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Identification of microRNAs in Polycystic Kidney Diseases

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MicroRNAs comprise a recently discovered class of small, non-coding RNA molecules that regulate the gene expression by base-pairing with their targets, leading to down-regulation or repression of the target genes. They play key roles in diverse regulatory pathways and diseases. Most of the existing databases on miRNAs are restricted to mRNA 3'-UTR region and have several other limitations. To address these issues, we designed a new computational approach named "miRWalk algorithm" that simultaneously provides the predicted and validated information on miRNAs. Combined information was put into miRWalk database. In contrast to existing databases, miRWalk encompasses the putative miRNA binding site predictions on all the regions. Additionally, the results of miRWalk are presented together with the results obtained from 8 other programs for a comprehensive view of the putative miRNA binding sites. miRWalk also comprises a holistic view of genetic networks of miRNA-gene-pathway, miRNA-gene-OMIM and mitochondrial genome-miRNA interactions. Moreover, it amalgamates the scattered data and sub-classifies the collected information of miRNAs at one place. Furthermore, miRWalk hosts new and unique features on experimentally validated miRNAs.

We adopted a combinatorial approach involving meta-analysis of mRNA-target predictions and microarrays (mRNA and miRNA) profiling to generate a comprehensive atlas of miRNAs involved in PKD. Taken together, our study suggests the presence of complex layers of regulation in ADPKD. Our microarray data revealed genes that specifically changed during disease condition. Further we identified genes related to cyst formation. The PKD/Mhm model suggests a cascade of signaling events involving up-regulation of several biological processes and down-regulation of metabolic pathways. These dysregulated pathways suggest their association in cyst expansion. We also observed up-regulation of secreted modulators and integrin receptors subunit. In addition, we also noticed many differentially regulated TFs in PKD. Interestingly, the down-regulation of genes associated with ciliary function or renal cystic kidney diseases were also differentially regulated. Moreover, we add 8 miRNAs to the regulatory layers of ADPKD. We predicted that several deregulated genes/pathways are the targets of these 8 miRNAs. It is interesting to note that 7 out of these 8 miRNAs have not been previously reported in PKD.

Additionally, we scanned all known genes of human, mouse and rat for the possible binding sites of cross-kingdom (soybean and rice) miRNAs. Unexpectedly, many genes were observed to harbour the possible motifs for these cross-kingdom miRNAs. Moreover, many genes (out of 3,333 significantly regulated members) of PKD/Mhm animals were predicted as the potential targets of cross-kingdom miRNAs. Interestingly, many cross-kingdom miRNAs and their families were found highly significantly overrepresented within mammalian, CDK and deregulated genes (PKD/Mhm animals).

Altogether, this study suggests novel candidates that have not been previously investigated for their possible regulatory roles in the regulation of already known biological pathways associated with ADPKD. Thus, extensive functional analyses of these 8 miRNAs and their target genes by performing knockout and over-expression studies (using antagomirs), individually and in combination, are likely to open up new avenues for PKD research. Also, the cross-kingdom miRNAs may be considered as future therapeutics for ciliopathies, as they are resistant to heat and enzymatic reactions as well as they are inexpensive and they can be easily delivered to host via food.