

Al collegio docenti del Dottorato in Medicina Molecolare

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- Introduction

Mutations in the ryanodine receptor 1 (RyR1) gene are causative for several human skeletal muscle diseases, referred to as RyR-related myopathies (RyR-RMs). Among these, central core disease (CCD) is the most frequent congenital myopathy caused by RyR1 mutations. RyR^{Y524S/WT} and RyR^{I4895T/WT} knock-in mice (YS and IT mice, respectively) are the most studied mouse models of CCD. These knock-in mice, in addition to the development of muscle damage (cores), display reduced muscle performance, mitochondrial ROS production, impaired Ca²⁺ homeostasis and induction of ER/UPR stress. Despite substantial progresses, there are no FDA-approved drugs to cure RyR-RMs.

miR-486 is a skeletal muscle enriched microRNA that epigenetically regulates the expression of various genes, including some genes encoding for proteins participating in the AKT pathway. Accordingly, miR-486 is actively involved in regulating muscle metabolism and trophism. Recently, skeletal muscle-specific overexpression of miRNA-486 in mdx dystrophin-deficient mice resulted in improved exercise capabilities of dystrophic mice, and also ameliorated different muscular symptoms associated with Duchenne muscular dystrophy.

On this basis, we wanted to verify whether skeletal muscle-specific overexpression of miR-486 might also represent a strategy for the treatment of RyR1-RMs.

- Methods

To evaluate the potential effect of miR-486 overexpression in improving muscle performance, YS and IT mice were both crossed with transgenic mice where miR-486 is selectively overexpressed in skeletal muscle (Tg^{miR-486/WT}, Tg486), thus obtaining two novel mouse lines, namely RyR^{Y524S/WT}/Tg^{miR-486/WT} (YSx486) and RyR^{I4895T/WT} / Tg^{miR-486/WT} (ITx486).

Selective skeletal muscle miR-486 overexpression was verified by real-time PCR.

To investigate the effect of miR-486 overexpression, we start assessing, by hanging wire and grip tests, whole-body muscle function in 3-, 6- and 9-months old Wild Type (WT), YS, IT, Tg486, YSx486 and ITx486 congenic mice.

- Results

Following hanging wire test, a significant improvement of muscle function in ITx486 mice compared to age-matched IT mice was observed as early as 3 and up to 9 months of age. In YSx486 mice, such improvement of muscle function was observed only in mice of 9 months of age although not reaching statistically significant levels. The results obtained following grip test experiments showed an improvement of muscle force in both YSx486 and ITx486 mice starting from 6 months of age. These preliminary data indicate that the overexpression of miR-486 improves muscle performance of RyR-RM-affected muscles, suggesting that miR-486 might represent a promising strategy to treat RyR1-RMs.

• **partecipazione a congressi e corsi:**

- I finanziamenti europei nel settore digitale: il programma “Europa Digitale” (11/05/23)
- Europrogettazione: programmi, progetti e rendicontazione” (18/05/23)
- Comunicare in ricerca (21/06/23)
- PhD and then? Overview on career paths inside and outside the academia (21/06/23)
- Corso di formazione in materia di protezione degli animali utilizzati a fini scientifici (dal 5/06/23 2023 al 5/07/2023)
- How to study genetics in complex diseases I, Prof.Stefano Landi – Pisa (Italy), 19/01/2023
- How to study genetics in complex diseases II, Prof. Stefano Landi – Pisa (Italy), 26/01/2023
- Microvesicles in cell-to-cell communication, Dr.ssa Laura Governini – Siena (Italy), 27/02/2023
- Biomarkers discovery in precision medicine, dr.ssa Alice Luddi – Siena (Italy), 27/02/2023
- Through thick and thin... and titin: defining titin’s role to muscle function, Dr. Anthony Hessel – Florence (Italy), 04/04/2023
- Advanced optical methods to monitor and control the cardiac electrical activity, Prof. Leonardo Sacconi – Florence (Italy), 04/04/2023
- Cellular mechanisms of heart failure, prof. Pieter de Tombe – Florence (Italy)
- Drug development, sex-dependent difference, pharmacovigilance, Prof.ssa Elisabetta Cerbai e dr.ssa Elisabetta Bigagli – Florence (Italy), 04/04/2023
- 50 th European Muscle Conference (EMC) – Florence (Italy), (dal 2/09/2023 al 06/09/23)

• **Pubblicazioni scientifiche e abstract**

- E. Pierantozzi, L. Raucci, S. Buonocore, E. M. Rubino, Q. Ding, A. Laurino, F. Fiore, M. Soldaini, J. Chen, D. Rossi, P. Vangheluwe, H. Chen & V. Sorrentino. “Skeletal muscle overexpression of sAnk1.5 in transgenic mice does not predispose to type 2 diabetes” Scientific Reports, 2023
- E. M. Rubino, F. Fiore, L. Raucci, M. Soldaini, S. Buonocore, D. Rossi, E. Pierantozzi, V. Sorrentino. “Deletion of the muscle-specific internal promoter in the ANK1 gene validates a causative role of the ANK1 locus in predisposing to Type 2 Diabetes”. European Muscle Conference 2023
- F. Fiore, A. Laurino, M. Serano, E. M. Rubino, D. Rossi, E. Pierantozzi, V. Sorrentino. “Overexpression of miR-486 improves muscle function in mouse models of RyR1-related diseases”. European Muscle Conference 2023
- M. Soldaini, E. M. Rubino, F. Fiore, B. Pacchioni, C. Millino, D. Rossi, E. Pierantozzi, G. Lanfranchi, S. Cagnin, V. Sorrentino. “Deletion of a tissue-specific stretch-/super-enhancer alters gene expression in skeletal muscle and predisposes to type 2 diabetes”.
- E. Pierantozzi, E. M. Rubino, M. Soldaini, F. Fiore L. Raucci, S. Buonocore, D. Rossi, G. Lanfranchi, S. Cagnin, V. Sorrentino. “Deletion of the muscle-specific internal promoter of the ANK1 gene results in a pre-diabetic phenotype”. Interuniversity institute of myology (IIM) 2023