Genomic profiling of pathological R-loop formation in human diseases.

https://neurodegenerationresearch.eu/survey/genomic-profiling-of-pathological-r-loop-formation-in-human-diseases/

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Genomic profiling of pathological R-loop formation in human diseases.

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NIH (NINDS)

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4

The project/programme is most relevant to:

Motor neurone diseases

Keywords

genomic profiles, Ewings sarcoma, single molecule, Cover-up, Amyotrophic Lateral Sclerosis

Research Abstract

PROJECT SUMMARY/ABSTRACT R-loops are three-stranded nucleic acid structures that universally form during transcription upon invasion of the duplex DNA by the nascent RNA

behind the advancing RNA polymerase. Recent profiling studies from my group have established that R-loop formation is prevalent, covering up to 5% of the human and mouse genomes. This makes R-loops the most abundant non-B DNA structure to date. Under normal conditions, R- loops are thought to be facilitate important nuclear processes such as open chromatin patterning, efficient transcription termination, and DNA replication origin licensing. Under pathological conditions associated with various gene mutations, however, dysfunctional R-loop metabolism is thought to cause DNA replication stress, mutagenesis, DNA breakage, and genomic instability. These negative outcomes are relevant for the pathogenesis of human disorders, including neurodevelopmental / degenerative diseases such as Fragile X syndrome, Amyotrophic Lateral Sclerosis (ALS), and myelodisplastic syndromes (MDS). The main goal of this proposal is to understand what distinguishes “good” from “bad” R-loops. The main hypothesis driving the work is that R-loop dysfunction in disease states entails changes in R-loop distribution, abundance, size, and/or turnover rates. The overall objectives of the proposal are to: 1) develop new technologies that can accurately measure R-loop footprints on a single molecule basis, and R-loop turnover on a global scale; and 2) apply these methods to three important human disease models (ALS, MDS, Ewing sarcoma) that exemplify the suspected links between disease pathogenesis and R-loop dysfunction. The following Aims are proposed. Aim 1: Develop a single-molecule, SMRT-based, R-loop footprinting method. Aim 2: Measure R-loop turnover on a global scale. Aim 3: Measure R-loop formation and turnover under pathological conditions associated with splicing dysfunction. Aim 4: Measure the impact of EWSR1 deficiency on R-loop formation and turnover in Ewing sarcoma. This proposal will lead to new genomics technologies to comprehensively assess R-loop formation and dynamics at the single molecule and global levels. These tools will enable us to identify, for the first time, the salient molecular features that distinguish “normal” from “pathological” R-loops and provide novel insights into molecular mechanisms involved in cancer and neurodegenerative diseases.

Lay Summary
PROJECT NARRATIVE Proper gene expression is critical for all life forms. Yet, gene expression is increasingly recognized as a destabilizing force for our genomes. In certain human disorders, gene expression is in fact thought as triggering damaging events of chromosomal DNA breakage. This proposal seeks to understand how gene expression can cause DNA damage and to decipher the molecular differences between normal gene expression and disease-associated gene expression. This will be accomplished by developing new cutting- edge genetics technologies and applying them to important disease models ranging from neurodegenerative disorders to cancers.

Further information available at:

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Investments > €500k

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United States of America

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Motor neurone diseases

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