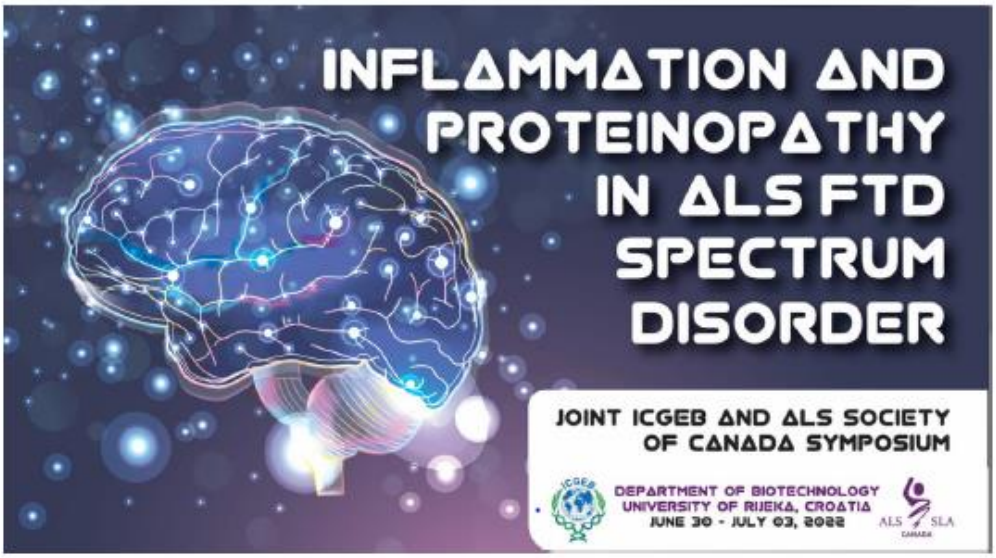

ABSTRACT BOOK

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Investigating the molecular mechanisms involved in KIF5A-related neurodegeneration

Mutations targeting the neuron-specific kinesin KIF5A lead to neurodegenerative diseases (NDs), including amyotrophic lateral sclerosis (ALS). Distinct phenotypes develop according to which of the three KIF5A domains is affected by mutations, but the reasons behind such heterogeneity are not known yet. Our aim is to gain insight into the molecular mechanisms underlying KIF5A-related NDs by functionally characterizing four domain-specific KIF5A mutants (R17Q, R280C, R864*, N999Vfs*39). Overexpression in SH-SY5Y cells evidenced altered protein turnover for R17Q KIF5A and the ALS-related N999Vfs*39 mutant with respect to wild-type (WT) KIF5A, with the two mutants displaying shorter half-life upon cycloheximide chase. Higher accumulation was observed for R17Q and N999Vfs*39 KIF5A compared to WT KIF5A and the other KIF5A variants following proteasomal blockage, indicating that the ubiquitin-proteasome system might represent the main degradation route for the two mutants. R17Q and N999Vfs*39 KIF5A also displayed preferential partitioning in the detergent-insoluble protein fraction upon proteasome inhibition, which suggests they may form harmful inclusions when proteostasis is impaired. Altered intracellular distribution was evidenced for R864* and N999Vfs*39 KIF5A overexpressed in NSC-34 cells, with the two mutants mainly localizing at cell periphery instead of being diffused within the whole motoneuron like WT KIF5A. In particular, the ALS-related N999Vfs*39 mutant formed puncta inside cell processes, which hints at reduced protein solubility even in basal conditions, and partially sequestered WT KIF5A within them. The abnormal distribution displayed by R864* and N999Vfs*39 KIF5A was paralleled by limited colocalization between the two mutants and mitochondria, whose axonal transport is largely reliant on WT KIF5A in motoneurons. Taken together, our preliminary observations indicate that both unique and shared mechanisms might underlie the pathogenesis of KIF5A-related NDs.