Circulation Research

FREE ACCESS | ARTICLE

POSTER ABSTRACT PRESENTATIONS
SESSION TITLE: POSTER SESSION 2

Abstract 602: Mir-182-5p is a Conserved Downstream Effector of Tbx5 Involved in Heart Development and Arrhythmia in Zebrafish

Elena Guzzolino, Mario Pellegrino, Neha Ahuja, Deborah Garrity, Romina D'Aurizio, Marco Groth, Mario Baumgart, Cathy Hatcher, Alberto Mercatanti, Monica Evangelista, Chiara Ippolito, Elisabetta Tognoni, Ryuichi Fukuda, Vincenzo Lionetti, Letizia Pitto1Clinical Physiology- CNR Pisa, Pisa, Italy2Scuola Superiore Sant'Anna, Pisa, Italy3Institute of Optics- CNR Pisa, Pisa, Italy4Colorado State Univ (CSU), Dept of Biology, Fort Collins, CO5Colorado State Univ (CSU), Dept of Biology, Fort Collins, Fort Collins, CO6Laboratory of Integrative Systems Medicine (LISM), Institute of Informatics and Telematics, CNR, Pisa, Italy7The Leibniz Institute on Aging – Fritz Lipmann Institute (FLI), Jena, Germany8Dept of Bio-Med Sciences, Philadelphia College of Osteopathic Medicine, Philadelphia, PA9Dept of Clinical and Experimental Medicine, Univ of Pisa, Pisa, Italy10Dept of Developmental Genetics, Max Planck Institute for Heart and Lung Rsch, Bad Nauheim, Germany

Originally published 16 Oct 2019 | https://doi.org/10.1161/res.125.suppl_1.602 | Circulation Research. 2019;125:A602

Abstract

Background: TBX5 mutations cause Holt-Oram syndrome (HOS) characterized by upper limb and cardiac malformations, but can also contribute to early-onset of atrial fibrillation. Focusing on miRNAs involved in TBX5 regulatory circuits with a cardiac relevant role, we identified miR-182-5p, belonging to miR-183 cluster, found upregulated in Tbx5-depleted hearts of mouse and zebrafish embryos.

Methods: To functionally analyse the miR-182-5p role in developing heart, miR-182-5p was dysregulated in zebrafish zygotes of Tg(Myl7:EGFP) and Tg(myl7:gCaMP) transgenic lines. To stably deregulate miR-182-5p in zebrafish heart we exploited the Gal4/UAS system to restrict the miR-182 expression into cardiac context. For physiological analyses we performed the mechanogram of cardiac contraction and electrocardiogram recording. To understand miR-182-5p downstream regulation, in silico analyses, followed by ddPCR/real-time quantifications on

dissected zebrafish hearts and rescue experiments both in transient and stable miR-182-5p overexpressing zebrafish embryos were performed.

Results: Depletion of Tbx5 from cardiomyocytes increased the expression of miR-182 cluster family that is controlled by Kruppel-like factor 4 (KLF4), a transcription factor repressed by Tbx5. Both transient and stable upregulation of miR-182 in zebrafish affect heart morphology, calcium handling and the onset of arrhythmia while its cardiac-specific downregulation decreases cardiac defects in zebrafish HOS hearts. Expression analyses on selected miR-182-5p putative targets revealed that several calcium channel proteins resulted downregulated in miR-182-5p overexpressing hearts. Transgenic zebrafish line stably overexpressing miR-182-5p in the heart manifested arrhythmia overtime with or without cardiac structural defects.

Conclusion: We identified miR-182-5p as a potential suitable target to interfere in the circuit between upstream genetic abnormalities and downstream effectors leading to arrhythmia occurrence.

Footnotes

Author Disclosures: **E. Guzzolino:** None. **M. Pellegrino:** None. **N. Ahuja:** None. **D. Garrity:** None. **R. D'Aurizio:** None. **M. Groth:** None. **M. Baumgart:** None. **C. Hatcher:** None. **A. Mercatanti:** None. **M. Evangelista:** None. **C. Ippolito:** None. **E. Tognoni:** None. **R. Fukuda:** None. **V. Lionetti:** None. **L. Pitto:** None.

Back to top