Identification of muscular MIRNAs as biomarkers and co-adjuvant treatment for spinal muscular atrophy.

KEYWORDS

- SPINAL MUSCOLAR ATROPHY (SMA)
- BIOMARKERS
- MIRNA
- MIRNA INHIBITORS
- MOLECULAR THERAPY FOR SMA

AREA

- CHEMISTRY & BIOTECHNOLOGIES

CONTACTS

- PHONE NUMBERS
+39.06.49910888
+39.06.49910855
- EMAIL
u_brevetti@uniroma1.it

Priority Number
n. 102018000004359 _ 10.04.2018.

Patent Type
Patent for invention.

Co-Ownership
Sapienza University of Rome 40%, Catholic University "Sacro Cuore" 40%, Italian Institute of Technology 20%.

Inventors
Francesco Danilo Tiziano, Paola Infante, Lucia Di Marcotullio, Emanuela Abiusi.

Industrial & Commercial Reference
microRNAs as prognostic markers for SMA and their inhibition for the co-adiuvant therapy of this condition.

Time to Market
Combined administrations of the 3 antagomiRs, also in association with Nusinersen treatment are ongoing.

Availability
Cession, Licensing, Research, Development and Experimentation.

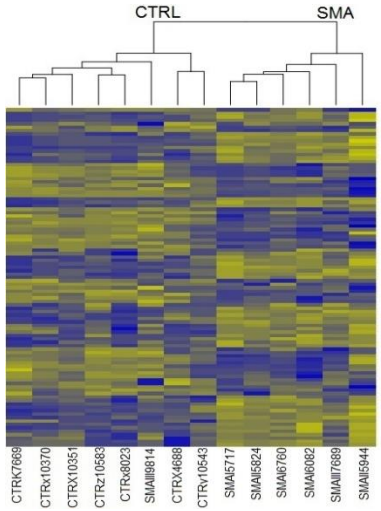

Fig. 1 The heatmap shows miRnoma analysis of muscle biopsies of SMA patients and controls. The graph shows the differential expression of miRNAs deregulated in muscolar biopsies. Blue bands indicates the miRNA down-regulated, the yellow ones are for up-regulated miRNAs. Heatmap shows that the two groups analyzed forms two separate clusters.

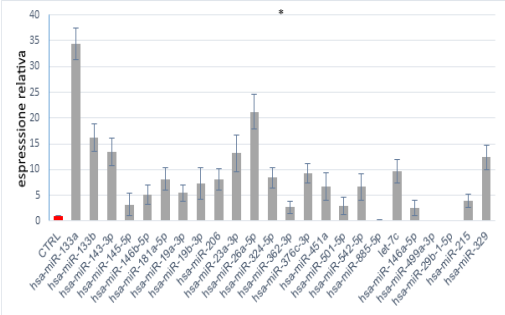

Fig. 2 Deregulated miRNAs in serum of SMA patients, emerged from a validation performed by relative qRT-PCR on 10 SMA samples and 10 controls (*α≤0.05).

Abstract

Spinal muscular atrophy (SMA) is a rare genetic disease that leads to death in severe cases. At the moment there are no definitive cures for SMA, or prognostic biomarkers useful for evaluating the response to therapies. The miRnoma analysis of muscle biopsies of SMA patients and controls showed 99 miRs differentially expressed between the two groups. The quantification of serum levels of these miRs in patients and controls revealed 3 miRs as biomarkers for the condition, because over-expressed in patients. Treatment of SMA mouse models with the inhibitor of one of the 3 miRs emerged showed an increase in their survival.

Publications

- Waller R, et al. "Serum miRNAs miR-206, 143-3p and 374b-5p as potential biomarkers for amyotrophic lateral sclerosis (ALS)." Neurobiol Aging. (2017) 55:123-131.
- Catapano F, et al. "Altered levels of MicroRNA-9, -206 and 132 in Spinal Muscular Atrophy and their response to antisense oligonucleotide therapy" Mol Ther Nucleic Acids. 2016 Jul 5;5(7):e331.

SAPIENZA UNIVERSITÀ DI ROMA

ASuRTT _ UFFICIO VALORIZZAZIONE E TRASFERIMENTO TECNOLOGICO
SETTORE BREVETTI E TRASFERIMENTO TECNOLOGICO
- http://uniroma1.it/ricerca/brevetti

Identification of muscular MIRNAs as biomarkers and co-adjuvant treatment for spinal muscular atrophy.

