TITLE

Exploring The Pathogenetic Basis of ICF Syndrome With Human Induced Pluripotent Stem Cells

DESCRIPTION

Immunodeficiency, Centromeric instability and Facial anomalies (ICF) syndrome is an autosomal recessive disorder mainly affecting the immune response. Human genetic studies have identified that most patients carry genetic mutations in the DNA methyltransferase DNMT3B. Consequently, cells derived from patients exhibited significantly reduced CpG methylation. Transgenic mouse modelling genetic mutations in human ICF syndrome do not fully recapitulate the human pathogenesis of the syndrome. Also, being a very rare disease the patients' cells mainly come as immortalized lines.
Therefore, we plan to use a human stem cell model that is better suited to explore the molecular basis of ICF syndrome. Human iPSCs carrying ICF-like DNMT3B mutations, with well-characterized pluripotency and capacity to differentiate in vitro in tissue culture and form teratomas, are available in our laboratory. First, we aim at comparing the hematopoietic differentiation of control and ICF-mutant iPSCs to determine the mechanisms by which DNMT3B deficiency gives rise to ICF immune dysfunction. Secondly, we aim at identifying the kinetics of transcriptional and epigenetic disorders in ICF-iPSCs and thus, to detect at which stage of B-lymphocyte differentiation defects in methylation, transcriptional and chromatin profiles occur and in which order. We will address the hypothesis that mutant DNMT3B is mistargeted to genomic sites through the aberrant interaction with non-coding RNAs, thereby leading to hypomethylation and epigenetic gene dysregulation. The proposed research is expected to establish a more appropriate model to clarify the pathogenesis of ICF syndrome and the role of DNMT3B in human cell physiology. Overall, we believe that our findings may provide fundamental insights to get closer to therapeutic interventions for ICF syndrome.

SELECTION CRITERIA

Eligibility Criteria

- Academic degree: Applicants shall have a master degree or equivalent in **Life** or **Natural sciences** (e.g. Biology, Biochemistry, Biotechnology, Molecular biology, or related fields), corresponding to the second level of studies.
- Mobility rule: There will be no nationality restrictions. Applicants can be from any Country. However, according to the mobility rule, at the time of the application deadline researchers should not have resided or carried out their main activity (work, studies, etc.) in Italy for more than 12 months in the 3 years immediately prior to the reference date. Compulsory national service and/or short stays such as holidays will not be taken into account.
- Research experience: Applicants shall, at the time of the application deadline, be in the first four years (full-time equivalent research experience) of their research careers and not yet awarded a doctoral degree.

Full-Time Equivalent (FTE) Research Experience will be determined from the date when a researcher obtained the degree which would formally entitle him or her to embark on a doctorate, either in the country in which the degree was obtained or in Italy, irrespective of whether or not a doctorate is or was ever envisaged.

Evaluation Criteria

Step 1 -Evaluation of documentation provided by the candidate: a) Academic record and training b) Research activities c) CV/motivation letter; d) Level of English; e) Reference letters.

Step 2 - Interview: a) Scientific knowledge in the field of interest; b) Research experience in the field of interest c), Motivation; d) English proficiency.