MicroRNAs in human cardiac aging: therapeutic targets and biomarkers

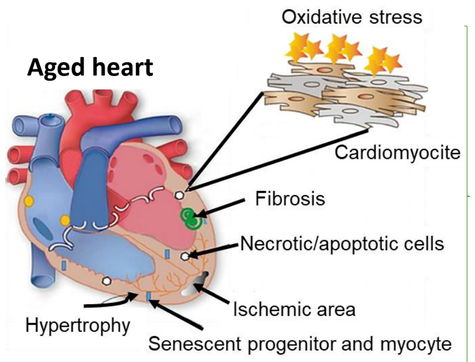
Hernández-Bellido N[1,2] *, Ramos-Marquès E[1,2], Hernández-Vicente A[3,4], García-Mendívil L[1,2], Santanter-Badules H[1,2], Mercanti G[1,2], Garrido-Huéscar E[1,2], Garatachea N[3,4,5,6], Kohler R[7], Pueyo E[1,2,8], Ordovás L[1,2,9]

[1] Biomedical Signal Interpretation and Computational Simulation group (BSICoS), University of Zaragoza, Spain [2] BSICoS group, IIS Aragon, Zaragoza, Spain [3] Growth, Exercise, Nutrition and Development (GENUD), University of Zaragoza, Spain [4] Department of Physiatry and Nursing, Faculty of Health and Sport Sciences (FCSD), University of Zaragoza, Huesca, Spain [5] Centro de Investigación Biomédica en Red de Fisiopatología de la Obesidad y Nutrición (CIBER-OBN), Madrid, Spain [6] Instituto Agroalimentario de Aragon (IA2), University of Zaragoza, Zaragoza, Spain [7] Aragones Institute of Health Sciences (IACS), Zaragoza, Spain [8] Centro de Investigación Biomédica en Red de Bioingeniería, Biomateriales y Nanomedicina (CIBER-BBN) [9] ARAID Foundation

*nhbellido@unizar.es

Introduction

Cardiovascular diseases



microRNA (miRNA)

- Regulators of biological processes. Therapeutic targets.
- Actively and pasively released to body fluids. Biomarkers.

Role of miRNAs in age-related cardiac remodelling is poorly understood in humans.

Bioinformatic identification of age-related miRNAs (**BIO-AGEmiRNAs**) in human left ventricle and their predicted downstream target genes[1].

Goals

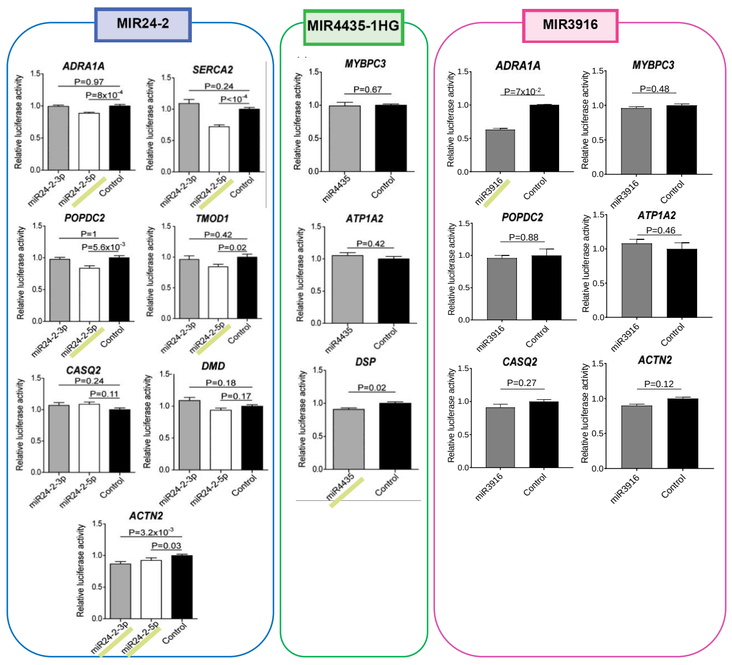
- Validate the bioinformatic BIO-AGEmiRNA regulatory network.
- Investigate miRNAs as indicators of the biological age of the heart.

