The therapeutic relevance of microRNA-199b in preclinical models of heart failure

Citation for published version (APA):

Document status and date:
Published: 01/01/2017

DOI:
10.26481/dis.20171027bd

Document Version:
Publisher's PDF, also known as Version of record

Please check the document version of this publication:

• A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher’s website.
• The final author version and the galley proof are versions of the publication after peer review.
• The final published version features the final layout of the paper including the volume, issue and page numbers.

Link to publication

General rights
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

• Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
• You may not further distribute the material or use it for any profit-making activity or commercial gain.
• You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the “Taverne” license above, please follow below link for the End User Agreement:
www.umlib.nl/taverne-license

Take down policy
If you believe that this document breaches copyright please contact us at:
repository@maastrichtuniversity.nl
providing details and we will investigate your claim.

Download date: 16 Sep. 2023
Valorization

Relevance

Heart failure remains one of the major public health problems with increasing morbidity and mortality worldwide. More than 20 million people currently suffer from heart failure and this prevalence steeply increases with age.\textsuperscript{1,2} According to the American Heart Association (AHA) 1 out of 5 adults at the age of 40 and above will likely to develop heart failure in their lifetime.\textsuperscript{3} Although current heart failure medication can ameliorate signs and symptoms, mortality rate 5 years after diagnosis has been reported to be as high as 45-60\%.\textsuperscript{4,5} and survival rate is lower than some of the most common forms of cancer.\textsuperscript{6,7} These reports are clearly pointing to the need for developing novel therapeutic strategies for the treatment of heart failure.

In the European Society of Cardiology (ESC) guidelines (2016), heart failure is defined as ‘a clinical syndrome caused by structural and/or functional abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress.’\textsuperscript{8} Being a complex syndrome, the etiology of heart failure is highly diversified and patients may develop various pathologies. As summarized in Chapter 2, both genetic factors and epigenetic mechanisms can significantly contribute to the development and progression of heart failure.\textsuperscript{9} Thus, a better understanding of these underlying mechanisms hold great significance in successfully developing effective therapies for heart failure patients.

Target groups

Scientific community

Among epigenetical mechanisms, microRNAs (miRNAs) have drawn great attention for their ability to regulate gene expression and thereby to be involved in various human diseases including heart failure.\textsuperscript{10,11} miRNAs exert their regulatory function by disturbing protein production after binding to target mRNAs and in that way, they are able to influence different cellular processes.\textsuperscript{12} To date, numerous miRNAs have been identified as regulators of pathological remodeling processes leading to heart failure including hypertrophy, fibrosis, apoptosis and angiogenesis.\textsuperscript{13,14} Previously, microRNA-199b (miR-199b), a miRNA associated with cardiac hypertrophy, has been established by our group as a promising therapeutic target using an animal model mimicking human aortic stenosis.\textsuperscript{15} However, differential expression patterns of miRNAs depending on the etiology of heart failure (ischemic, aortic stenosis and/or idiopathic) have been reported.\textsuperscript{16} In this regard, further analysis of miR-199b has been performed in this thesis using different animal models consisting of myocardial infarction
(Chapter 5) and right ventricular failure (Chapter 4). In accordance with our previous data, targeting miR-199b in an animal model of myocardial infarction was also shown to be beneficial, even though our molecular studies suggested that miR-199b carried out its function in this animal model via a different molecular pathway. Thereby, the findings reported in this thesis are of great importance for the scientific community, indicating that comprehensive studies into the distinct subtypes of heart failure are required to determine therapeutic significance of a molecule before extrapolating preclinical data to clinical application.

