

Fonctions de FMRP (Fragile X Mental Retardation Protein) dans les complexes ribonucleoprotéiques neuronaux et liens avec la physiopathologie du syndrome de l' X Fragile



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FRAXA-mRNP: Mechanism of function of FMRP (Fragile X Mental Retardation Protein) in the neuronal ribonucleoparticles and link with the physiopathology of the Fragile X syndrome

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Fragile X syndrome is the most common form of inherited mental retardation. It is due to the silencing of *FMR1* gene encoding FMRP (Fragile X Mental Retardation Protein), an RNA binding protein involved in several steps of mRNA metabolism: nucleocytoplasmic trafficking, translational control and also transport of mRNAs to specific locations for localized translation (i.e. synapses). The loss of FMRP is involved in the consolidation of a form of long-term depression that is enhanced in *Fmr1* null mice and in the elongation of dendritic spines, resembling synaptic phenotypes over-represented in Fragile X brain. The consolidation of memory and several distinct forms of synaptic plasticity considered to be substrates of memory require mRNA translation and may be associated with changes in spine morphology. A better understanding of the composition of FMRP-containing ribonucleoparticles, their dynamic and the function played by FMRP and its interactors within them is crucial to unravel the fine tuning of proteins expression within neuro

Analysis of the functions of FMRP neuronal ribonucleoparticles: mRNA targets, interacting proteins, regulatory pathways involved

To better understand the function of FMRP in the context of its containing complexes, we proposed (and performed) an integrated approach to define the molecular basis of fragile X syndrome by dissecting the function of FMRP in neuronal ribonucleoparticles :

a) Characterization of the RNA binding properties of FMRP: By re-analyzing the FMRP target mRNAs already identified, we identified novel RNA sequences/structures directly bound by FMRP. The functional significance of these interactions as well as previously identified ones was analyzed in primary neurons.

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b) Characterization of FMRP-containing ribonucleoparticles: Combining different techniques we identified and characterized several FMRP-interacting proteins. In particular we studied their function and the influence they have on the functional properties of FMRP.

c) Identification of FMRP implication in several pathways in neurons. We determined the functional importance of the implication of FMRP in the micro-RNA pathway, splicing and transport along dendrites.

This project was coordinated by Barbara Bardoni (Team 1-Nice) with the collaboration of Hervé Moine (Team 2-Strasbourg) and Michel Simonneau (Team3-Paris). The project started on January 2007 and ended on July 2010. The project received 360000 € from ANR and had a global cost of 2943000 €. We produced 12 articles on this subject in international scientific journals, most of them with high impact factor. 6 additional papers have been produced on subjects related to the project. 6 students obtained a PhD related to this project.

The results obtained have been the starting point to develop new projects and to ask new grants.

List of Publications

A total of 18 publications have produced by this consortium A selection of them is reported here:

-Davidovic L, et al. (2007) The fragile X mental retardation protein is a molecular adaptor between the neurospecific KIF3C kinesin and dendritic RNA granules. *Hum Mol Genet.*16: 3047-58.

-Bechara EG, et al. (2009) A novel function of Fragile X Mental Retardation Protein in translational activation of *Sod1* mRNA. *Plos Biology*, 7(1):e16.

-Didiot MC, et al., (2009). Cells Lacking the Fragile X Mental Retardation Protein (FMRP) have Normal RISC activity but exhibit altered stress granule assembly. *Mol Biol Cell.* 20: 428-437.

-Subramanian M, et al., (2011) G-quadruplex RNA structure as a signal for neurite mRNA targeting. *EMBO Report.* May 13. [Epub ahead of print]

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