MULTI-OMICS DATA INTEGRATION IN THE CONTEXT OF PRIMARY GLOMERULONEPHRITIS

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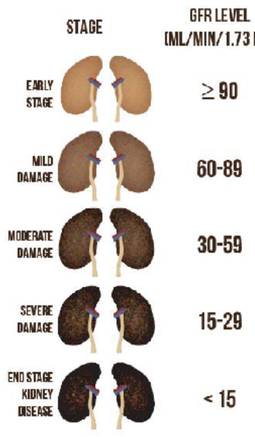
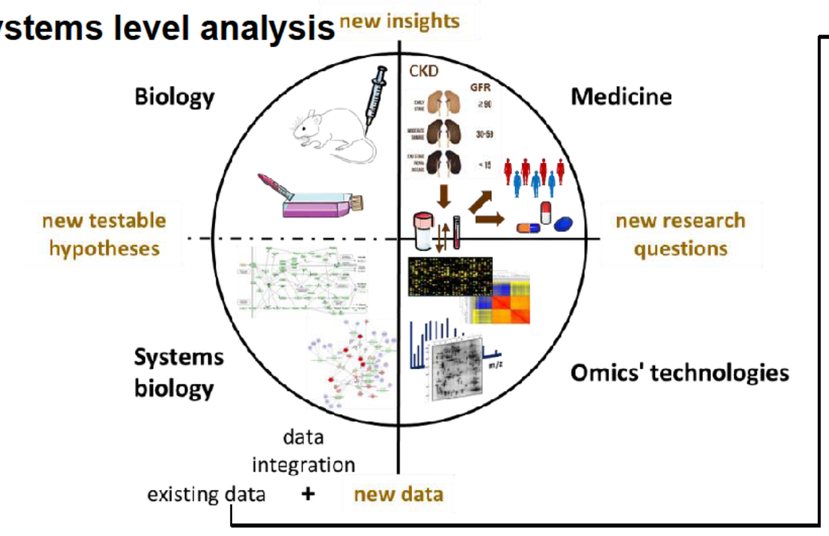
Background

CKD stage classification based on the estimated glomerular filtration rate (eGFR)

Chronic kidney disease (CKD) is a term that encompasses all degrees of decreased renal function, from damaged at risk through mild, moderate, and severe chronic kidney failure. CKD is a worldwide public health problem.



Systems level analysis



Query of the CKD chronic kidney disease database

"Glomerulonephritis": retrieved **81** studies

data selection criteria: human data sets with associated clinical data; retrieved **12** studies

Immunoglobulin A (IgA) nephropathy: seen as an chronic form of glomerulonephritis

Methods

Dataspace description

Table 1 Dataspace description of the experimental setup of studies included in in the analysis. Only human data was used from IgA nephropathy patients. Multi-omics platforms were used, such as: seven proteomics studies, three miRNAs studies and two metabolomic studies.

PMID	total	N (case)	N (control)	disease control	source	subcell	detection method	type
24339887	13	n/a	n/a		urine	whole	GeLC-MS/MS	PRO
24434790	10	5	5	MCNS	kidney	glomeruli	MALDI-TOF/TOF	PRO
16372274	25	n/a	n/a		urine	whole	MALDI-TOF-MS	PRO
23577616	33	19	14		urine	whole	MALDI-TOF-MS	PRO
18095357	38	18	20	healthy	urine	whole	nano-HPLC-ESI-MS/MS	PRO
24244321	61	26	35	healthy	urine	whole	1H NMR	MET
22522762	58	35	23	healthy	blood	serum	1H NMR	MET
20364043	56	43	13		urine	whole	qRT-PCR	MIR
19901913	63	43	20		kidney	biopsy	qRT-PCR	MIR
25279147	12	8	4	healthy	kidney	biopsy	MALDI TOF/TOF	PRO
21694443	63	43	20	biopsy	kidney	whole	RT-qPCR	MIR
21595033	12	5	7	healthy	urine	exosomes	LC-MS/MS	PRO

Data pre-processing

234 molecular entries (redundant)

combine repeats within studies

200 molecular entries (non-redundant)

data thresholding based on fold-change values

159 differentially expressed molecules

Split into two lists:

A - molecules found more than once and **B**- molecules found less than once across the datasets

