SYSTEMS BIOLOGY
BUILDING A USEFUL MODEL FROM MULTIPLE MARKERS
AND PROFILES
THE SYSKID APPROACH IN EARLY DIABETIC NEPHROPATHY

Gert Mayer

Department of Internal Medicine IV
Nephrology and Hypertension

Medical University Innsbruck

on behalf of the SysKid Consortium

G.M. 2013
STATE OF THE ART TREATMENT OF PATIENTS WITH TYPE II DIABETES AND ADVANCED RENAL DISEASE

Subjects (%)

Follow-up (mo)

Irbesartan

Amlodipine

control

inclusion criteria:

at least 900 mg proteinuria /day

serum creatinine 1.0 (1.2) - 3.0 mg /dl

% doubling of creatinine, ESRD or death

months of follow up


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inclusion criteria:
- at least 900 mg proteinuria /day
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WHAT NOW?

* inclusion criteria:
- at least 900 mg proteinuria /day
- serum creatinine 1.0 (1.2) - 3.0 mg /dl

Irbesartan
Amlodipine
control

NEW TREATMENT OPTIONS
BARDOXOLON

NEPHROPATHY IN TYPE II DIABETES MELLITUS IS NOT A HOMOGENOUS DISEASE

- No nephropathy
- Microalbuminuria
- Proteinuria
- Increased creatinine or RRT

Adler A et al. Kidney Int 2003
PATIENTS WITH TYPE II DIABETES AND NEPHROPATHY NOT HOMOGENOUS

- age

- comorbidities (heart failure, vascular disease, cancer etc.)

- medication (polypharmacy)

- etc
Current phenotypic characterization (stratification) of patients with renal disease leaves room for improvement

Stratification based on pathophysiology might

- improve the prediction of prognosis (who should be treated?)
- help to develop new treatments
- help in drug repositioning
- increase the efficacy of trials
- allow tailored therapy
REDUCTIONISTIC APPROACH TO COMPLEX PROBLEMS

What is the role of the RAAS in patients with type II diabetes and nephropathy?

ok

limits

- are we looking at a „causal“ pathway (is our hypothesis right)?
- even if it is a „causal“ pathway, is it the only one?
- if there are more, are they interacting and if so how?
- etc
EXPLORATIVE APPROACH TO COMPLEX PROBLEMS

- genetics/SNPs
- mRNA/miRNA
- proteomics
- metabolomics

ok

limits

- how to translate the findings into useable information?
- etc
INTEGRATIVE APPROACH TO COMPLEX PROBLEMS WITH THE USE OF SYSTEMS BIOLOGY

GROUP ALTERED FEATURES IN PATHWAYS / PROCESSES AND LOOK AT THE COMBINATION OF PATHWAYS / PROCESSES IN A PATIENT / A GROUP OF PATIENTS

damaging pathway 1 (RAAS → All)
damaging pathway 2 (oxidative stress)
damaging pathway 3 (TGF β)
damaging pathway 4 (yet unknown)

protective pathway 1 (RAAS→ACE 2)
protective pathway 2 (nrf 2)

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SEVENTH FRAMEWORK PROGRAMME
HEALTH-2009-2.4.5-2: Cellular and molecular mechanisms of the
development of chronic kidney disease (CKD)

Grant agreement for:
Collaborative project (Large-scale integrating project)

Annex I – “Description of Work”

Project acronym:
SysKid

Project full title:
Systems Biology towards Novel Chronic Kidney Disease
Diagnosis and Treatment

Grant agreement number:
241544

Date of preparation of Annex I (latest version):
2009-09-29

Date of approval of Annex I by Commission (to be completed by
Commission):
2009-09-30
‘Systems Biology towards novel Chronic Kidney Disease diagnosis and treatment‘ (SysKid)

• SysKid started in January 2010
  • Duration: 5 years
  • 25 partner institutions from 15 countries
  • strong advisory board (academia, industry, ethics, patients)
  • project volume: EUR 16mio
STEP 1
EXPLORATIVE ANALYSIS

2.175  DN associated unique protein coding genes \textit{from omics}
       13 SNPs, 12 miRNA target, 1.583 mRNA, 5 proteomics, 53 metabolomics, 509 multiple sources

287   DN  associated unique protein coding genes from pubmed \textit{MeSH} and \textit{gene2pubmed}

\~1.000 DN associated unique protein coding genes from \textit{patent} and \textit{clinical trials} search

\textit{Mayer}^3  \textit{Nephrol Dial Transplant 2012}  G.M. 2013
FROM FEATURES TO PROCESSES/PATHWAYS

e.g. biological processes as defined in specific databases (GO, PANTHER, KEGG)

Angiogenesis

Meiosis

signal transduction

*Mayer*³ *Nephrol Dial Transplant* 2012
experimentally derived set of differentially expressed genes / proteins

e.g. biological processes as defined in specific databases (GO, PANTHER, KEGG)

enrichment analysis

statistically non significant enrichment

statistically significant enrichment

FROM FEATURES TO PROCESSES/PATHWAYS

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signal transduction

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Angiogenesis

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Meiosis

GO, PANTHER, KEGG

Mayer ³ Nephrol Dial Transplant 2012
current databases (protein interaction networks)

- have a low coverage (many protein coding genes are not included) and thus a lot of information from -omics experiments cannot be analysed
FROM PROTEIN INTERACTION NETWORKS TO SOCIAL NETWORKS AND BACK
A NETWORK PROVIDERS PERSPECTIVE

