Nuclear cap binding protein CBP20 accumulates in neurofibrillary tangles in temporal cortex of Alzheimer's disease patients

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A cap-binding complex (CBC) comprising two cap-binding proteins (CBPs) binds to the 5'-cap of all eukaryotic nuclear pre-mRNAs. The 20kd protein CBP20 binds directly to the cap structure; the 80kd protein CBP80 binds to CBP20, stabilizing its interaction with the cap. The CBC enhances various aspects of RNA processing e.g. pre-mRNA splicing and is exported from the nucleus along with spliced mature mRNA.
Prior to cytoplasmic translation every mRNA is subjected to a quality control mechanism called mRNA surveillance or nonsense-mediated mRNA decay (NMD); this mechanism is conserved from yeast to man. Cytoplasmic CBC-bound mRNA is scanned by a ribosomal complex; if approved for translation, the CBC is replaced by cytoplasmic cap-binding proteins. Interestingly, abnormally carboxy-truncated proteins have been shown to accumulate in hallmark neuropathological structures of Alzheimer's disease (AD) patients e.g. neurofibrillary tangles and amyloid plaques. Normally, mRNAs that give rise to such proteins should be degraded by NMD, suggesting that this mechanism may be altered or deficient in AD.
We performed immunohistochemical staining of CBP20 on formalin-fixed paraffin-embedded human postmortem sections from 7 controls (CON), 6 AD (Braak stages 5/6) and 2 Down syndrome patients. CBP20 was expressed at high levels in tangle-bearing neurons, and in some plaques in all AD sections so far. Tangles in aged non-demented controls also stained for CBP20. To further examine the relationship between NCBP20 and tangles, double staining was carried out with MC1 (marker for hyperphosphorylated tau). Confocal imaging revealed a similar pattern of distribution – however, unlike MC1, CBP20 is found in small clusters. Therefore CBP20 may be present either in stress granules or P-bodies, dynamic cytoplasmic foci containing stalled translation initiation complexes or mRNAs to be decapped and degraded, respectively. We are presently investigating both these possibilities.

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