Finanziato dall'Unione europea NextGenerationEU | Ministero dell'Università e della Ricerca | Italiadomani PIANO NAZIONALE DI RIPRESA E RESILIENZA | Consiglio Nazionale delle Ricerche

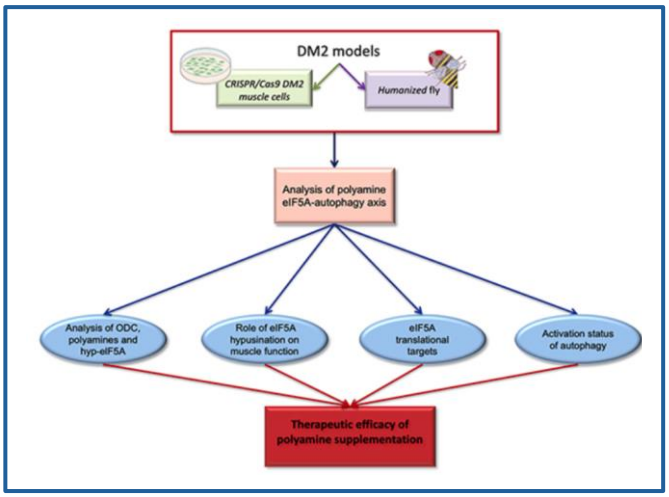
Titolo del progetto Understanding the role of eIF5A and autophagy in Myotonic Dystrophy Type 2 pathogenesis

Acronimo RoAD-M2

Partners:

- IBPM-CNR: Maria Patrizia Somma
- Università Sapienza: Laura Ciapponi PI

mariapatrizia.somma@cnr.it



Descrizione:

Myotonic Dystrophy type 2 (DM2) is a genetic multi-systemic disease, affecting skeletal muscle caused by CCTGn expansion in intron1 of the CNBP/ZNF9 gene. We demonstrated that depletion of CNBP in muscle tissues of Drosophila melanogaster caused both locomotor dysfunctions reminiscent of DM2 and reduced translation of ornithine decarboxylase (ODC), the rate limiting enzyme of polyamine metabolism. Depletion of CNBP in flies also impairs polyamine mediated eIF5A hypusination and autophagy, while impairment of eF5A hypusination pathway phenocopies CNBP-dependent locomotor defects. Our working model is that decreased CNBP-ODC-Polyamine axis observed in DM2 fly model may cause locomotor defects by affecting eIF5A-mediated autophagy

Finalità:

Our working model is that mutation of the CNBP gene causes: i.reduced ODC biosynthesis; ii. polyamine depletion; iii. decreased eIF5A hypusination; iv. reduction of its key translational targets involved in autophagy. To address this hypothesis, we plan to 1). generate and characterize new animal and cellular models of DM2; 2) analyze the polyamine-eIF5A-autophagy axis in DM2 pathogenesis; 3) evaluate the therapeutic efficacy of polyamine supplementation in the new models

Risultati attesi:

Our results will provide new mechanistic insights into the pathogenesis of DM2 and translation of this knowledge into future therapeutic tools. If our results will confirm the key role played by polyamine deficiency in DM2 muscle dysfunction and the therapeutic efficacy of polyamine supplementation in our models, this will lead to further studies in mice and in preclinical models and DM2 patients to investigate at both diagnostic and therapeutic level the clinical relevance of these findings.

Finanziato dall'Unione Europea – Next Generation EU, M4C2 – CUP B53D23024810001