Materials and methods

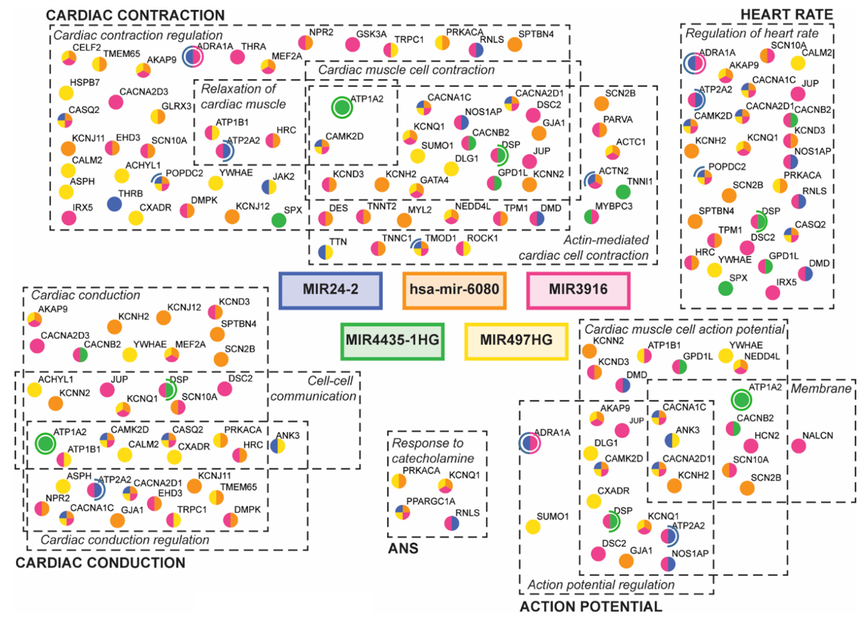
- Luciferase reporter assays conducted in order to validate interactions between BIO-AGEmiRNAs and cardiac-related genes.
- Description of a new individual transcriptomic age index (Apparent Age, AppAge) in white blood cells (WBC) from young to centenarian human donors adapting published metods[2].
- Quantification of expression levels of cardiac-enriched BIOAGE-miRNAs and myo-miRNAs in plasma from healthy young (20-30 y.o.), adult (40-50 y.o.), elder (60-70 y.o.) and centenarian (100 y.o.) donors.

Results

8 of 23 predicted interactions between miR-24-2-5p, miR-24-2-3p, miR-4435 and miR-3916 and predicted targets are positive



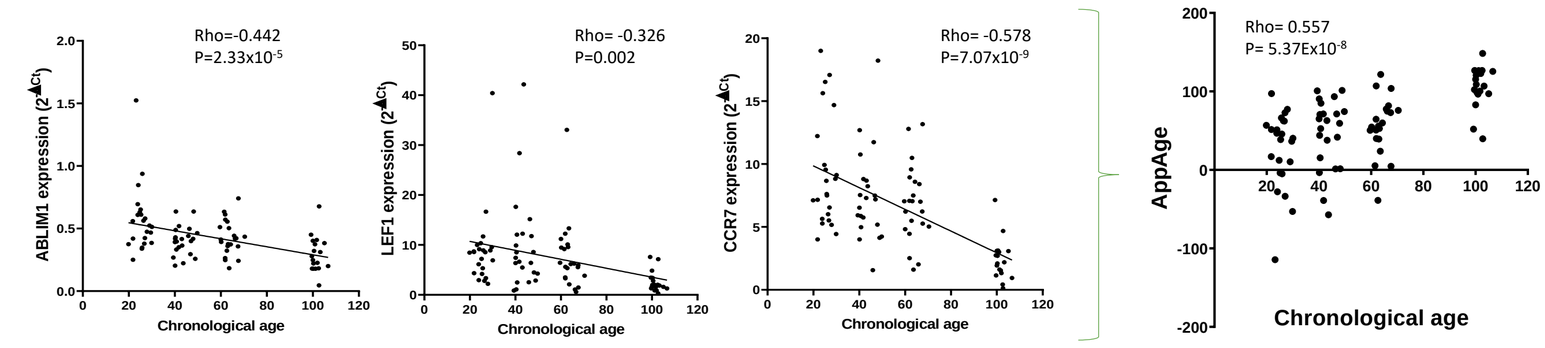
Cardiac BIO-AGEmiRNA gene regulation network with positive interactions highlighted as external lines



