miR-24-2 modulation in cardiac dysfunction through DNA nanotechnology

Laura Ordovás[1-4], Natalia Hernández-Bellido[2-3], Alejandro Postigo[5], Marcos Sánchez-Barat[2,3], Marina Ripalda-Paredes[3-5], Sebastián Usón[2], Jhydell J. Ruíz-Araca[6], Eduardo Candeal[3], Julia Ramírez[2-4], Beatriz Ranera[6], Myriam Gorospe[7], Jesús del Barrio[5], Silvia Hernández-Ainsa[5]

[1] Fundación ARAID, Zaragoza, Spain
[2] Instituto de Investigación en Ingeniería de Aragón (I3A) - UNIZAR, Zaragoza, Spain
[3] Instituto de Investigación Sanitaria Aragón (IISA), Zaragoza, Spain
[4] CIBBER-BBN, Zaragoza, Spain
[5] Instituto de Nanociencia y Materiales de Aragón (INMA), Zaragoza, Spain
[6] Universidad San Jorge (USJ), Zaragoza, Spain
7 National Institute on Aging-NIH, Baltimore, USA

lordovas@unizar.es

MicroRNAs (miRs) are well-known players of cardiac ageing and disease. Their dysregulation is associated with different pathological processes occurring in both, and miRs have shown to be therapeutic. For instance, cardiac miR modulation regenerates the infarcted myocardium in large animal models [1,2], providing proof of concept for their therapeutic efficacy and holding promise for solving medical challenges that generate enormous health and societal burden. Ageing is an unavoidable but environmentally modifiable process [3] that constitutes a major risk factor for heart disease [4]. Heart failure (HF) is a life-threatening syndrome that affects more than 64 million people worldwide [5] and atrial fibrillation (AF) is the most prevalent cardiac arrhythmia [6]. Results from our group and others find miR-24-2 upregulated with age [7], HF [8] and AF [9] in human cardiac tissue. Consistent with bioinformatic data [10], we observe miR-24-2 among the most highly expressed miRs in the human myocardium and iPSC-derived cardiomyocytes (iCMs). We have also determined that the cardiac overexpression of miR-24-2 with age is maintained across species (mouse and monkey), and confirmed its dysregulation in AF patients in a cross-ancestry transcriptomic meta-analysis. Overall, these data support the key role of miR-24-2 in regulating cardiac cell homeostasis in ageing and disease. Therefore, we have leveraged the exceptional programmability and biocompatibility of DNA nanotechnology to develop nanohydrogel (NHG) loaded with anti-miR-24-2 (Figure 1a) and evaluated its potential to modulate the miR levels and its targets in cardiac cells. The anti-miR-24-2 nanohydrogel successfully assembled, demonstrated proper stability up to 24 hours in serum, selectively captured miR-24-2 and internalized in both Hek293 and iCMs without loss of viability. The NHG efficiently captured the miR-24-2, restoring the protein levels of a known target (SERCA2) in a Hek293 model system (Figure 1b). In iCMs overexpressing miR-24-2, NHG increases the mRNA expression levels of a predicted target gene. In conclusion, the described biocompatible nanohydrogel demonstrates its suitability to carry functional anti-miR-24-2 therapies in human cardiac cells.

References

[1] K Gabisonia et al. Nature 569 (2019) 418–422
[2] R Hinkel et al. Circulation 128 (2013) 1066–1075
[3] R. Pálovics et al. Nature. 7900 (2022) 309–314
[4] WHO, Cardiovascular diseases, (2024)
[5] G Savarese el al. Cardiovasc. Res. 118 (2023) 3272–3287
[6] D Linz et al. Lancet Regional Health – Europe. 37 (2024) 100786
[7] E Ramos-Marquès et al. Aging Cell 20 (2021) e13383
[8] E Van Rooij et al. Proc. Natl. Acad. Sci. USA 103 (2006) 18255–18260
[9] NWE van den Berg et al. Cell Tissue Res. 394 (2023) 497
[10] G Senesi et al. Cardiovasc. Res. 121 (2025) 143–156

Figures

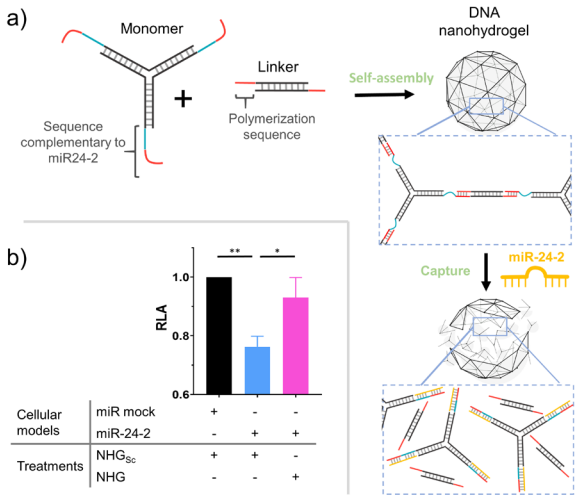

Figure 1. a) Design of NHG featuring the ability to trap miR24-2 while undergoing disassembly. b) Functional assessment of NHG in a cellular model system: cells transfected with miR (mock or miR-24-2) and treated with the NHG or an equivalent bearing scramble capture sequences (NHG_{Sc}).