TDP-43 PROCESSING IS MODULATED BY C-JUN N-TERMINAL KINASE AND COPPER: IMPLICATIONS FOR THERAPEUTIC TREATMENT OF TDP-43 PROTEINOPATHIES

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Introduction: TDP-43 proteinopathies (FTD and ALS) are characterized by loss of nuclear TDP-43 expression, C-terminal fragmentation and accumulation in the cytoplasm. Recent studies have shown that TDP-43 can accumulate in RNA stress granules (SGs) in response to cell stresses. This could be associated with subsequent formation of aggregates. However, the pathway of TDP-43 accumulation in SGs is not understood.

Aims: In this study we investigated the mechanism of TDP-43 processing and accumulation in SGs in neurons exposed to oxidative stress.

Methods: Neuronal cultures were treated with the mitochondrial inhibitor paraquat and examined for TDP-43 and SG processing.

Results: We found that paraquat induced loss of nuclear TDP-43 and led to formation of TDP-43 and HuR-positive cytoplasmic SGs. Paraquat-mediated TDP-43 SG accumulation was associated with increased caspase-dependent C-terminal TDP-43 cleavage, which was not observed with alternative stress inducers. The co-localization of TDP-43 with SGs could be completely blocked by co-treatment with the c-Jun N-terminal kinase (JNK) inhibitor, SP600125. JNK inhibition did not prevent formation of HuR-positive SGs. Co-treatment of neurons with a copper-bis(thiosemicarbazone) complex (Cu²⁺(atsm)) inhibited JNK activity and TDP-43-positive SG formation, increased expression of key survival proteins and reduced oxidative stress. Cu²⁺(atsm) also inhibited altered TDP-43 processing, delayed disease onset and extended life in a G93A SOD1 murine model of ALS.

Conclusion: Our studies are the first to demonstrate a specific stress-mediated pathway of TDP-43 accumulation in SGs and inhibition by a potentially therapeutic copper complex. These findings may have important implications for development of treatments for FTD and ALS.