Molecular Model of Acute Kidney Injury from Integrating 'Omics' Data

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Background

Large scale molecular characterization of acute renal allograft injury is essentially based on transcriptomics data with rather weak test characteristics of diagnostic or predictive markers. Therefore, the integration of multi-omics levels (genetic predisposition, protein coding and non-coding transcripts, as well as proteomics and metabolomics signatures) appears a promising strategy to study such complex phenomena like acute kidney injury (AKI), and to cover and classify the heterogeneous pathophysiology with a multi-marker profile.

Methods

We studied this enigma by incorporating a broad range of publicly available omics data for the analysis of AKI with focus on early diagnosis. We conducted a systematic literature search for AKI omics studies by using two sample sources: AKI in the ICU (proteomics, metabolomics) and AKI after renal transplantation (mRNA/miRNA). Despite the multifactorial causes for the development of AKI the diagnosis is mainly based on creatinine in both clinical settings (AKIN criteria ≥ Stage 1 in the ICU or the need of more than one dialysis after renal-TX).
We used a hybrid molecular interaction network covering about 15,000 molecular features from the human protein coding gene set, and holding about 800,000 molecular relations covering experimental as well as predicted interactions for integrating the given cross-omics data sets (Figure 1). This AKI-specific network was then segmented into distinct molecular segments (processes) apparently relevant in AKI pathology, in their entirety providing us with a molecular model of the clinical phenotype (Figure 2).

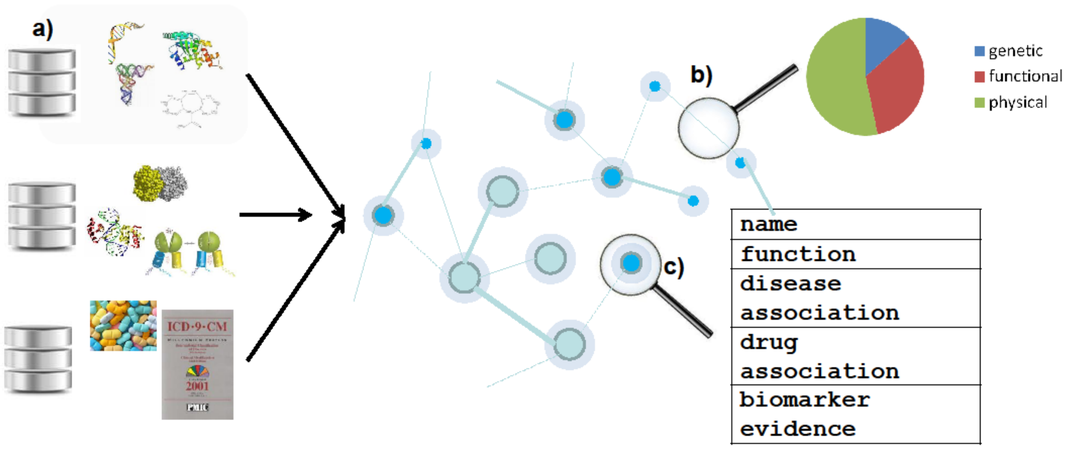

Figure 1. Composition of the hybrid relations network. **a)** Relevant information on molecular features, their interaction and their drugs/targets and associated diseases were combined. **b)** Edges represent the available interaction source and **c)** Nodes encode the human protein coding gene space holding further annotation (1).

