Dr Peter Hamar and a team of researchers from Semmelweis University and Harvard Medical School have been investigating what role the miRNA network has in kidney problems such as reperfusion injury and transplants. Projects finds out more about this vital work

Important first steps in fight against kidney disease

Renal Ischemia/Reperfusion and inset, Hydrodynamic Injection into Mouse.

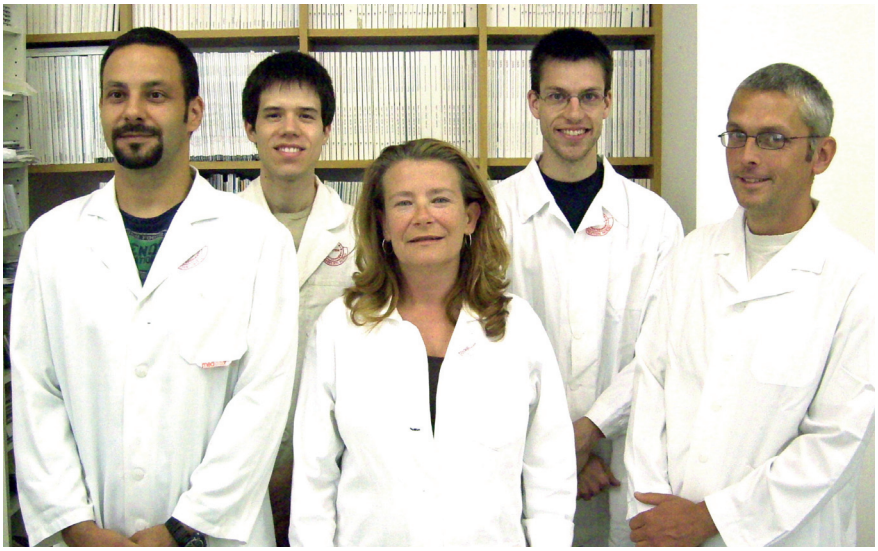
While current work taking place at Semmelweis University and Harvard Medical School is focused on trying to identify the miRNAs that are involved in kidney problems in mice, Dr Peter Hamar and his team of researchers hope that their data will allow them to gain a deeper insight into exactly what the pathophysiological roles of these molecules and their target proteins are. The hope is that in the future they will be able to use this knowledge to help fight human renal problems by in vivo influencing the expression of these miRNA molecules. Peter Hamar explains how he first began pursuing this line of study:

"I first became interested in this field back when I was studying renal diseases in a nephrology laboratory," says Hamar. "Back then RNA interference was a new field, and a good friend and colleague of mine had caught my eye with some of his preliminary investigations into mice at Harvard University. This was what eventually led our team to be the first to apply siRNA gene therapy for the kidney in mice, which we published the results of in 2004."

RNA interference, or RNAi, is an inherent system present within cells that controls which genes are active and also their level of activity. There are at least two types of molecules involved in this process, two of which are microRNA (miRNA) and small interfering RNA (siRNA). By artificially manipulating the action of these molecules, scientists have in recent years been able to gain a much better understanding of diseases that are controlled or partly controlled by gene function, as well as using it as a therapeutic tool against these diseases.

"The main function of RNAi is the post-transcriptional regulation of gene expression," explains Hamar, "and it is a physiological mechanism that functions in nearly all cells. miRNAs work by regulating numerous proteins at the same time, acting as hubs in the gene expression regulatory network, and therefore if we can influence the expression of a certain miRNA, we are able to completely modulate pathways within cells."

The present phase of the project involves



The team: (from left to right), Csaba Revesz, Csaba Szalay, Maria Godo, Tamas Kaucsar and Peter Hamar

investigating which miRNAs expression changes during different kidney pathological problems in mice. One of these problems is renal ischemia-reperfusion injury, which is essentially the damage caused to kidney tissue when there is a restriction of blood supply (ischemia), and the subsequent damage caused when blood flow returns to the tissue after the period of ischemia.

This can happen in many situations, such as the obstruction of a blood vessel, circulatory shock or dehydration, making it an area of great medical interest.

The methods used by the team from Semmelweis University involve applying multiplex assays to different renal disease models in mice. During this multiplex processing, some miRNAs are shown to be differentially expressed in diseased and control animals, singling them out as molecules that could potentially be involved in the genetic control of the disease.

After this step, in-silico analysis is used to look for proteins and pathways that might possibly be targeted by the identified miRNAs.

The team will then attempt to verify whether these hypothetical targets are influenced by these miRNAs in the particular animal model that they are investigating.

"Once we have identified a target, the next thing we try to do is to therapeutically influence the expression of the identified miRNAs," explains Hamar.

"If we can do this, then we have basically functionally proved that the hypothetical targets are indeed the targets, and so we can then look for therapeutic advantages of influencing these miRNAs, and consequently the protein pathways."

As mentioned before, this team is the first to have applied RNA interference in renal disease models in vivo in mice, and so far they have achieved some remarkable findings. They have managed to silence the apoptosis receptor, which is involved in post-ischemic reperfusion damage of renal tubule epithelial cells; this has manifested itself in a very impressive survival benefit to the mice. Also, they have demonstrated that RNAi can be safely applied to mice in vivo without activating deleterious mechanisms such as the interferon response. More recently, they have identified miRNAs differentially regulated during reperfusion of the kidney. However, there is still a long way to go before these findings can start to yield practical medical benefits for humans.

"After the identification of the targets and verification of the functional relevance of these miRNAs in ischemia-reperfusion injury, we need to see whether these singular pathways are functional in the human system in cell culture models," explains Hamar. "From there, we can begin to formulate medical treatments.

"We are still only really touching the surface of what can be done with this type of research," continues Hamar. "We would also like to investigate cellular pathways in other disease models such as autoimmune renal diseases and renal transplantation." Renal diseases and their associated problems are a major cause of illness and death around the world, and so the promising signs of this research bode well for those suffering from such afflictions. ★

At a glance

Project Information

Project Title:
The role of miRNA network in renal ischemia-reperfusion injury and renal transplantation

Project Objective:
We have detected significant miRNA expression changes during mouse renal ischemia-reperfusion injury and aim to in vivo influence the expression of the detected miRNAs, to gain deeper insight into their target proteins and pathophysiologic role played in ischemia-reperfusion injury and validate our data in a human in vitro system.

Project Duration and Timing:
4 years
2011: publication of identified miRNAs relevant in renal ischemia reperfusion injury.
2012: functional investigations of the identified miRNAs in our mouse renal IRI model.
2013: functional investigations in human in-vitro model systems.
2014: initiation of clinical trials.

Project Funding:
OTKA:100 000 euro
Fogarthy-FIRCA: 100 000 USD

Project Partners:
Prof. Judy Liebermann, MD Immune Disease Institute, Harvard Medical School
Zsombor Lacza, MD, PhD, Semmelweis Innovations Ltd.
Tibor Krenács, Semmelweis University, Dept. of Pathology, Tissue Microarray lab.

Peter Hamar

Peter Hamar, MD, PhD, DSc at Semmelweis University/ Pathophysiology conducted research at Universities in Germany (Essen, Heidelberg) and USA (Harvard) in the fields of renal transplantation and fibrosis. He was first to apply RNAi in vivo to target the kidney. His research team investigates the renal miRNA network.

Contact

Main contact name:
Peter Hamar

Tel: +36-20-825-9751
Email: hampet@net.sote.hu
Web: www.immunopathophysiology.sote.hu