only residual amounts were found for pure A**β** or in the presence of copper or H_2O_2 alone.

Next, we assessed the impact of such dimers on the amyloid generation process using thioflavin T, an amyloid-selective fluorescent dye. Surprisingly, a dimer proportion no greater than 3% was sufficient to completely inhibit amyloid formation (in the presence of both copper and H_2O_2). In contrast, when we incubated the A**β**-copper-H_2O_2 system with the copper-binding tripeptide HAH (A = alanine), the production of dimers decreased to levels comparable to the A**β**-H_2O_2 sample (without copper) and, most importantly, amyloid formation was restored.

In conclusion, we have shed light on the copper-mediated mechanism of A**β** oligomer stabilization by showing that, in the presence of copper and H_2O_2, low amounts of A**β** dimers hampered aggregation into amyloids. Furthermore, we restored natural amyloid formation by using a copper-binding agent, encouraging further exploration of copper depletion as a viable anti-AD approach. Our humble contribution adds to the massive combined effort of the scientific community which will undoubtedly lead to the victory of mankind over this devastating disease.

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