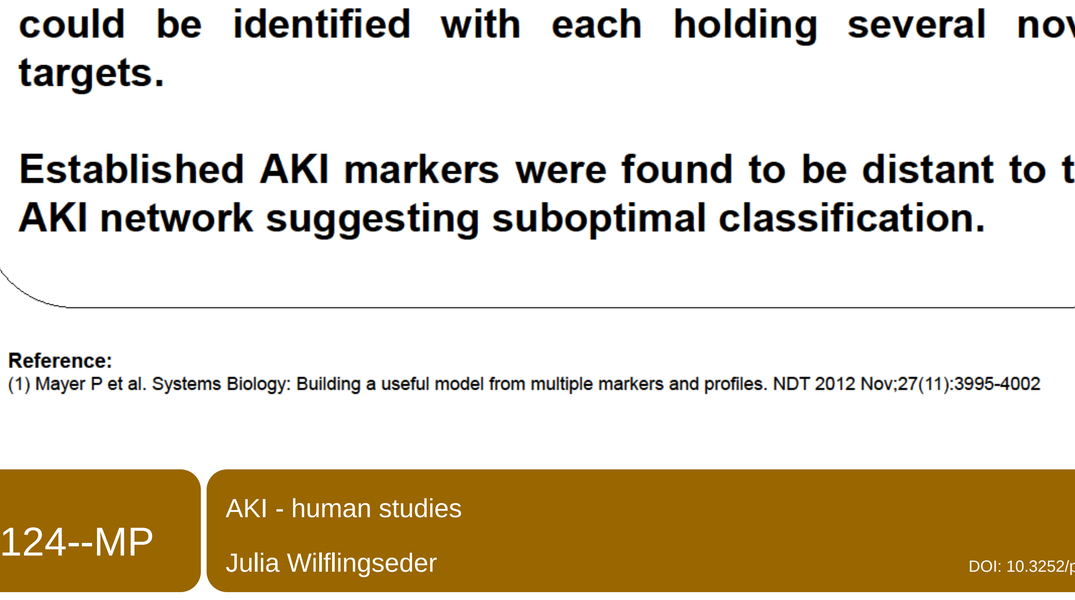

Figure 2. Generating a disease (AKI) specific subgraph. **a)** identification of human AKI Omics studies, **b)** identification of AKI associated features **c)** mapping the signature on the hybrid network, **d)** extracting the disease specific subgraph (1).

Conclusion

We integrated human cross-omics data to elucidate novel AKI biomarkers. Molecular clusters of candidates could be identified with each holding several novel targets.

Established AKI markers were found to be distant to the AKI network suggesting suboptimal classification.

Reference:
(1) Mayer P et al. Systems Biology: Building a useful model from multiple markers and profiles. NDT 2012 Nov;27(11):3995-4002

Results

The systematic literature search for human omics studies revealed 4 studies from the renal-TX setting (1 SNP, 3 transcriptomics) and 14 studies from the ICU setting (3 SNPs, 2 metabolomics, 8 proteomics, 1 miRNA) complemented with one miRNA data set from our group (Table 1).

Table 1. Identified omics studies relevant in the context of AKI

level	paper	source	outcome	# of genes
SNPs	Israni, 2008	donor	AKI after TX	1
SNPs	Alam, 2010	-	AKIN ≥ stage 1	1
SNPs	Haase-F., 2009	-	AKIN ≥ stage 1	1
SNPs	Isbir, 2007	-	AKIN ≥ stage 1	2
metabolomics	Sun, 2012	serum	AKIN ≥ stage 1	140 (9 metabolites)
metabolomics	Beger, 2008	urine	AKIN ≥ stage 1	5 (1 metabolite)
Proteomics	Ho, 2009 & 2011	Urine	AKIN ≥ stage 1	3
proteomics	Devarajan, 2010	Urine	AKIN ≥ stage 1	3
proteomics	Bennett, 2008	urine	AKIN ≥ stage 1	1
proteomics	Aregger, 2010	urine	AKIN ≥ stage 1	3
proteomics	Zhou, 2006	urine	AKIN ≥ stage 1	1
proteomics	Metzger, 2010	urine	AKIN ≥ stage 1	6
proteomics	Varghese, 2010	urine	AKIN ≥ stage 1	2
transcriptomics	Hauser, 2004	0h biopsy	AKI after TX	45
transcriptomics	Mas, 2008	0h biopsy	AKI after TX	68
transcriptomics	Perco, 2009	0h biopsy	AKI after TX	29
miRNA	personal data	0h biopsy	AKI after TX	39 (10 miRNAs)
miRNA	Lorenzen, 2011	plasma	AKIN ≥ stage 1	79 (13 miRNAs)

Table 2. AKI biomarker candidate list

purpose	Text-mining	manual search	biomarker candidates
early	x	x	FABP1, IL18, IL8
early		x	AP, γ-GT, π-GST, ITGAM, LDH, Pro-ANP
diagnostic		x	NHE3
prognostic	x	x	CRP, IL6
prognostic		x	ACR, β-2 microglobulin, GGT, IL10, RBP
early, diagnostic		x	GST, MMP9, NAG
early, prognostic		x	α-GST
diagnostic, prognostic		x	α-1 microglobulin
early, diagnostic, prognostic	x	x	Cystatin C (CST3) KIM1 (HAVCR1) NGAL (LCN2)
-	x		CCL3, CCL4, CX3CL1, CXCL10, CYBA, EGF, EPO, HAMP, IGF1, VCAM1

red → prominent biomarker candidates

AKI specific subgraphs derived from integrating AKI associated molecular features from the different omics levels on the relations network are shown in Figure 3A. Based on the disease specific subgraph, biological networks (units; highly connected protein coding gene nodes based on the hybrid relation network) were identified and are represented in Figure 3B. We interpret each unit as a distinct molecular aspect (process) being relevant in AKI.
We further evaluated which units are addressed by currently discussed biomarker candidates. AKI biomarker candidates were derived from text mining and a manual literature search (Table 2). IL6 is a member of unit-3. All other biomarkers are not in the consolidated omics feature list, and not in any of the identified units. To address this issue, we calculated the connectivity scores of the biomarker candidates to the units. Biomarkers with at least one direct edge to one of the units are shown in Table 3. Additionally, prominent biomarker candidates were drawn in Figure 3B to illustrate the distance to the units.

