Abstract

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Title of Doctoral Thesis: The role of microRNA in physiology and pathology

MicroRNAs (miRNAs) are small single-stranded non-coding RNA molecules that play an important role in the regulation of gene expression. They are evolutionarily highly conserved and are present in the genome of all eukaryotic organisms, suggesting their importance in physiological processes. Due to the tissue specificity and their involvement in the pathogenesis of various diseases, miRNAs have been widely studied in connection with their potential use as specific and early biomarkers, or as a therapeutic target.

The doctoral thesis, written in the form of an annotated set of publications, dealt with the study of miRNAs in various systems *in vitro* and *in vivo*, focusing on their role in adipogenesis and their use as biomarkers of pathological conditions. The introduction summarizes the theoretical information on epigenetic regulation with a more detailed focus on miRNAs, followed by comments on the author´s individual publications and brief conclusions.

In two studies using mouse models, several miRNAs were identified to have their expression profile altered due to the pathological condition, and which would be interesting to be studied in more depth. For instance, in a study of the effect of a high-fat diet and fructose, miR-335 and miR-221 were overexpressed in obese individuals in the liver as well as in all three types of adipose tissue. In a study of cardiotoxicity induced by the administration of drugs doxorubicin and imatinib, altered expression of some miRNAs, which are considered specific

for cardiac tissue, was demonstrated in the plasma of treated mice. These miRNAs could serve as early biomarkers of heart damage at a time when the level of classically used markers (e.g. Troponin) is not yet affected. Furthermore, decreased expression of miR-205 was observed in the cardiac tissue of these mice. This miRNA may play a role in the pathogenesis of heart damage or may aim to protect the heart from drug-induced toxicity.

Next part of the thesis is focused on microRNAs that could be involved in the regulation of glutathione peroxidases (GPxs). GPxs are important antioxidant enzymes whose altered expression/activity is associated with a number of pathological conditions, including obesity. After a thorough bioinformatics analysis and the search for potential miRNAs that could regulate all GPx isoforms, the binding of miRNAs itself and the effect of certain miRNAs on the selected GPx7 enzyme were investigated. Bioinformatically predicted direct binding of miR-29b-3p and miR-137 to 3´UTR GPx7 was confirmed in various cell lines, while in the case of miR-335-5p this theory was refuted. Although the regulatory effect of miR-29b-3p and miR-137 on the GPx7 expression has been demonstrated, the importance of these miRNAs in relation to adipogenesis and obesity is not yet fully understood.