G-quadruplex Structures as Targets and Tools in ALS

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Principal Investigators

IVANOV, PAVEL

Institution

BRIGHAM AND WOMEN'S HOSPITAL

Contact information of lead PI
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Research Abstract

? DESCRIPTION (provided by applicant): Amyotrophic Lateral Sclerosis (ALS) is a fatal neurodegenerative disease that currently has no cure. We propose to investigate the roles of G-quadruplex (G4) structures and G4-assembling molecules in neurodegeneration and ALS pathogenesis. G4s are unique structures associated with multiple biological processes including genetic instability, transcriptional and post-transcriptional regulation of gene expression. We have previously identified novel stress response pathway, which is triggered by the ribonuclease

angiogenin (ANG) by cleavage of cytoplasmic tRNA molecules to produce tRNA-derived stress-induced RNAs (tiRNAs). In turn, selective tiRNAs that are capable of assembling G4 structures (G4-tiRNAs) protect motor neurons from stress-induced injuries and death. This neuroprotection is achieved by the ability of G4-tiRNAs to reprogram gene expression on post-transcriptional level and by promotion of Stress Granules (SGs), pro- survival RNA granules implicated in the pathogenesis of ALS. Significantly, the disease-associated hexameric GGGGCC (G4C2) repeat expansion in the first intron of C9ORF72 gene is the most common genetic cause of frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (C9-FTD/ALS). Number of studies has shown that C9ORF72 transcripts with pathological G4C2 repeats (referred as RNA-G4C2 or rG4C2) significantly contribute to the development of C9-FTD/ALS. We and others have recently discovered that rG4C2 repeats assemble G4s. We hypothesize here that G4s play important regulatory roles, which are altered upon their amplification (such as observed during G4C2 expansion). Understanding of the physiological roles of G-quadruplexes in the context of neurodegeneration will provide important insights into the cellular and molecular mechanisms of ALS, and will evaluate novel G4- based therapeutic approaches for the treatment of motor neuron disease.

Further information available at:

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