TARGETING MITOCHONDRIA IN NEURODEVELOPMENTAL DISEASES

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RATIONALE
Mitochondrial function integrates signalling networks in several metabolic pathways controlling neurogenesis and neuroplasticity (1). Disturbance in mitochondrial function and signalling leads to change in neural cell fate and negatively affects neurogenesis and neuroplasticity processes. Indeed, intellectual disability-related diseases from different aetiology, as Down syndrome (DS), Rett syndrome (RTT), Fragile X syndrome (FRAX) and autism spectrum disorders (ASD), correlate with mitochondrial dysfunctions (2,3).

In this light we have studied:
- whether and how deficit in mitochondrial function is critical in the pathogenesis of some neurodevelopmental diseases of genetic origin;
- how to improve neurogenesis process targeting mitochondrial bioenergetics.

RELEVANT RESULTS
We have identified and characterized the molecular mechanisms responsible for mitochondrial dysfunction and energy deficit occurring in Down, Rett, CDKL5 and Fragile X syndromes (4-12). Functional and molecular analyses were performed in vitro in neural progenitor cells (NPCs) isolated from hippocampus of the Ts65Dn mouse model of DS, in vivo in cryopreserved whole brain and in specific brain areas (13) from animal models of DS (Ts65Dn), RTT (MeCP2-null or -deleted mice) and FRAX (Fmr1 KO mouse), as well ex vivo in human trisomy 21 fibroblasts and lymphocytes from DS patients.

Dysregulation of selective signaling pathways, as a result of the genetic alterations, lead, as common features shared in DS, FRAX and RTT, to an impairment of mitochondrial OXPHOS apparatus resulting in cell and brain energy deficit and oxidative stress.

We disclose the capability of some bioactive drugs of natural origin, such as epigallocatechin 3-gallate and resveratrol in DS (14-16) or a drug already used for treatment of other diseases, such as metformin in RTT (17), to target selective mitochondrial regulatory signaling pathways, to reverse mitochondrial impairment and to improve neurobiological alterations and some neurobehavioral phenotypes.

REMARKS AND PERSPECTIVE
- We collected evidences demonstrating that mitochondrial alterations principally affect the brain, which is highly vulnerable to energy deficit and susceptible to oxidative stress.
- We propose that mitochondrial function inadequacies could be a central etiologic mechanism in the poor brain function leading to intellectual disability representing a key hallmark in neurodevelopmental diseases.
- Natural bioactive compounds, such as polyphenols, due to their long-term safety profile and efficacy could be recommended as early therapeutic interventions in DS and other neurodevelopmental diseases.
- A pilot clinical trial is actually underwear to test, in children with DS and ASD, the effect of nutraceutical supplementation in early infancy on mitochondrial function and other biological parameters.
- We plan to develop new nutraceutical formulation for improving drug delivery and anticipate treatment in early childhood.
References:
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