

Non-coding RNA species in heart failure

Citation for published version (APA):

Peters, T. (2016). *Non-coding RNA species in heart failure: regulators of cardiac hypertrophy, fibrosis and inflammation*.

Document status and date:

Published: 01/06/2016

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.

Valorization

SOCIETAL RELEVANCE

Cardiovascular diseases (CVD) are today the most common cause of death worldwide¹ and almost everyone has experienced neighbors, friends, or relatives dying from heart attack, stroke, or heart failure. The burden of CVD lies especially in the suffering of the patients and the grief of the relatives, but objectively speaking also in major health care costs, amounting to more than 100 billion euros in the EU in 2009². Several cardiovascular diseases, most importantly ischemic heart disease, hypertension, and inherited or acquired cardiomyopathies ultimately result in heart failure (HF), a disabling condition in which the heart cannot maintain sufficient blood flow through the circulation. The consequences for the patient begin with shortness of breath during physical activity and progress into complaints at rest, the inability to walk, and eventually death. Standard treatment of heart failure currently relies on reducing the hemodynamic strain on the heart and to improve muscle contraction. However, the prognosis for HF patients is very poor with reported 5-year mortality ranging from 40% to 65%^{3,4}. A better option than treating HF would be to prevent the progression of the underlying disease but our knowledge about the determining molecular mechanisms are limited. The aim of this thesis was to contribute to a better understanding of the molecular features of HF and its development due to cardiac pressure overload or viral myocarditis.

TARGET GROUPS

The focus of this thesis is on HF as consequence of pressure overload or viral infection. In 2014, the global prevalence of hypertension was 20-25%⁵, and the incidence of myocarditis is estimated to be up to 12%⁶. These numbers indicate that a large fraction of the general population may at some point suffer from HF and underlines the importance of basic research in this field. The ultimate target groups of this thesis are therefore patients with hypertensive heart disease or myocarditis that are at risk of developing HF. Above that, the findings may be transferrable to HF of different origin in which similar mechanisms are activated in the same cell types.

INNOVATION, PRODUCTS, AND IMPLEMENTATION

This thesis presents data from basic research, which only in rare cases results in directly applicable findings. However, the acquired knowledge will directly contribute to the expertise of the researchers involved, allowing them to further advance our understanding of the molecular mechanisms of HF. In addition, the resulting publications will enable scientists world-wide to build on the research presented in this thesis. The long-term societal value of basic research is often difficult to predict but in the following I will try a brief prognosis on how our finding may be helpful in the future.

The improvement of diagnostic tools and treatment options for HF will depend on a comprehensive knowledge of the cellular and molecular disease mechanisms. This thesis contributes to a better understanding by describing the role of three different non-coding RNAs in HF:

1) Cyclic adenosine monophosphate (cAMP)-signaling is deregulated in HF and inhibition of cAMP-degrading phosphodiesterases (PDEs) was thought to strengthen the failing heart. On the long run, however, the side-effects of PDE inhibition overshadowed the benefits⁷. MiR-139 may constitute an innovative target to improve cardiac contractility by specifically regulating certain PDE isoforms and thereby fine-tuning subcellular cAMP compartmentalization with reduced side-effects (chapter 2).

2) The miR-221/222 family is a fine-tuner of fibroblast function and may allow for adjusting the level of fibrosis in the myocardium (chapter 3). This is important because connective tissue is critical to stabilize wounds, for example after myocardial infarction, but is also involved in arrhythmogenesis and myocardial stiffening in HF⁸. Inhibition or activation of the miR-221/222 family as fine-tuner of fibroblast function could therefore be beneficial for stabilizing infarcted myocardium or preventing excessive scarring of hypertrophic hearts, respectively.

3) Infection with enteroviruses, such as CVB3, only induces mild symptoms in the vast majority of people but in some cases leads to massive inflammation of the heart that can progress to dilated cardiomyopathy and heart failure. A better knowledge of the molecular determinants of VM could help to explain this discrepancy and to develop better diagnostic tools and treatments. Malat1-associated small cytoplasmic RNA (mascRNA) is the first reported lncRNA-derived regulator of VM and therefore an innovative target with possibly broad applicability in viral diseases (chapter 6).

Future steps will have to confirm the findings from this thesis in larger animal models and human tissue samples. After successful translation, the named non-coding RNAs can be defined as possible targets for pharmaceutical research companies. Above that, further research into molecular pathways related to these candidates may uncover additional pharmaceutical target RNAs and proteins. Currently, there are several companies working on RNA-based therapeutics and the first drugs targeting microRNAs are in clinical trials^{9,10}. It remains to be seen how the findings from this thesis can be utilized for the development of applicable drugs.

REFERENCES

1. World Health Organization. *Fact Sheet 310*. In: World Health Organization [Internet]. World Health Organization; 2013 July [cited 2013 Dec 11]. Available from: <http://www.who.int/mediacentre/factsheets/fs310/en/>
2. Nichols M, Townsend N, Luengo-Fernandez R, Leal J, Gray A, Scarborough P and Rayner M. *European cardiovascular disease statistics 2012*. Brussels: European Heart Network, Sophia Antipolis: European Society of Cardiology; 2012.
3. Mosterd A and Hoes AW. Clinical epidemiology of heart failure. *Heart*. 2007;93:1137-46.
4. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, Bravata DM, Dai S, Ford ES, Fox CS, Franco S, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Huffman MD, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Magid D, Marcus GM, Marelli A, et al. Heart disease and stroke statistics--2013 update: a report from the American Heart Association. *Circulation*. 2013;127:e6-e245.
5. World Health Organization. *World health statistics 2015*. Geneva: World Health Organization; 2015.
6. Blauwet LA and Cooper LT. Myocarditis. *Prog Cardiovasc Dis*. 2010;52:274-88.
7. Packer M, Carver JR, Rodeheffer RJ, Ivanhoe RJ, DiBianco R, Zeldis SM, Hendrix GH, Bommer WJ, Elkayam U, Kukin ML and et al. Effect of oral milrinone on mortality in severe chronic heart failure. The PROMISE Study Research Group. *N Engl J Med*. 1991;325:1468-75.
8. Lopez B, Gonzalez A, Ravassa S, Beaumont J, Moreno MU, San Jose G, Querejeta R and Diez J. Circulating Biomarkers of Myocardial Fibrosis: The Need for a Reappraisal. *J Am Coll Cardiol*. 2015;65:2449-56.
9. Janssen HL, Reesink HW, Lawitz EJ, Zeuzem S, Rodriguez-Torres M, Patel K, van der Meer AJ, Patick AK, Chen A, Zhou Y, Persson R, King BD, Kauppinen S, Levin AA and Hodges MR. Treatment of HCV infection by targeting microRNA. *N Engl J Med*. 2013;368:1685-94.
10. Bouchie A. First microRNA mimic enters clinic. *Nat Biotechnol*. 2013;31:577.