9° Giornata della Ricerca della Svizzera Italiana
Venerdì 15 marzo 2019

Modulo per la sottomissione abstract ricerca di LABORATORIO

Titolo (massimo **15 parole**)

Hunter's syndrome: characterization of four nonsense mutations in iduronate 2-sulfatase

Autori (cognome e iniziali, es: Grassi L.)

Marazza A.(1, 2), Quadroni M. (3), Galli C. (1), Fasana E. (1), Fassi E. (1), Sgrignani J. (1), Cavalli A. (1), Molinari M. (1, 4)

Affiliazioni (ospedale o istituto, servizio o reparto, indirizzo, es: Ospedale Regionale di Lugano, Servizio di angiologia, Lugano)

(1) Institute for Research in Biomedicine, Faculty of Biomedical Sciences, Università della Svizzera italiana, CH-6500 Bellinzona, Switzerland
(2) Graduate School for Cellular and Biomedical Sciences, University of Bern, 3000 Bern, Switzerland
(3) Center for Integrative Genomics, University of Lausanne, CH-1015 Lausanne, Switzerland
(4) School of Life Sciences, École Polytechnique Fédérale de Lausanne, CH-1015 Lausanne, Switzerland

Testo (massimo **250 parole**, preferibilmente in italiano (accettato anche in inglese), suddiviso in Introduzione, ***Metodi***, ***Risultati***, ***Conclusioni*** e ***Finanziamento***

Hunter's syndrome (or mucopolysaccharidosis type II) is a rare X-linked lysosomal storage disease where an enzyme involved in heparan and dermatan sulfate degradation, known as iduronate 2-sulfatase (IDS), is dysfunctional. This results in glycosaminoglycan accumulation within the lysosomes. Although more than 400 mutations have been described in several populations, little is known concerning biogenesis, trafficking and degradation of IDS. In this project, we analyze the intracellular fate of four disease-related nonsense mutations of IDS (W337X, R443X, Y452X and L482X) and of the wild type (WT) form of the protein. Our analyses showed that the nonsense mutants as well as WT IDS are efficiently and co-translationally formylated at cysteine 84. This posttranslational modification is required for the IDS enzymatic activity. However, IDS W337X is degraded by the ubiquitin-proteasome system (UPS), whereas R443X, Y452X, L482X are appropriately transported to the lysosome, where they should exert their hydrolytic activity, but are rapidly destroyed by lysosomal enzymes resulting in a loss of function phenotype. Only WT IDS is post-translationally modified (formylated), correctly targeted to the lysosomes and shows enzymatic activity, which can be measured with a fluorimetric enzymatic assay. The nonsense mutations introduce a stop codon causing premature termination of the IDS chains. Thus, all mutants lack an 18 kDa polypeptide that, based on crystallographic and dynamic-molecular analysis, could play a regulatory role. Studies to evaluate the possibility to complement lack of the C-terminal polypeptide portion to re-establish stability and function of the IDS mutant is ongoing.

Visto superiore* (prego indicare **Nome e Cognome** del superiore) ***campo obbligatorio**

Maurizio Molinari

Criteri per sottomissione Abstract:
NO Case report
NO Abstract senza nessun risultato
VISTO da un superiore

Invio Abstract