MicroRNAs in Cholangiociliopathies
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Background

- Cholangiociliopathies are associated with:
  - Autosomal Dominant Polycystic Kidney Disease (ADPKD),
  - Autosomal Recessive Polycystic Kidney Disease (ARPKD),
  - Autosomal Dominant Polycystic Liver Disease (ADPLD).
- Mutations in disease-related genes (Figure 1) lead to formation of multiple hepatic cysts derived from bile duct epithelial cells (i.e., cholangiocytes).
- Mechanisms of hepatic cystogenesis in cholangiociliopathies are linked to abnormalities in a variety of cellular events, including miRNA expression (Figure 1).
- We have shown recently that in the PCK rat (an animal model of one of the cholangiociliopathies, ARPKD) growth of liver cysts is associated with increased cholangiocyte proliferation and alterations in the cell cycle (Gastroenterology, 2006).
- The cell division cycle 25A (Cdc25A) protein is an important cell cycle regulator.
- Accumulating evidence suggests that expression of genes involved in many cellular processes, including cell proliferation, is regulated by miRNAs.

Aims

- To describe the profiling and role of microRNAs in the pathogenesis of cholangiociliopathies

Results

Figure 1
MicroRNA deregulation is one of the potential mechanisms of hepatic cystogenesis

- Normal liver
  - Mitotic cell planar polarity
  - Centrosomal hyper-amplification
  - Increased apoptosis
  - Increased fluid secretion
  - Increased cell proliferation
  - Cell cycle deregulation
  - Abnormalities in miRNA expression

- Poly cystic liver

Figure 2
MicroRNA profiles are altered in the PCK cholangiocytes with majority of them being down regulated

Figure 3
miR-15a is significantly decreased in cystic cholangiocytes

- Normal cholangiocytes
- PCK cholangiocytes

Figure 4
Cdc25A, the cell cycle regulator and one of the potential miR-15a targets, is overexpressed in cystic cholangiocytes

- Normal cholangiocytes
- PCK cholangiocytes

Figure 5
Modulation of miR-15a alters the expression of Cdc25A in transiently transfected normal rat cholangiocytes

Figure 6
Up-regulation of miR-15a in PCK cholangiocytes decreases Cdc25A levels, rate of cell proliferation and cyst growth

- Normal cholangiocytes
- PCK cholangiocytes

Figure 7
Down-regulation of miR-15a in normal cholangiocytes increases Cdc25A levels, rate of cell proliferation and cyst growth

- Normal cholangiocytes
- Cdc25A WT
- Cdc25A Mutant

Figure 8
miR-15a affects Cdc25A by binding to the 3'UTR region

Conclusions

In cystic cholangiocytes, down-regulation of miR-15a is associated with elevation in Cdc25A levels leading to cyst formation. Experimental up-regulation of miR-15a restores balance between Cdc25A and miR-15a decreasing growth of hepatic cysts. In contrast, in normal rat cholangiocytes, experimental down-regulation of miR-15a results in Cdc25A over-expression accelerating cyst growth.

Future Directions

Reduced expression of miR-15a in cystic cholangiocytes occurs via transcriptional activation of the CREB/ICER pathway as a result of elevated cAMP.