Functional group cluster analysis

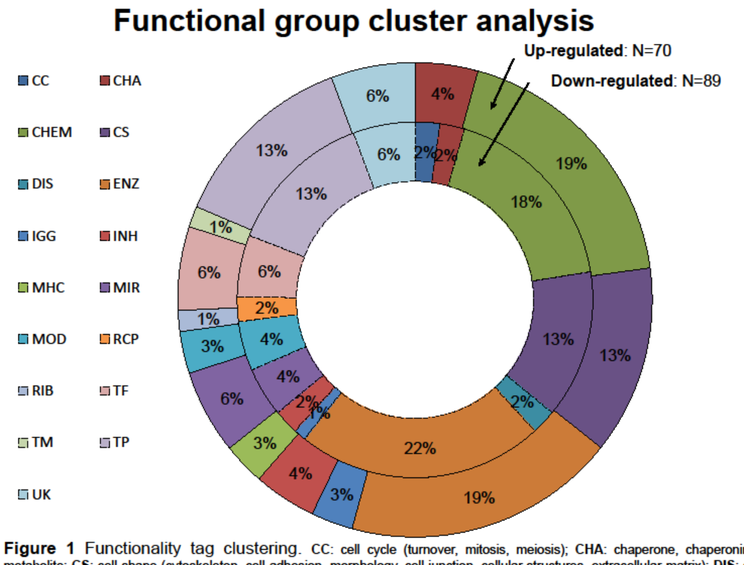


Figure 1 Functionality tag clustering. **CC**: cell cycle (turnover, mitosis, meiosis); **CHA**: chaperone, chaperonin; **MET**: metabolite; **CS**: cell shape (cytoskeleton, cell adhesion, morphology, cell junction, cellular structures, extracellular matrix); **DIS**: disease; **ENZ**: enzyme, enzymatic properties; **IGG**: immunoglobulin; **INH**: inhibitor (protease, kinase, other enzymes, pathways); **MHC**: major histocompatibility complex component/protein cluster (MHC, HLA); **MIR**: microRNA; **MOD**: modulator, regulator; **RCP**: receptor; **RIB**: ribosome; **TF**: transcription and translation, gene regulation; **TM**: transmembrane; **TP**: transport, storage, endocytosis, exocytosis, vesicles; **UK**: unknown.

Results: meta-analysis

Table 2 Expression correlation of the molecules found more than once across the datasets (list **A**). Down-regulated: green coloured; Up-regulated: red coloured.

molecule	exp1	exp2	exp3
ALB	3.85	11.46	48.53
KNG1	-20.00	-1.19	-114.63
A1A	8.33	780.48	0
ALDH2	-2.13	-1.94	0
C3	1.70	3.41	0
UMOD	-2.52	-1.11	0
MIR192	2.00	0	0
MIR200C	-2.00	0	0
MIR205	2.00	0	0
AMBP	1.90	-4.17	-50.90
B2M	31.00	2.99	-1.21
ACTA1	-41.88	2.76	0
HSPG2	1.56	-5.00	0
RBP4	52.00	-2.78	0
MIR141	2.00	-2.00	0
D-3-hydroxy-butyrate	1.21	0	0
Alanine	1.02	0	0
L-valine	-1.22	0	0
L-lysine	1.07	0	0
L-isoleucine	-1.34	0	0
glycine	1.07	0	0
3-methylhistidine	-1.52	0	0
tyrosine	-1.11	0	0
glutamine	-1.03	0	0

Term Clustering: ClueGO

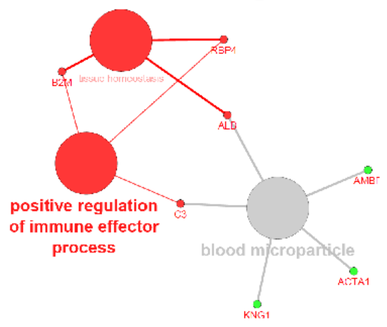


Figure 2 Genes/proteins from list **A**. GO Biological process, cellular location and molecular function. Down-regulated: green coloured; Up-regulated: red coloured.

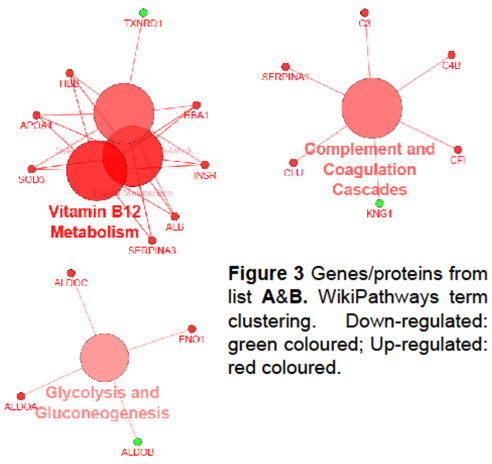


Figure 3 Genes/proteins from list **A&B**. WikiPathways term clustering. Down-regulated: green coloured; Up-regulated: red coloured.

miRNA analysis: CluePedia

Figure 4 miRNAs from list A and their predicted targets (miRanda v5). Down-regulated: green coloured; Up-regulated: red coloured.

