Research project:

Molecular mechanisms of R-loop-mediated frataxin gene silencing

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Scientific Summary

Friedreich's ataxia (FA) is the most common inherited ataxia, characterised by progressive sensory ataxia and cardiomyopathy. It is caused by an expanded GAA repeat sequence in intron 1 of the frataxin (*FXN*) gene, resulting in frataxin mRNA and protein deficiency. The molecular mechanism, underlying the pathology of FA, is not well understood, however it was proposed that unusual DNA/RNA structures may form over the expanded repeats of *FXN* gene and cause disease pathology.

Using unique methodology established in their lab, this group recently demonstrated that *FXN* silencing involves formation of RNA/DNA hybrids (R-loops) over the expanded repeats. The main focus of this research project is to understand the molecular mechanism of R-loop-mediated *FXN* gene silencing.

In particular, they will investigate the interplay between R-loops, repressive heterochromatin formation and *FXN* transcriptional silencing in iPS-derived neuronal cells. They hypothesise that R-loops may directly recruit chromatin modifying enzymes or RNA interference factors to silence the *FXN* gene. Using comparative proteomic approaches, they will identify such R-loop-interacting factors and study their contribution to pathology of FA.

In the longer term, the knowledge obtained in this project will be utilised to design R-loop-targeting therapeutic strategies to treat FA.

Lay Summary

Friedreich's ataxia (FA) is caused by mistakes (or mutations) in the frataxin gene. The frataxin gene contains instructions that allow cells to make the frataxin protein. The mutation in the gene results in the production of less frataxin protein, which causes the symptoms associated with FA.

Genes are a code made up of the letters A, T, G and C. A specific region of the frataxin code contains the letters 'GAA', repeated up to 33 times in people without FA. In the genetic code of people with FA, the number of repeats of 'GAA' is increased, up to 1000 times. Even though this was discovered as the genetic cause of FA in 1996, we still do not fully understand how this causes FA, representing a major challenge in the development of efficient therapies. This project intends to bridge this gap by studying the role of unusual structures, called R-loops, which are formed over the GAA repeats in

cells from FA patients. These R-loops accumulate in patient cells and trigger a chain of damaging cellular events which lead to FA.

These researchers will use their extensive knowledge of R-loops, combined with innovative technologies, to uncover how R-loops contribute to neurodegeneration in FA. They will also examine how R-loops influence the severity of the FA condition, and which other proteins are involved. This research project will make a significant impact on our understanding of the underlying cause of FA and, in the long term, this could lead to new treatment approaches.

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