CEREBRAL VASCULAR AMYLOID SEEDS DRIVE AMYLOID SS-PROTEIN FIBRIL ASSEMBLY WITH A DISTINCT ANTI-PARALLEL STRUCTURE

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Background: Cerebrovascular accumulation of the amyloid beta-protein (Abeta), a condition known as cerebral amyloid angiopathy (CAA), is a common pathological feature of patients with Alzheimer’s disease. Additionally, familial forms of Abeta, with specific Abeta mutations such as Dutch E22Q and Iowa D23N, cause severe cerebral vascular accumulation of amyloid that serves as a potent and early driver of vascular cognitive impairment and dementia (VCID). The distinctive features of vascular amyloid that underlie its unique pathological properties remain unknown. Here we investigated how cerebral vascular fibrillar amyloid seeds influence the assembly, accumulation and structure of Abeta.

Methods: A combination of biochemical and biophysical approaches were used to study amyloid fibril formation in vitro. Transgenic mice were then used in conjunction with quantitative pathological, biochemical and structural analyses to study how CAA mutant and wild-type Abeta interact in brain to drive vascular amyloid formation. Results: In the in vitro that CAA mutant amyloid fibril seeds can adopt a parallel or anti-parallel configuration and that both can promote rapid fibril assembly of wild-type Abeta peptides that adopt corresponding fibrillar signatures. In the in vivo studies we first show that intrahippocampal administration of biotin-labeled wild-type Abeta peptides strongly accumulate on pre-existing cerebral microvascular amyloid deposits in Tg-SwDI mice, a model that preferentially develops early-onset CAA mutant microvascular amyloid. Subsequently, we crossed Tg-SwDI mice with Tg2576 mice, a model that produces high amounts of human wild-type Abeta in brain. The bigenic mice exhibited markedly elevated accumulation of microvascular fibrillar amyloid in brain compared to either single transgenic line that was largely composed of human wild-type Abeta. Further, isolated microvascular amyloid seeds from Tg-SwDI mice drive assembly of human wild-type Abeta into distinct anti-parallel amyloid fibrils. Conclusions: These findings indicate that cerebral vascular amyloid can serve as an effective scaffold to promote rapid assembly and strong deposition of Abeta into a unique structure that likely contributes to its distinctive pathology.

PATHOLOGICAL TAU IMPAIRS RIBOSOMAL FUNCTION AND DECREASES PROTEIN SYNTHESIS

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Background: Alzheimer’s disease (AD) is one of 20 crippling neurodegenerative disorders characterized by the aberrant intracellular deposition of the microtubule-associated protein tau. One of the first symptoms of tauopathic patients is progressive memory loss and cognitive decline. Since the pathogenic mechanism by which tau induces neurotoxicity and leads to memory impairment is unknown, therapeutic strategies are limited. Methods: We performed subcellular fractionation of human AD and control brains coupled with tandem mass spectrometry peptide identification to identify tau-protein interactions. We performed cell free in vitro translation assays to measure translation of green fluorescent protein (GFP) in the presence of oligomeric proteins. Finally, we performed cell culture assays in immortalized lines and primary neuronal cultures to measure changes in protein translation as a result of pathological tau. Results: We show that pathological tau associates differentially with endoplasmic reticulum (ER) proteins in AD compared to control brains. We also show that pathological tau associates with ribosomes in AD brains, and that this association leads to a decrease in overall translation as well as translation of vital synaptic proteins. Conclusions: Our data suggest that pathological tau impairs protein production. Since protein biosynthesis is necessary for memory formation, our work establishes a direct link between tau aberrations and memory impairment. We also show that there is a decrease in translation of synaptic proteins, which could be a reason for neuronal dysfunction observed in diseased brains. These data support the exploration of the tau-ribosome complex for therapeutic target identification, and it opens a new window of treatment strategies for tauopathies.

ALTERING THE TRAJECTORY OF SYNUCLEINOPATHIES BY TARGETING DOWNSTREAM TOXICITY OF TAU OLIGOMERS

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Background: Currently, the only available treatments for neurodegenerative disease target the symptoms without directly affecting their causes. Two of the most common neurodegenerative disorders, Parkinson’s disease (PD) and Lewy body dementia (LBD), are primarily characterized by the accumulation of alpha-synuclein into fibrillar structures known as Lewy bodies. However, evidence shows that smaller, oligomeric aggregates are likely the most toxic form of the protein. We have recently shown that oligomeric alpha-synuclein coexists with tau oligomers in disease and that alpha-synuclein oligomers can seed the aggregation of natively unfolded tau protein. This toxic synergy implicates tau oligomers as a potential therapeutic target for synucleinopathies. We have previously shown that passive immunotherapy with a tau oligomer-specific antibody (TOMA) effectively protects against toxicity in tauopathy and Alzheimer’s disease model systems. Here, we have evaluated the efficacy of targeting tau oligomers in a synucleinopathy mouse model for the first time. Methods: Seven-month-old mice overexpressing A53T mutated alpha-synuclein were injected intravenously with either TOMA (specific for tau oligomers), Tau-13 (recognizes all forms of tau) or a control IgG and wild-type mice were treated with saline. Two weeks post-injection, mice were behaviorally evaluated using the open field, novel object recognition, footprint, and nesting tasks. Following
testing, levels of tau, alpha-synuclein, dopamine, and synaptic proteins were measured by ELISA, Western blot, and immunohistochemistry. Results: We found that TOMA-treated A53T mice performed at the same level as wildtype mice on cognitive and motor tasks, when compared to control IgG-treated mice that were impaired in all tasks. Treating with an antibody for all forms of tau, Tau-13, was not similarly protective and actually appeared to exacerbate the phenotype on certain tasks. We found A53T mice treated with TOMA had lower levels of tau oligomers, while levels of dopamine and synaptic proteins were elevated in TOMA-treated mice. The alpha-synuclein aggregation pathway also appeared to be altered by TOMA treatment. Conclusions: An antibody specific to tau oligomers, as opposed to non-selective targeting of tau protein, effectively protects against toxicity in a synucleinopathy mouse model. This strategy represents a new route for the treatment of diseases with a synergistic relationship between tau and alpha-synuclein.