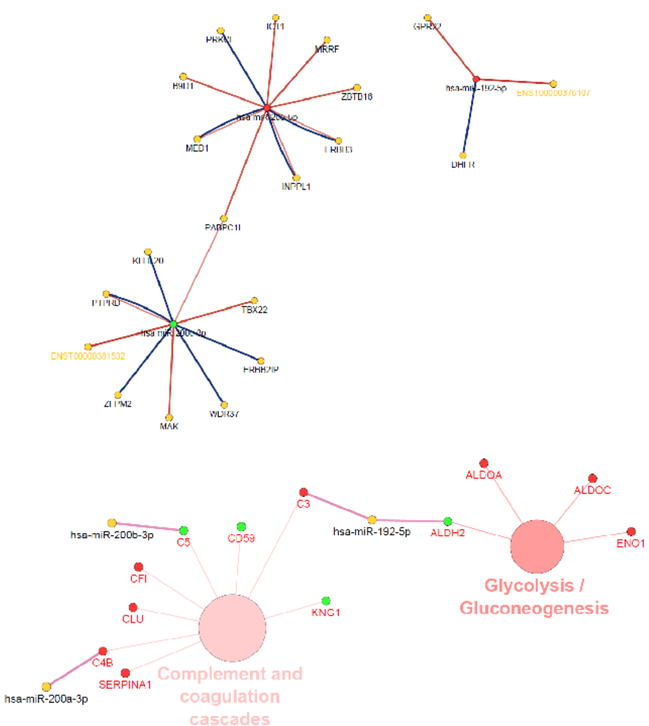


Figure 5 miRNAs and genes/proteins from list **A&B** and their predicted targets (miRanda v5). Down-regulated: green coloured; Up-regulated: red coloured.

Integrative analysis: metabolite and genes/proteins

Table 3 Association to KEGG pathway metabolic maps of the metabolites and gens/proteins form both list **A&B**.

Pathway	Total	Expected	Hits	P.Value
Aminoacyl-tRNA biosynthesis	87	1.277	9	2.70E-06
Valine, leucine and isoleucine biosynthesis	13	0.19082	4	2.58E-05
Alanine, aspartate and glutamate metabolism	56	0.82198	6	0.000127
Glycolysis / Gluconeogenesis	91	1.3357	7	0.000276
Valine, leucine and isoleucine degradation	82	1.2036	6	0.001038
Arginine and proline metabolism	102	1.4972	6	0.003215

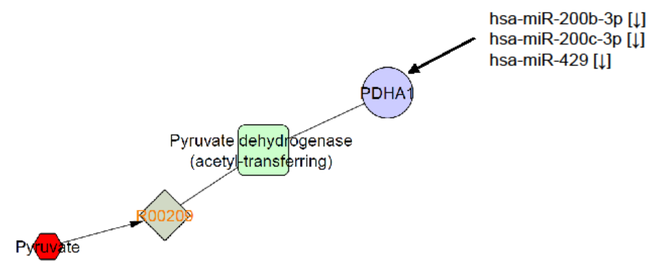


Figure 6 Snippet of one of the reactions from the Glycolysis and Gluconeogenesis (Metscape). Three miR from our list were found to regulate PDHA1 expression. The pyruvate compound was found decreased in expression.

Table 4 PathVisio analysis using list **A**. Involvement of the Complement and Coagulation cascades.

Pathway	positive (r)	measured (n)	total	Z Score	p-value (permuted)
Complement and Coagulation Cascades	3	6	65	2.91	0.001
Bile acid and bile salt metabolism	1	1	229	2.71	0.004
Formation of Fibrin Clot (Clotting Cascade)	1	1	162	2.71	0.005
SREBP signalling	1	1	77	2.71	0

Discussion & Conclusions

- Multidimensional -omics data can be used to construct models of molecular interaction networks, using both prior and de novo knowledge, therefore linking genes with disease based on genome-wide association studies, miRNAs and mRNAs targets, protein-DNA interactions, protein-protein interactions, protein-substrate binding, metabolic pathway interactions and drug-target interactions, where these molecular entities are represented as nodes and their interactions as edges;
- As known IgAN encompasses two phases: acute and a chronic, in which complement components (C3, C4, C5) and CFI leads to leukocyte recruitment that in this way leads to damage to the glomerular cells. On the other side, coagulation factors leads to fibrin deposition and crescent formation.

References

CKD chronic kidney disease database

http://www.padb.org/ckddb

Acknowledgments

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