Y526 phosphorylation of ALS/FTLD protein FUS impairs its nuclear transport /

Forsorilacija tirozina 526 zmanjša jedrni transport proteina FUS, ki sodeluje pri boleznih ALS in FTLD

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Frontotemporal lobar degeneration (FTLD) and amyotrophic lateral sclerosis (ALS) are neurodegenerative disorders with clinical, genetic, and neuropathological overlap. Aberrant cytoplasmic aggregation of fused in sarcoma (FUS) is associated with 3 % of familial ALS and 10 % of all FTLD cases (FTLD-FUS). FUS is a nuclear RNA/DNA binding protein with PY type nuclear localization signal present at its C-terminus which enables interaction with Transportin-1 (TNPO1) and its transport into the nucleus. ALS patients with FUS positive cytoplasmic inclusions contain mutations in gene encoding FUS. The majority of these mutations fall within the nuclear localization signal which disables its transport to nucleus. On the other hand, patients with FTLD-FUS do not have FUS mutations but FUS still accumulates in cytoplasmic inclusions, suggesting a different mechanism of inclusion formation in ALS and FTLD. Our aim is to elucidate if the nuclear localization signal of FUS is subjected to posttranslational modifications that have impact on its localization. We have identified a novel posttranslational modification on the C-terminal tyrosine of FUS. This modification significantly reduces interaction with TNPO1 and consequently affects transport of FUS into the nucleus. We have also identified the tyrosine kinases that lead to the phosphorylation. Our study implicates the 526Y phosphorylation as one of the mechanisms by which nuclear transport of FUS is regulated and potentially perturbed in ALS and FTLD.