O5-06-06 TAU TUBULIN KINASE ACTIVATION COINCIDES WITH NEUROPATHOLOGY IN DEMENTIA

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Background: Pathological aggregates of phosphorylated TDP-43 characterize many neurodegenerative diseases including frontotemporal lobar degeneration (FTLD), amyotrophic lateral sclerosis (ALS) and Alzheimer’s disease (AD). The regulation of phosphorylated TDP-43 accumulation is poorly understood. Kinase hyperactivity may be a consistent feature of FTLD, as phosphorylated TDP-43 is not observed in the absence of neurodegeneration. Likewise, tau neuropathology can be triggered by hyperphosphorylation of tau which depends on kinase hyperactivity. Methods: We previously identified Tau Tubulin Kinases 1 and 2 (TTBK1 & TTBK2) as disease relevant TDP-43 kinases in FTLD and ALS using a reverse genetic approach (1). Translational studies in human cells, transgenic mice, and post-mortem dementia patient brain samples are underway to dissect the translational relevance of these findings. We designed these experiments to test whether activation of TTBK1 & TTBK2 underpin the genesis of neurotoxic protein aggregates in dementia. Results: Tau Tubulin Kinase 1 and Tau Tubulin kinase 2 (TTBK1/2) directly phosphorylate both tau and TDP-43 in vitro. Overexpression of TTBK1/2 in cultured cells causes rapid accumulation of neurotoxic hyperphosphorylated tau and TDP-43. TTBK1 & 2 activation drives neurotoxicity in transgenic C. elegans models of tauopathy and TDP-43 proteinopathy. TTBK1/2 processing is aberrant in FTLD patient brain tissues suggesting hyperactivation of the kinase domain. Immunohistochemistry demonstrates strong upregulation of TTBK1/2 kinase levels in affected neurons. Conclusions: Aberrant activation of TTBK1/2 promotes both tau and TDP-43 mediated proteinopathy. These findings suggest activation of both TTBK1 and 2 may be common upstream triggers of neurodegeneration in FTLD. Furthermore, TTBK1 and 2 may contribute to the neuropathology of AD. Reference: 1Nicole F. Liachko, Pamela J McMillan, Timothy J. Strovas, Elaine Loomis, Lynne Greenup, Jil Murrell, Bernardino Ghetti, Murray A. Raskind, Thomas J. Montine, Thomas Bird, James B. Leverenz, Brian C. Kraemer, 2014. The tau tubulin kinases TTBK1/2 promote accumulation of pathological TDP-43. PLOS Genetics 2014 Dec 4;10(12):e1004803. http://dx.doi.org/10.1371/journal.pgen.1004803.

THURSDAY, JULY 28, 2016

ORAL SESSIONS

OS-07 CLINICAL (NEUROPSYCHIATRY AND BEHAVIORAL NEUROLOGY): MEASURING FUNCTIONAL AND COGNITIVE DECLINE

O5-07-01 RACIAL AND ETHNIC DISPARITIES IN MEASURES OF COGNITIVE FUNCTION: IMPACT OF SOCIOECONOMIC STATUS, PHYSICAL FUNCTION, AND MOOD

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Background: Racial and ethnic disparities in cognitive function have long been recognized but most research effort has been focused on Black-White or Hispanic-White comparisons. Large representative epidemiologic studies have identified socioeconomic status (SES), most often measured as years of education, to be an important factor explaining the observed lower performance on cognitive tests among minorities. Health-related factors (cardiovascular risks, physical functionality, mood, psychosocial characteristics) may also play a key role underlying racial/ethnic differences in cognitive performance. However, it is not clear whether the effects of racial, ethnic, and health-related factors are consistent across different measures of cognition (performance vs. self-report).

Methods: In a diverse sample of 351 community-dwelling adults (mean age=69.4±10.1), we compared global cognitive performance (with MoCA) and self-reported cognitive dysfunction (with AD8) among Black (N=69), Hispanic (N=154), and White (N=126) participants. Associations between race/ethnicity, cognitive function, and covariates were assessed with hierarchical linear models with sequenced inclusion of demographic, socioeconomic (combined score of education and occupation), health, functional, and mood indicators. Results: Minorities performed poorer on MoCA and had higher AD8 scores compared to Whites with Hispanics scoring worst. Inclusion of covariates reduced the effect of race/ethnicity on both cognitive outcomes, however an independent effect of race/ethnicity remained. Mediation analyses suggested lower SES contributed up to 1/3 of observed differences in cognitive function in Hispanics on both performance and self-report cognitive measures, and in Blacks on performance-based measures. Decline in physical functionality explained 36% of the MoCA performance differences in Blacks, and depression 38% of the AD8 variability in Hispanics. Conclusions: SES plays a significant role explaining racial/ethnic differences in cognitive performance regardless of type of measurement. Other contributors include health-related characteristics but what factors are important vary by cognitive measure and racial/ethnic group. Lower cognitive performance observed in Blacks was largely due to poor...