Figure 3A

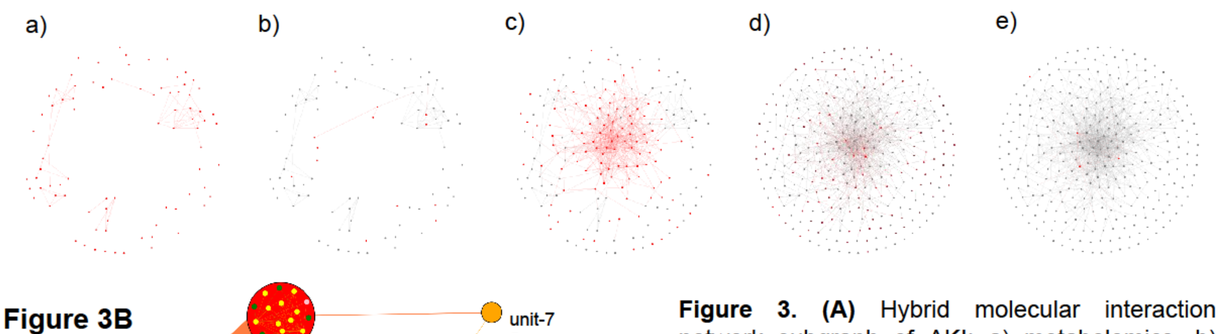

Figure 3B

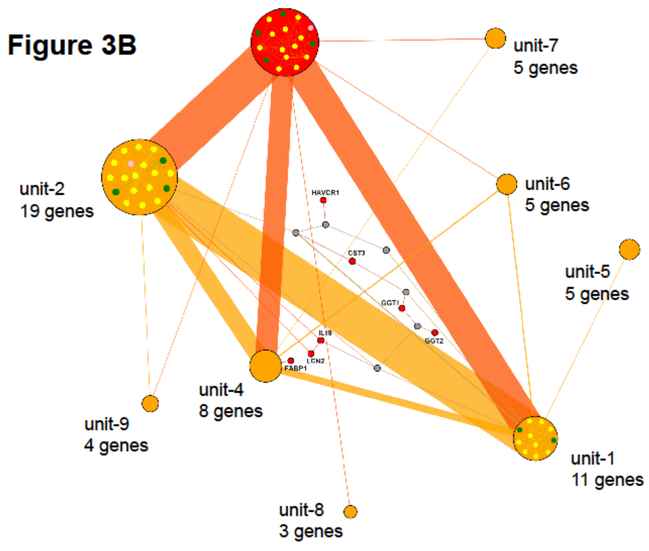

Figure 3. **(A)** Hybrid molecular interaction network subgraph of AKI: a) metabolomics, b) adding proteomics, c) adding miRNA targets, d) adding mRNA e) adding SNPs data. Features of the full reference network not associated with AKI (according to the profiling experiments, Table 1) were removed.
(B) Functional units derived from the AKI subgraph given in (A,e). A segmentation algorithm selects groups of nodes with strong associations from the AKI subgraph and forms units. Unit size correlate with number of nodes, and weighted edges between units indicates their level of connectivity. The unit given in red holds a biomarker candidate (IL6) already discussed in the context of AKI. Color code of nodes within units indicates the omics level: green - mRNA, yellow - miRNA targets, pink – SNPs

Table 3. Connectivity score of biomarker candidates

marker	unit-1	unit-2	unit-3	unit-4	marker	unit-1	unit-2	unit-3	unit-4
IL10	5.4 (49%)	6.3 (33%)	2.3 (14%)	2.3 (29%)	GSTP1			2.6 (15%)	0.8 (10%)
EGF	2.3 (21%)	2.3 (12%)	3.4 (20%)	3.3 (41%)	NPPA	2.0 (18%)	1.0 (5%)		
EPO	3.0 (26%)	1.5 (8%)	3.1 (18%)	2.3 (28%)	CXCL10		2.0 (11%)		
IGF1	2.4 (22%)	2.4 (12%)	2.6 (15%)	1.5 (19%)	MMP9		1.0 (5%)	0.7 (4%)	
CCL3	2.2 (20%)	0.8 (4%)	1.6 (9%)	0.7 (9%)	IL18		1.5 (8%)	0.8 (5%)	
CYBA	1.0 (9%)	0.7 (4%)			FABP1				1.0 (13%)
VCAM1	2.0 (18%)	1.0 (5%)	1.0 (6%)		RENBP			0.8 (5%)	
LCN2		2.3 (12%)	1.5 (9%)		CCL4			0.8 (5%)	
IL8	0.8 (7%)	2.0 (11%)		0.8 (9%)	CX3CL1	0.7 (7%)			

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