New insights that link Fragile X syndrome and autism spectrum disorders

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Fragile X syndrome (FXS) is the most common cause of inherited intellectual disability (ID), as well as the most frequent monogenic cause of autism spectrum disorders (ASD). FXS is caused by the absence or incorrect production of the protein FMRP (Fragile X Mental Retardation Protein). Scientists at VIB and KU Leuven (Belgium), in collaboration with Tor Vergata University (Italy) and VU University of Amsterdam (The Netherlands) have pinpointed a novel role that FMRP plays during the embryonic development of the brain cortex. The study reveals that the absence of FMRP leads to a delay in the proper formation of the cortex and shows that FMRP is responsible for transformation of neurons into a "locomotion mode" to reach their final position in the cortex. This delay in the neurodevelopmental program has an effect on the early postnatal life and the fine-tuning of brain connectivity.

"Our research underlines the critical role of FMRP in brain development, more specifically in the correct positioning of brain cells during the early stages of development of the cortex. These findings contribute to our current understanding of Fragile X and might provide insights into the cellular mechanisms affected in patients with Fragile X that have autism spectrum disorders and epilepsy: two neurological disorders marked by affected cortical development and brain connectivity" says Claudia Bagni (VIB/KU Leuven/University Tor Vergata) who led the work.

The discovery in brief: FMRP, an important player in

the development of our brain

The study of the Fragile X syndrome (FXS) has been the research object of Claudia Bagni and her team for more than 15 years. Using a mouse model for FXS, her collaborators Giorgio La Fata, Annette Gärtner and Nuria Domínguez-Iturza could prove that FMRP regulates the maturation (multipolar to bipolar) and positioning of the brain cells in the cortex during embryonic development. Furthermore the team unraveled the molecular mechanism through which FMRP regulates this processes and were able, upon the reintegration of FMRP in the embryo, to normalize the early postnatal brain wiring deficits.

The brain cortex is the domain of the brain where information from the rest of the body is received, processed and interpreted. The elaborated information is then converted into thoughts and concrete driving signals for the body. Thus, mistakes or delays in the correct development of the brain cortex are thought to lead to an impaired ability to interpret and process information required for our daily life. Because affected brain connectivity is a hallmark of ASD, this study might explain why some patients with FXS have autism-related symptoms.

FMRP is a key regulator of cell shape and polarity

The team could demonstrate that in a healthy brain FMRP assures the correct production of the protein N-Cadherin. In the absence of FMRP the levels of N-cadherin are reduced with the consequence that neuronal cells are delayed in their maturation, a developmental program called multipolar to bipolar transition, which is prerequisite for correct positioning in the cortex during development. In collaboration with Carlos Dotti (VIB/KULeuven) and Meredith Rhiannon (VU University of Amsterdam), the team showed that the re-introduction of FMRP or N-cadherin before birth normalized the maturation and positioning of the

brain cells and the wiring deficits observed at early postnatal stages.

Into sophisticated MRI for diagnosis of intellectual disabilities

Finally, in collaboration with the team of Uwe Himmelreich (MOSAIC, KU Leuven) the VIB/KUL/TV scientists combined the cellular and molecular approaches with high-resolution DTI-MRI (Diffusion-Tensor Imaging - Magnetic Resonance Imaging). Currently, DTI-MRI is one of the most powerful tools to anatomically investigate brain connectivity, as it can be used to study the orientation and integrity of white matter tracts. Taking advantage of an extremely powerful MRI system for small animals, which enables to scan the brains of FXS mice, the scientists obtained structural information of the juvenile FXS mouse brain that revealed abnormalities in the connectivity of the cortex.

Claudia Bagni: "Our observations, while contributing further to the understanding of the wide spectrum of FXS symptomatology, strengthen the importance of embryonic development for postnatal brain activity and circuitry in FXS and related disorders. Impaired brain connectivity has been recognized as a candidate key defect in ASD. The future challenge will be to understand how to ameliorate those deficits at very early postnatal stages, for example "enriched environmental conditions" and also to establish sophisticated MRI strategies with prognostic value for FXS to ultimately guide parental counseling."

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