A SOCIAL NETWORK WITH 3 MEMBERS

NICE BUT NOT INTERESTING
OMICS NET
PROTEIN CODING GENES ARE THE NODES

approximately 20,000 nodes from NCBI and ENSEMBL

Mayer ³ Nephrol Dial Transplant 2012
G.M. 2013
WHAT CAN YOU SELL FROM A SOCIAL NETWORK?
INFORMATION ON WHO IS INTERACTING
approximately 145,000 edges from Reactome, BioGrid and IntAct cover about 13,000 nodes

Mayer ³  Nephrol Dial Transplant 2012
YOU CAN ALSO SELL INFORMATION ON WHO MIGHT INTERACT (HAVE SOMETHING IN COMMON)
WHO MIGHT INTERACT?

attended Budapest Nephrology School 2013
attended a Rammstein concert in 2012
hates music

attended Budapest Nephrology School 2013
attended a Rammstein concert in 2013
OMICS NET
A HYBRID INTERACTION NETWORK

a) protein function  
b) protein as drug target or with disease annotation  
c) etc

d) edges: composite representation of interactions (omicsNET 600k)

e) nodes: hold metadata (omicsNET 14k)

Mayer ³ Nephrol Dial Transplant 2012
current databases (protein interaction networks)

- are not disease specific
experimentally derived set of differentially expressed genes / proteins

FROM FEATURES TO PROCESSES / PATHWAYS

Angiogenesis
signal transduction
statistically significant enrichment

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e.g. biological processes as defined in specific databases (GO, PANTHER, KEGG)

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Mayer 3 Nephrol Dial Transplant 2012
FROM FEATURES TO PROCESSES/PATHWAYS

experimentally derived set of differentially expressed genes / proteins

FROM FEATURES TO PROCESSES/PATHWAYS

e.g. biological processes as defined in specific databases (GO, PANTHER, KEGG)

Angiogenesis

Meiosis

signal transduction

Omics Net

Mayer 3 Nephrol Dial Transplant 2012
WHAT DO WE KNOW ABOUT NEPHROPATHY IN DIABETIC PATIENTS ON THE MOLECULAR LEVEL OF PROTEIN CODING GENES?

Mayer ³ Nephrol Dial Transplant 2012

2.175 DN associated unique protein coding genes \textit{from omics}

13 SNPs, 12 miRNA target, 1.583 mRNA, 5 proteomics, 53 metabolomics, 509 multiple sources

287 from pubmed \textit{MeSH} and \textit{gene2pubmed}

~1.000 from \textit{patent} and \textit{clinical trials} search

93 already DN biomarker candidates
A DISEASE SPECIFIC SUBGRAPH
FOR DIABETIC NEPHROPATHY

nodes: human protein coding genes

identified
trquoise: via SNPs
green: via miRNA
blue: via mRNA
pink: via proteomics
light red: via metabolomics
red: via multiple sources

edges: relations consolidated from multiple sources

Mayer ³ Nephrol Dial Transplant 2012
 NODES WITH STRONG RELATIONS FORM DISEASE SPECIFIC FUNCTIONAL UNITS

UNIT 1
context: signaling, inflammation
biomarker: CCL-5

diameter: number of nodes/unit (nodes hold e.g. 691/2175 features identified by omics)
orange nodes hold 14/93 features already defined as biomarkers

weighted edges: level of connectivity between nodes of one unit with nodes of the other

UNIT 2
context: defense, chaperoning
biomarker: to be selected

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BIOMARKER PANELS REPRESENTATIVE FOR THE UNITS ALLOW PATIENT STRATIFICATION

$B\{...,b_i, b_j, \ldots, b_x\}$

$T\{t_1, t_2, t_3\}$

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Stratified medicine means looking at groups of patients to try and find ways of predicting which treatments they are likely to respond to.

Personalized medicine is an emerging practice of medicine that uses an individual's genetic profile to guide decisions made in regard to the prevention, diagnosis, and treatment of disease.
Experimental validation

Disease associated feature space

Biomarker selection

Segmentation

Network representation

Functional analysis

Literature, experimental multi-Omics
PROVALID is an prospective cohort study in at least 4,000 individuals with type II diabetes in five European countries (Austria, Hungary, Netherlands, Poland and Scotland). The patients will be followed and treated according to local practice.

Objectives

Primary: Determine the cumulative incidence of renal outcomes in patients with type II diabetes in different European countries. Renal outcomes are defined as:
- Progression from normoalbuminuria to microalbuminuria (including > 30% increase in albuminuria from baseline)
- Progression from microalbuminuria to macroalbuminuria (including > 30% increase in albuminuria from baseline)
- Progression to doubling of serum creatinine, end stage renal disease (ESRD) or death

Secondary: Annual collection of blood and urine specimen during the first 3 years of the study to allow validation of biomarkers potentially of use in renal disease diagnosis, prognosis, prevention and therapy at the genome, transcriptome, proteome and metabolome level after 5 years
Collection of serum and urine at least once a year allowing centralized analysis of routine laboratory parameters throughout the entire study

Tertiary: Determine the cumulative incidence of cardiovascular outcomes in patients with type II diabetes in different European countries. Cardiovascular outcomes are defined as:
- cardiovascular death
- non fatal myocardial infarction or non fatal stroke
- hospitalization because of heart failure
DN biobanks & clinical data repositories

molecular process validation

clinical validation

multilevel Omics

clinical statistics & epidemiology

computational Systems Biology

visit www.syskid.eu

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a human disease-specific subset