Poster P.04.24

PRE-CLINICAL IDENTIFICATION OF DRUGS TARGETING POLG DISORDERS BY USING A ZEBRAFISH/YEAST TRANS-SPECIES APPROACH (ZIPPY)

Baruffini E.[1], Lodi T.[1], Donnini C.[1], Delahodde A.[2], Beffagna G.[4], Facchinello N.[3], Tiso N.*[3], Argenton F.[3]

[1]Department of Chemistry, Life Sciences and Environmental Sustainability, University of Parma ~ Parma ~ Italy, [2]Institute for Integrative Biology of the Cell, Université Paris-Sud ~ Orsay ~ France, [3]Department of Biology, University of Padova ~ Padova ~ Italy, [4]Department of Cardio-Thoraco-Vascular Sciences and Public Health ~ Padova ~ Italy

In humans, the mitochondrial DNA (mtDNA) is replicated by the DNA polymerase gamma (POLG) and its accessory unit POLG2, both encoded by nuclear genes. Mutations in these genes cause at least six mitochondrial diseases with Mendelian inheritance, collectively named POLG-related disorders, characterized by mtDNA depletion or accumulation of multiple deletions. To date, more than 300 pathogenic mutations have been reported in the Human DNA Polymerase Gamma Mutation Database. The mutations are associated with a spectrum of clinical presentations, ranging from infantile-onset epilepsies, liver failure, polyneuropathy, ataxia, dilated/hypertrophic cardiomyopathy to late-onset ophthalmoplegia and muscle weakness. To a limited extent, clinical phenotypes correlate with the mtDNA phenotype.
The therapeutic treatment of POLG diseases is currently limited to symptom management.
Taking advantage of simple and cost-effective models, such as the unicellular yeast and the invertebrate C. elegans, we have already identified a panel of yeast/worm-prescreened drugs, worth to be investigated in a vertebrate setup; in parallel, we have generated Polg and Polg2 mutants in the vertebrate zebrafish, faithfully modelling the human condition.
The main goal of our project is the identification of drugs with therapeutic effects on mitochondrial pathologies linked to POLG or POLG2 genes. We will adopt a multi-species approach, based on drug pre-screen in Polg-deficient yeast (mip1) and C. elegans (polg-1) strains, followed by drug validation in zebrafish (zf) Polg and Polg2 mutants.
The screen of drugs in yeast will be performed by evaluating the rescue of respiratory growth defects due to mtDNA instability (“petite” phenotype) in mip1 mutants. More in-depth analysis will include quantitative evaluation of Mip1 expression, respiratory activity and mtDNA levels. Positive hits will be analyzed in zf Polg models, evaluating the rescue of pathological phenotypes, including mtDNA depletion, impaired respiratory activity and altered mt-nucleus retrograde signaling.

Identificazione di farmaci per le patologie POLG tramite test su sistemi lievito-zebrafish (ZIPPY)

All’interno delle cellule umane esistono degli organelli, chiamati mitocondri, che assolvono il compito di piccole centrali energetiche. Questi organelli sono dotati di un proprio patrimonio genetico, chiamato DNA mitocondriale, la cui quantità ed integrità viene mantenuta dal lavoro di due proteine, POLG e POLG2. Se, a causa di mutazioni, queste due proteine non funzionano, si genera una serie di malattie chiamate collettivamente patologie POLG-collegate. Questi disordini possono manifestarsi, a seconda dei casi, con epilessie infantili, insufficienza epatica, neuropatia, cardiomiopatia, disfunzione della mobilità oculare, perdita di coordinazione e debolezza muscolare.
Allo stato attuale non esistono farmaci per contrastare le patologie POLG e il loro trattamento si limita alla gestione dei sintomi.
Il nostro progetto intende saggiare una rosa di farmaci che ha già avuto dei riscontri positivi su due organismi molto semplici, il lievito S. cerevisiae e il verme C. elegans. Questi farmaci verranno ora testati su nuovi modelli per queste malattie, altrettanto miniaturizzati ma molto più complessi,

rappresentati da embrioni di pesce zebrafish, mutati negli stessi geni per le proteine POLG e POLG2. Poiché recentemente il nostro gruppo ha identificato un farmaco con effetti curativi simili in lievito, verme e pesce, questo ci incoraggia a tentare l'impresa su ampia scala, alla ricerca di un maggior numero di molecole con efficacia terapeutica per le patologie POLG.

Rahman S, Copeland WC. POLG-related disorders and their neurological manifestations.
Nat Rev Neurol. 2019 Jan;15(1):40-52. PMID: 30451971

Patologie POLG-collegate

Coordinator: Francesco Argenton
Partner: Enrico Baruffini
Duration (N. Years): 3
Starting year: 2019

Telethon Project (nr):

GGP19287

Disease Name:

Polg-Related Diseases

Keywords:

POLG, yeast, zebrafish