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Axotrophin a RING-variant domain protein acts as E3-ubiquitin-ligase and ubiquitinates the microtubule-associated protein tau

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A number of neurodegenerative diseases, among others Alzheimer's disease (AD), are characterized by aggregation and accumulation of misfolded proteins. These protein aggregates are partly ubiquitinated. Tau protein, which aggregates during AD, is poly-ubiquitinated in AD brain to some extent.

In order to find modifiers of tau aggregation and post-translational modification we screened for proteins, which interact with tau protein. In previous experiments we showed that the tau protein interacts with the protein axotrophin of unkown function.

Affinity-purified antibodies against axotrophin C-terminus labeled tau protein aggregates in AD brains.

Axotrophin harbours a C4HC3 zinc-finger-like motif in the C-terminus, which is referred to as Ring-variant domain and has been implicated in protein ubiquitination. Recombinant expression and refolding of the C-terminus of axotrophin allowed us to test the E3-ubiquitin-ligase activity. We found that axotrophin shows E3-ubiquitin-ligase activity in combination with several E2 enzymes and becomes autoubiquitinated. Ubiquitination of tau protein but not KLC1, another axotrophin-interacting protein, was mediated by axotrophin.

Further investigation of ubiquitination effects on the protein tau will give more insights about the E3-ubiquitin-ligase axotrophin and especially its role in AD.