Technical Description

The miRNome analysis of muscle biopsies of SMA patients and controls, performed by new generation sequencing (NGS), led to the identification of 99 miRNAs differentially expressed between the two groups.
Deregulated miRNAs were validated as potential biomarkers for SMA and quantified in serum samples of SMA and controls, by an in-house absolute quantitative PCR (qRT-PCR). Three miRNAs were significantly overexpressed in SMA patients, and showed a correlation with the severity of the condition.
Finally, the potential therapeutic role of miRNAs was evaluated in SMA mouse models. Treatment with specific inhibitors (antagomiR) of one miRNAs here studied, resulted in an increase of the survival of treated animals compared to controls.

Technologies & Advantages

This invention concerns the identification of miRNAs as sensitive biomarkers for the prognosis of SMA. To date, prognostic biomarkers for this condition monitoring its development or response to therapies are still unavailable. The copy number of the SMN2 gene may be predictive of the SMA phenotype, but with limited power in the less severe forms, SMAII and SMAIII. The microRNAs identified show predictive power independently of SMN2. The invention concerns also the use of specific miR inhibitors for the treatment of SMA.
The increased survival of SMA mouse models treated with antagomiRs, demonstrates for the first time that the in vivo modulation of miRNAs levels in a neurodegenerative disease could be considered a therapeutic approach, independently of the correction of the basic genetic defect. The invention offers some advantages: 1) the use of absolute qRT-PCR for the quantification of serum miRs levels has reduced experimental variability; 2) the data were obtained from human biological material and not from cell cultures or tissues of pre-clinical models; 3) the use of skeletal muscle has allowed studying a tissue involved in the pathogenetic mechanisms of SMA.

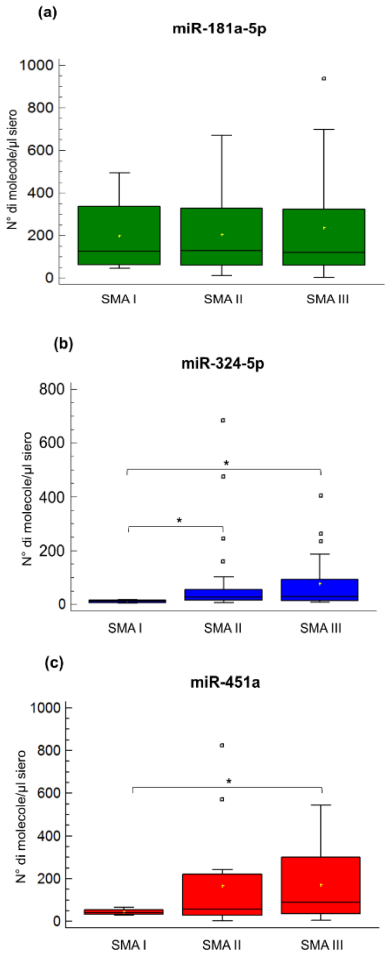

Fig. 3 Correlation graphs between expression levels of miR-181a-5p, 324-5p and 451a and SMA type. The boxplot shows the number of molecules/µl serum detected for miR-181a-5p (a), miR-324-5p (b) and miR-451a (c) in correlation with the type of SMA (I, II, III) (* P≤0.05).

Applications

The invention offers two main clinical applications: 1) the identification of 3 miRNAs as sensitive and specific prognostic biomarkers for SMA provides a reliable, reproducible and easy-to-use in vitro method for evaluating the prognosis of SMA, monitoring its development and the efficacy of a treatment, by determining the serum levels of one or all of the 3 miRNAs;
2) specific miRNA inhibitors of this invention, in the form of antagomiRs, antisense oligonucleotides partially or totally complementary to the target miRNAs, may be used fo the prevention and/or treatment of SMA, through the development of kits for the simultaneous, separate or sequential administration of miRNAs or in combination with the Nusinersen compound.

CONTACTS

- PHONE NUMBERS
+39.06.49910888
+39.06.49910855

- EMAIL
u_brevetti@uniroma1.it

SAPIENZA UNIVERSITÀ DI ROMA

ASuRTT _ UFFICIO VALORIZZAZIONE E TRASFERIMENTO TECNOLOGICO
SETTORE BREVETTI E TRASFERIMENTO TECNOLOGICO
- http://uniroma1.it/ricerca/brevetti