An in vivo model of intractable R257C-ACTG2 Visceral Myopathy to study pathogenesis and to identify new disease targets

Giulia C. Vitale [1], Antonio Galeone [2], Federica Viti [3], Thomas Vaccari [1]

[1] Department of Bioscienze, University of Milan, Milano, Italy
[2] CNR Instituto di Nanotecnologia, Lecce, Italy
[3] Institute of Biophysics, National Research Council, Genova, Italy

Visceral Myopathies (VSCM) are a group of rare genetic diseases characterized by severe visceral smooth muscle disfunction that prevents efficient movement of air and nutrients through the bowel, impairs bladder emptying and affects normal uterine contraction. Forms of VSCM characterized by lack of visceral muscle contraction often result in chronic pseudo-obstruction (CIPO), a life-threatening condition requiring immediate medical attention. Diagnosis of CIPO is still challenging due to its low-incidence among population and non-specific clinical symptoms. Therapies are non resolutive and usually consist of total/partial parenteral nutrition, intestinal transplantation and ostomy.

Among types of CIPO, the most debilitating is called megacystis-microcolon intestinal hypoperistalsis syndrome (MMIHS).

To date, the study of MMIHS has been limited and no *in vivo* models for genetic analysis have been described. Our project aims to develop a *Drosophila melanogaster* model of one of the most common and intractable form of pediatric MMIHS due to a R257C mutation in the *actin gamma 2 gene* (*ACTG2*). Preliminary data suggest that the downregulation in the mesoderm of *Act79B*, the putative *Drosophila* homolog of the human *ACTG2*, mimics CIPO. In particular, *Act79B*-depleted L3 larvae fail to discharge food during the wandering stage and eventually die. Based on these findings, we are currently constructing flies to overexpress variants of *ACTG2* and of *Act79B* that include R257C. Also, we have obtained null mutants of *Act79B* and an *Act79B* to recreate in flies the genetics of MMIHS patients. We propose to use the model to explore fly gut structure, contractility and ability to allow food transit. We will also study the little explored cellular aspects of myopathy focusing on actin function and autophagy. Eventually, we hope to identify new genetic and pharmacological targets to develop effective and variant-specific treatments.