BURKE MEDICAL RESEARCH INSTITUTE

Weekly Colloquium

Tuesday, 1/16/2018, 12:30pm, Billings Building – Rosedale Conference Room

"Neuropathogenic contributions of dysregulated biogenesis of neuronal ribosomes: Zika virus and beyond"

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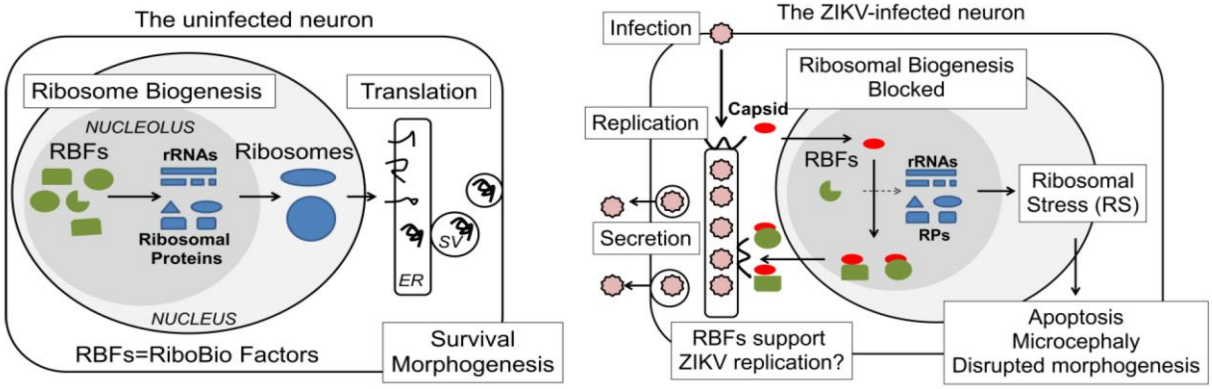
Research Summary:
In dividing cells, ribosome biogenesis not only maintains the translation apparatus but is also linked to a ribosomal stress pathway that provides a major mechanism of tumor suppression. High content of ribosomes and prominent presence of the ribosomal biogenesis center, the nucleolus are common characteristics of various types of neurons. Moreover, neuronal ribosome content and/or ribosome synthesis is reduced in various neurodegenerative diseases such as Alzheimer's, Huntington's or Parkinson's. However, neuropathogenic significance of these events are not clear. In an effort to define role of neuronal ribosomal biogenesis in health and disease we have studied consequences of perturbing that process in cultured forebrain neurons. In such a system, we found ribosomal stress- and Tp53-mediated apoptosis. That pathway required ribosomal protein L11 and was active in neurons that responded to DNA damaging agents regardless of their effects on nucleolar transcription and nucleolar integrity. If ribosomal biogenesis-inhibited neurons were protected from apoptosis, we observed selective impairment of dendritic growth and maintenance without inhibition of general protein synthesis. Such functional consequences fit well with our recent demonstration of nucleolar enrichment of 9 rat brain proteins whose human counterparts are mutated in microcephaly and/or intellectual disability syndromes. Most interestingly, we observed ribosomal stress in Zika virus infected neurons and neuroprogenitor cells. We also showed that the overexpressed Zika capsid protein accumulated in nucleoli and was sufficient to induce ribosomal stress- and L11/Tp53-mediated apoptosis. As with the live virus, also the Zika capsid protein was most anti-ribosomal and pro-apoptotic in the context of post-mitotic neurons. We speculate that this sensitivity is related to low spare capacity of ribosome synthesis in such cells. Hence, dysregulation of ribosomal biogenesis deserves more research effort to conclusively evaluate its pathogenic potential in both neurodevelopmental- and neurodegenerative diseases.



Publications:
Slomnicki L.P., M. Pietrzak, A. Vashishta, J. Jones, N. Lynch, S. Elliot, E. Poulos, D. Malicote, B.E. Morris, J. Hallgren, **M. Hetman (2016)** Requirement of Neuronal Ribosome Synthesis for Growth and Maintenance of the Dendritic Tree. ***J. Biol. Chem.*** 291: 5721-39. PMCID: PMC4786710.

Slomnicki L.P., A. Malinowska, M. Kistowski, A. Palusinski, J. J.Zheng, M. Sepp, T. Timmusk, M. Dadlez, **M. Hetman** (**2016**) Nucleolar enrichment ofbrain proteins with critical roles in human neurodevelopment. ***Mol. Cell. Proteomics.*** 15: 2055-2075. PubMed PMID: 27053602.

Slomnicki L.P.,J. Hallgren, A. Vashishta, S.C. Smith, S.R. Ellis, **M. Hetman (2016)** Pro- apoptotic requirement of ribosomal protein L11 in ribosomal stress-challenged cortical neurons, ***Mol Neurobiol.*** https://doi.org/10.1007/s12035-016-0336-y

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