A vicious cycle: Deconstructing the timeline of DNA damage response and mitochondrial alterations

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Keywords: DNA damage, Mitochondrial activity, cellular models

Abstract:

Background. DNA damage and impaired mitochondrial activity have been already extensively correlated in several types of neurodegenerative diseases, including amyotrophic lateral sclerosis (ALS). However, the exact mechanisms underlying this association is not yet completely understood. Indeed, it is still a matter of debate if the DNA damage causes the impairment of mitochondrial activity, or vice versa.

Aim. The aim of this work is to determine the connection between mitochondrial function and nuclear genome integrity and whether we can intervene to prevent the vicious feed-back loop that eventually leads to the death of neurons in ALS.

Models. We will try to dissect the link between these two hallmark of neurodegeneration in the context of the most common genetic cause of ALS - the C9orf72 G4C2 hexanucleotide repeat expansion (HRE) mutation, in which both DNA damage and mitochondrial dysfunction have been reported in cell and animal models, and in patient-derived iPSC neurons and tissue. Specifically, we are using a stable isogenic motor neuron-like NSC-34 cell model with Tet-inducible expression of the pathogenic repeats. In addition, we are using an inducible model of U2OS cells, called DiVA (for DSB Inducible via AsiSI), which rely on the inducible expression of the AsiSI restriction enzyme upon 4-hydroxy tamoxifen (4-OHT) induction to generate DNA double-strand breaks (DSBs) at known genomic positions.

Results. Our preliminar results in both model system indicate that the appearance of DNA damage in the nucleus precedes mitochondrial dysfunction supporting our working hypothesis. These preliminary data need to be further investigated by measuring not only mitochondrial membrane potential but also additional parameters of mitochondrial function. In addition, we will also test the effect of inhibitors of the cellular response to DNA damage and of antioxidant compounds to try and uncouple the two phenomena.