DOTTORATO DI RICERCA IN BIOLOGIA CELLULARE E DELLO SVILUPPO

40th CYCLE
Project proposal for a Sapienza PhD scholarship

Main research line

Title: Nr2f1-dependent regulation of Mitochondrial Function in Neural Development and Disease

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Summary

Mitochondria are essential organelles that are dynamically regulated in neural cells. Although it is becoming clear that mitochondria regulation is key to control neurogenesis, the mechanisms governing mitochondrial dynamics in neural stem/progenitor cell (NSPC) self-renewal and neuronal differentiation remain largely elusive. The transcriptional regulator Nr2f1 is expressed in NSPCs and neurons of the mouse hippocampus and plays a crucial role in adult hippocampal neurogenesis[1]. It was recently found that Nr2f1 regulates several genes involved in mitochondrial dynamics and function[2]. Accordingly, a reduced mitochondrial mass and an increase of mitochondrial fragmentation in Nr2f1-deficient hippocampal neurons was observed[2]. These results are particularly relevant considering that mutations in NR2F1 coding sequence cause Boonstra-Bosch-Schaff optic atrophy syndrome (BBSOAS), a rare human autosomal-dominant neurodevelopmental disorder[3,4]. BBSOAS is characterized by multiple clinical features, including optic nerve atrophy, intellectual disability and autistic traits which are compatible with altered mitochondrial function in the brain[3,4]. Thus, Nr2f1-mediated control of mitochondrial dynamics in neural cells may contribute to the pathogenesis of BBSOAS. However, the effects of Nrf21-deficiency on mitochondrial dynamics and mitochondrial metabolism, and the consequences of these effects on the self-renewal and differentiation of Nr2f1-deficient NSPCs are still unknown. In this project, we plan to use in vitro culture systems of mouse hippocampal NSPCs to assess the transcriptional and biological pathways regulated by Nr2f1 through genome-wide molecular profiling of Nr2f1-deficient cell cultures, and to characterize the role of Nr2f1 in mitochondrial function unraveling its implications in NSPC proliferation and differentiation. To achieve these goals, the project gains on the specific expertise of the host lab in neurogenesis, in the use of in vitro NSPC models and in transcriptomic/epigenomic approaches. By addressing the role of the Nr2f1-dependent mitochondrial alterations in hippocampal NSPCs, and their molecular underpinnings, this proposal shall lead to the identification of novel biomarkers and therapeutic targets for BBSOAS and other neurodevelopmental disorders associated with mitochondrial dysfunctions, paving the way towards the development of effective therapies.

Pertinent Publications of the proponent (last 5 years)

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