**Biotechnology and pharmaceutical industry**

What makes miRNAs valuable therapeutic targets for the treatment of heart failure is the feasibility to modulate miRNA expression levels in living organisms such as animals and humans. While microRNA mimics, synthetic double stranded RNA molecules, confer the ability to supplement microRNA function, antimiRs which are chemically modified single stranded small oligonucleotides, can block the function of targeted miRNA by direct binding. Preclinical investigation has provided invaluable information not only on the therapeutic efficacy of these new generation drugs in diseased animals but also on their limitations. Several antimiRs have been generated by using diverse chemical modifications in order to improve specific properties such as cellular uptake, stability, inhibitory capacity and thereby, to enhance their efficacy for in vivo applications. In Chapter 6, we have compared features of four promising antimiRs (against miR-199b), carrying distinct chemical moieties. The efficacy of these inhibitors was determined by analyzing expression of miR-199b levels after treatment with antimiRs compared to control treated animals. As a result, two of these antimiRs namely antagomir and locked nucleic acid (LNA) revealed similar effects on the miR-199b expression levels in the heart while Zen-AMO and FMOE were unable to inhibit miR-199b in any organ examined suggesting the difficulty to optimally develop such compounds with robust activity. In addition, antagomir and LNA manifested inhibitory capacity in other organs such as liver, lung and kidney besides heart, demonstrating organ aspecificity. Since most of the miRNAs identified to play a role in heart failure are not tissue specific, organ specific delivery of antimiR drugs is an important issue to overcome before clinical use considering the possible occurrence of unwanted side effects in patients. In a large animal model of heart failure this issue has been resolved by application of an antimiR with a catheter, which enables regional delivery. Even more, the stronger therapeutic effect was achieved after local delivery when compared to systemic injection. This approach is highly feasible in the clinic since patients suffering from myocardial infarction are undergoing this procedure for acute treatment.
Herewith, the comprehensive overview in Chapter 3 together with experimental findings in Chapter 6 provides substantial information to pharmaceutical and biotechnology companies developing and manufacturing antisense RNA therapeutics.

**Patients and society**

Increasing prevalence and incidence with poor prognosis of heart failure contribute to high cost to patients, society and health care system. Moreover, heart failure is a long-term condition that deteriorates slowly over time. Current treatment strategies involving multiple medications and changes in life style only aim to improve symptoms and quality of patients’ daily life. Therefore, a more innovative and effective treatment approach for heart failure is necessary to reduce this burden from patients and society. For instance, as demonstrated by animal studies, antimiRs have stable inhibitory effect on miRNA function for months\textsuperscript{21} and that can greatly decrease the need to apply medication (in this case antimiRs) at high frequency for chronic diseases such as heart failure. Thus, heart failure patients can benefit greatly from this advantage since they receive lifelong treatment with multiple drugs at changing frequencies. Although our approach is not yet applied in the clinic, we provide relevant findings to be used for future drug developments.

**Innovation and implementation**

In the past years, miRNAs have drawn considerable attention as key molecular players in development of various diseases. Their involvement in key signaling pathways and feasibility of miRNA modulation in vivo makes them invaluable therapeutic targets. There has been a rapid progress of miRNA based drug development by virtue of their therapeutic potential. Currently, TargomiRs containing miR-16 based mimic (NCT02369198) are under investigation in phase I clinical trials for their safety and efficiency in patients with different forms of cancer. Furthermore, phase I and Ila clinical trials for miRNA-122 anti-miRNA oligonucleotide (miravirsen) in chronic hepatitis C patients have been completed with successful outcome.\textsuperscript{22} Although there are no current clinical investigations with miRNA based drugs for the treatment of heart failure, the application of antimiR oligonucleotides or miRNA mimics in heart failure animal models have been carried out by numerous groups as extensively discussed in Chapter 3.

In this thesis, we further characterized ‘miR-199b’ and analyzed its function and therapeutic value in different etiologies of heart failure. Further investigation in large animal models of heart failure is obviously required to corroborate the clinical value of miR-199b before testing in patients. In addition, we have experimentally demonstrated the possibility to modulate amount of miRNAs in
the heart of small animals but also challenges of developing antisense RNA therapeutics against miRNAs and we extensively discussed literature presenting future directions for their improvement in the context of human heart failure. All in all, scientific findings from this thesis can be valorized as being a basis for the development of an innovative therapy against heart failure.
References