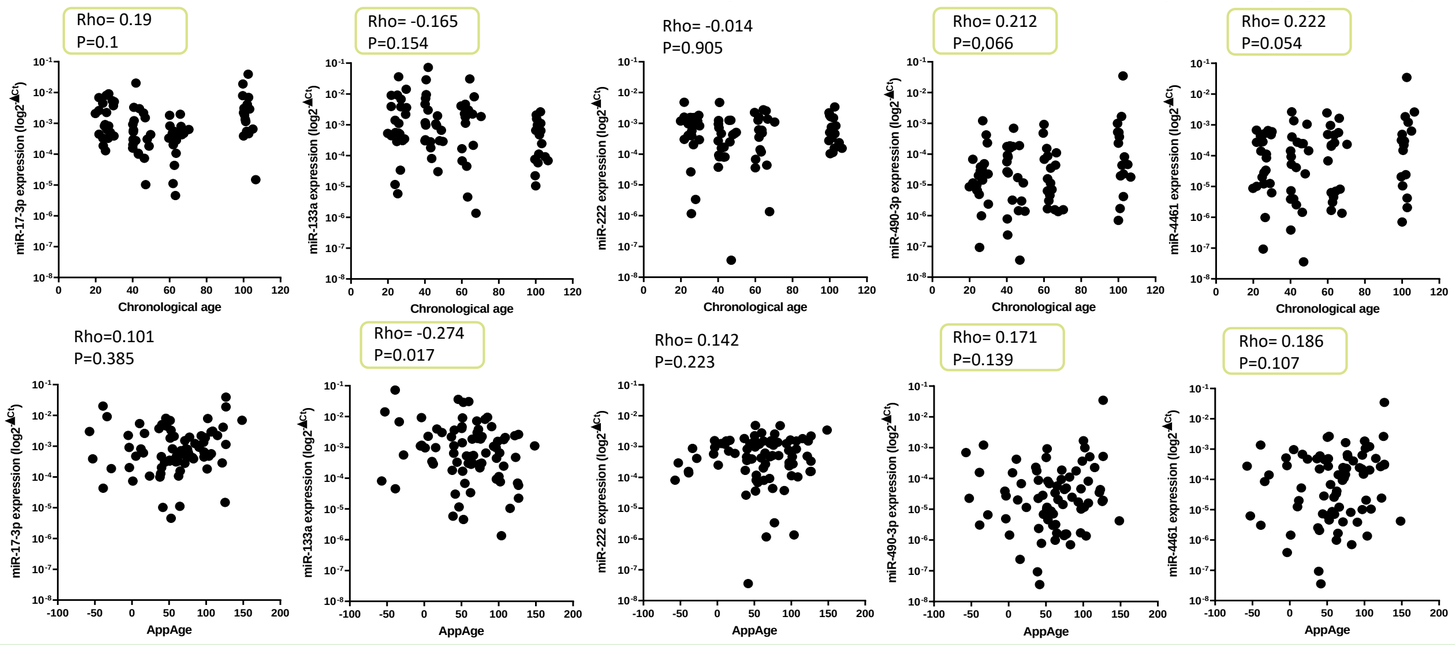
Definition of a transcriptomic biological age index (AppAge) in WBC of the individual

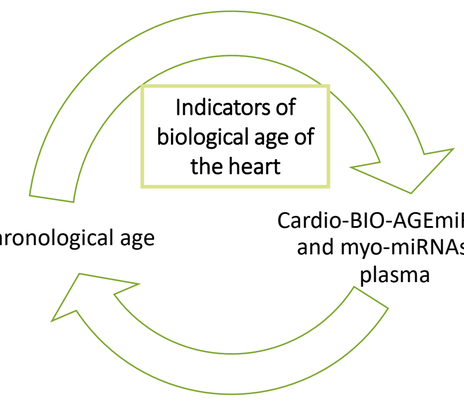
Identification of age-related genes in human WBC from published transcriptomic studies[3-6]

CCR7 LEF1 ABLIM1



The levels of the studied cardiac-enriched BIOAGE-miRNAs and myo-miRNAs reveal significant (*P ≤ 0.05) or nearly significant (P≤ 0.15) correlation with chronological age and AppAge





Conclusions

- 35% of tested interactions have been validated *in vitro*. Thus, miRNAs emerge as important regulators of gene expression in age-related cardiac dysfunction.
- AppAge is proposed as a potential indicator of the biological age of an individual.
- Circulating cardiac BIO-AGEmiRNAs or myomiRNAs could report biological age of the heart in relation to the chronological and/or AppAge.
- Our data promotes the deciphering of molecular mechanism underlying the process of cardiac aging and its minimal-invasive monitoring in human.

References

1 Ramos-Marquès, E. *et al.* Chronological and biological aging of the human left ventricular myocardium: Analysis of microRNAs contribution. *Aging Cell* **20**, e13383 (2021).

2 Rhinn, H. & Abeliovich, A. Differential Aging Analysis in Human Cerebral Cortex Identifies Variants in TMEM106B and GRN that Regulate Aging Phenotypes. *Cell Syst.* **4**, 404–415.e5 (2017).

3 Harries, L. W. *et al.* Human aging is characterized by focused changes in gene expression and deregulation of alternative splicing. *Aging Cell* **10**, 868–878 (2011).

4 Marttila, S. *et al.* Transcriptional analysis reveals gender-specific changes in the aging of the human immune system. *PLoS One* **8**, (2013).

5 Passtoors, W. *et al.* Transcriptional profiling of human familial longevity indicates a role for ASF1A and IL7R. *PLoS One* **7**, 1–10 (2012).

6 Peters, M. J. *et al.* The transcriptional landscape of age in human peripheral blood. *Nat. Commun. 2015 61* **6**, 1–14 (2015).

Fundings

This work was funded by several grants: MICINN (PID2019-105674RB-I00), European Research Council (ERC-StG 638284), Government of Aragon (LMP128_21) and a predoctoral fellowship from Government of Aragon (CPB_09_20).