PROGRESS IN NEUROSCIENCE PINS

Seminar Series of the
Brain & Mind Research Institute
Weill Cornell Medical College (WCMC)
&
The Graduate Program in Neuroscience of
WCMC and Sloan Kettering Institute

Thursday, 3/24/16, 4 PM, coffee at 3:45 PM
Room A-950

"The Retrotransposon Storm Hypothesis of Neurodegeneration"

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Abstract:

Amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD) are two incurable neurodegenerative disorders that exist on a symptomological spectrum and share both genetic underpinnings and pathophysiological hallmarks. Functional abnormality of TAR DNA-binding protein 43 (TDP-43), an aggregation-prone RNA and DNA binding protein, is observed in the vast majority of both familial and sporadic ALS cases and in ~40% of FTLD cases, but the mechanism by which cell death occurs is not understood. I will advance the novel hypothesis that the cumulative degeneration observed with TDP-43 pathology is due to a morbid loss of control of retrotransposons (RTEs). RTEs are inherited virus like repetitive elements that are capable of replicating and re-inserting into de novo locations within the genome. As a whole, retrotransposon sequences contribute a vast fraction of the genome, up to 40% in humans. My lab has used expression of human TDP-43 (hTDP-43) in Drosophila neurons and glia, a model that recapitulates many of the characteristics of TDP-43-linked human disease including protein aggregation pathology, locomotor impairment, and premature death. We find that expression of hTDP-43 impairs small interfering RNA (siRNA) silencing, which is the major post transcriptional mechanism for retrotransposon control in somatic tissue. The particularly aggressive effects we observe with hTDP-43 expression in glia correlate with early and severe loss of control of a specific retrotransposon (RTE), the endogenous retrovirus (ERV) gypsy. We deduce that gypsy causes degeneration specifically in these flies because we are able to rescue hTDP-43 toxicity by concomitantly blocking expression of this RTE in glia, but not in neurons. Moreover, we provide evidence that activation of DNA damage-mediated apoptosis underlies both neuronal and glial hTDP-43 toxicity, consistent with RTE-mediated effects in both cell types. These findings suggest a novel mechanism in which RTE activity drives neurodegeneration in hTDP-43-mediated diseases such as ALS and FTLD. This RTE hypothesis is consistent with recent findings implicating expression a human retrotransposon, HERV-K, in ALS patients. However, our findings also suggest that a general loss of RTE silencing may be at play.

Recent relevant publications:

1. Activation of transposable elements during aging and neuronal decline in Drosophila. http://www.nature.com/neuro/journal/v16/n5/abs/nn.3368.html. W Li, L Prazak, N Chatterjee, S Grüninger, L Krug, D Theodorou. Nature neuroscience 16 (5), 529-531
2. Transposable elements in TDP-43-mediated neurodegenerative disorders. http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0044099. W Li, Y Jin, L Prazak, M Hammell, J Dubnau. PloS one 7 (9), e44099-e44099
3. The role of transposable elements in health and diseases of the central nervous system. http://www.jneurosci.org/content/33/45/17577.short. MT Reilly, GJ Faulkner, J Dubnau, I Ponomarev, FH Gage The Journal of Neuroscience 33 (45), 17577-17586

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