Nonsense-mediated mRNA decay (NMD), a cellular quality control mechanism, may be altered in Alzheimer's disease (AD)

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In the nucleus, a protein complex called the exon-junction complex (EJC) binds to every mRNA splice junction. EJC components are actively involved in nuclear export, quality control and cytoplasmic localization of mRNA transcripts. Selected "core" EJC components are also exported from the nucleus along with spliced mature mRNA.
Prior to cytoplasmic translation, every mRNA is subjected to a highly conserved quality control mechanism called mRNA surveillance or nonsense-mediated mRNA decay (NMD). Mutations or insertions in genomic DNA, splicing proteins or their binding sites, pre-mRNA etc. which lead to splicing errors bring premature termination codons (PTCs) in-frame. Any such PTC-containing mRNAs are rapidly decapped and degraded by NMD to prevent their translation into abnormal COOH-truncated proteins with possible dominant-negative properties. An interaction between the EJC component Y14 and NMD components is required for NMD initiation. Interestingly, abnormal COOH-truncated "plus-one" proteins accumulate in hallmark neuropathological structures of AD i.e. neurofibrillary tangles and amyloid plaques. This strongly suggests that NMD is altered or deficient in AD.
We analyzed the expression of mRNAs encoding EJC proteins via real-time semi-quantitative PCR (QPCR) in the temporal cortex of AD and Down syndrome (DS) patients. Indeed, expression of critical NMD and EJC components e.g. Y14 were significantly altered. We have verified some of these findings at the protein level via Western blots. Our preliminary data therefore suggest that NMD efficiency is altered or even deficient in AD and DS, with possible implications for abnormal protein synthesis. To verify this, we are currently developing a GFP-based reporter system to measure NMD efficiency in suitable in vitro systems. Our data acquires particular significance given that the recessive nature and phenotypic severity of many diseases e.g. beta-thalassemia, Marfan's syndrome and Duchene's muscular dystrophy have recently been shown to be directly related to NMD-regulated mutant mRNA levels.

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