Study of the association of microRNA and mitochondria and their role in regulation of neuronal cell death in Fragile X Tremor Ataxia Syndrome (FXTAS)

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Study of the association of microRNA and mitochondria and their role in regulation of neuronal cell death in Fragile X Tremor Ataxia Syndrome (FXTAS)

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4

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Research Abstract

Fragile X-associated tremor/ ataxia syndrome (FXTAS) is an inherited neurodegenerative disorder characterized by progressive intention tremor, gait ataxia and cognitive decline. Nearly 1 in 3 000 adult male has a lifetime risk of developing FXTAS, which make of FXTAS one of the

most common single gene causes of tremor, ataxia and cognitive decline. Importantly, FXTAS shares some common features with other neurodegenerative diseases, such as Parkinson's disease.
FXTAS is caused by an expansion of 55 to 200 CGG repeats in the 5'-UTR of the FMR1 gene. Others and we found that expanded CGG repeats are transcribed and accumulate into nuclear RNA aggregates that sequester specific proteins and are deleterious to neuronal cells (Sellier et al., EMBO J, 2010). Recently, we identified that the enzymatic complex, DROSHA-DGCR8, specifically bind to expanded CGG repeats in vitro and in FXTAS cell models. DROSHA-DGCR8 complex is responsible of the processing and biogenesis of microRNAs, a class of small RNAs essential to cell function and survival. Consequently to DROSHA-DGCR8 sequestration, the expression of microRNAs is decreased in FXTAS patients, ultimately resulting in neuronal cell death (Sellier et al., Cell reports, 2013).
However, the precise molecular mechanisms of neuronal cell dysfunction and cell death in FXTAS are still unclear. A promising lead is the mitochondria, since mitochondrial alteration leads to parkinsonism, a promising feature of FXTAS; also, mitochondria are known to be altered in FXTAS cell models and finally, Prof. Rajesh Singh (University of Baroda, India) recently established that mitochondria expressed a specific pool of microRNAs (Sripada et al., 2012). Thus, we propose to take advantage of our recent discovery of microRNA misregulation in FXTAS to develop collaboration with Prof. Singh group in order to:
1 – Determine whether microRNAs associated with mitochondria are altered in FXTAS cell models, mouse models and patient brain samples;
2 – Determine whether the decreased expression of mitochondrial-specific microRNAs has any cellular consequences, notably on mitochondria function and neuronal cell survival.
3 – Determine whether re-expression of a specific subset of microRNAs could rescue neuronal cell death in models of FXTAS.
This is an innovative proposal since microRNAs and mitochondria are not yet linked in FXTAS, and mitochondria dysfunction is a key component of Parkinsonism, a key feature of FXTAS. Furthermore, microRNAs are known to be stable in body fluids and cellular environment, hence had great potential as biomarker and therapeutic potential. In conclusion, our proposal may open new avenue to better understand these neurodegenerative diseases, and potentially develop innovative therapeutic approaches.

Further information available at:

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