Conserved regulatory network of diabetic neuropathy and nephropathy

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ABSTRACT

Diabetic neuropathy (DPN) and nephropathy (DN), which result in significant mortality, morbidity and poor quality of life, are frequent complications in patients with diabetes mellitus (DM). To find improved intervention strategies, it is critical to comprehensively understand involved molecular mechanisms and gene regulatory networks of disease progression. To obtain more insight into the processes leading to these complications, gene expression profiles of human sural nerve and kidney tissues from diabetes patients were surveyed using DNA microarray. A total of 4,680 and 4,630 genes were found to be differentially regulated in nerve (between progressive and non-progressive DPN) and kidney (between albuminuric and non-albuminuric DN), respectively. A cross-tissue comparison of transcriptional networks using the suboptimal graph matching tool TALE of the NCIBI tool suite allowed the identification of a core network of 91 genes. This shared network includes well-studied diabetes-related genes such as peroxisome proliferator-activated receptor gamma (PPARG) and leptin receptor (LEPR). Identification of these key genes confirms the validity of the current approach of pursuing a shared transcriptional network. This conserved gene network is expected to lead us to a better understanding of disease progression and will serve as a starting point to define therapeutic strategies targeting micro-vascular complication of DM independent of organ manifestation.

GOAL

To identify the core transcriptional networks, shared by neural and renal tissues, that are likely to regulate the progression of DPN and DN.

METHODS

Samples

◆ **Human sural nerve biopsies** from DPN patients. Grouped by the amount of sural nerve myelinated fiber density (MFD) loss over 52 weeks.

Progressor group (n=18) : MFD ≥ 500 fibers/mm^2
Non-progressor group (n=18) : MFD ≤ 100 fibers/mm^2

* Baseline characteristics were matched between groups using O'Brien rank sum and baseline MFD.

◆ **Human kidney biopsies (glomeruli compartment)** from DPN patients in Pima tribe. Grouped by the development of microalbuminuria over 52 weeks.

Albuminuric group (n=9) : microalbuminuria
Non-albuminuric group (n=13) : normal albumin secretion in urine

Microarray

Affymetrix GeneChip® Human Genome U133 Plus 2.0 Array measuring gene expression levels of over 47,000 transcripts.

Differentially Expressed Genes (DEGs) Finding

Single-probe based approach using Genomatix ChipInspector (FDR < 1%)

Functional Enrichment Analysis

Database for Annotation, Visualization and Integrated Discovery (DAVID) (http://david.abcc.ncifcrf.gov/) and ConceptGen (http://conceptgen.ncibi.org/) to identify significantly enriched biological functions (Gene Ontologies).

Transcriptional Network

Transcriptional networks based on the co-citation of genes at sentence level in PubMed abstracts by Genomatix BiblioSphere using Natural Language Processing (NLP).

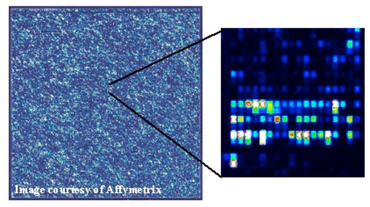
Shared Transcriptional Network

Tool for approximate large graph matching (TALE) to identify the sub-networks shared by the two tissues.

RESULTS

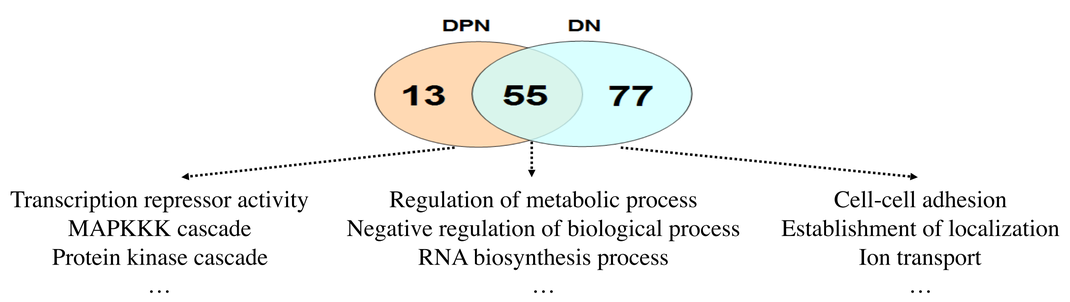
Microarray

Human sural nerve (progressor vs non-progressor)

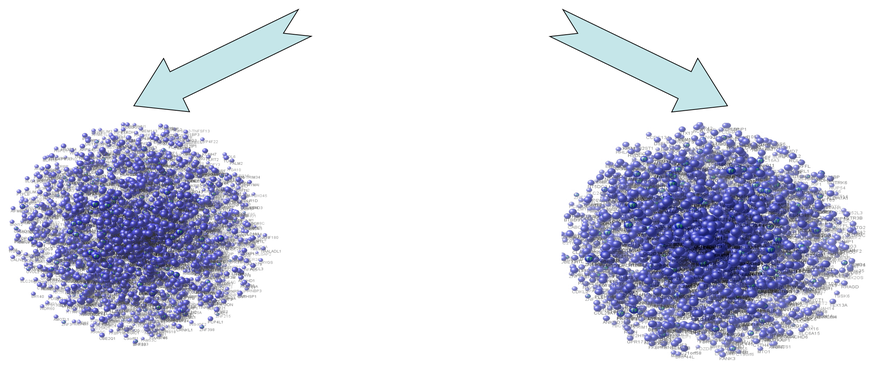


Human kidney (albuminuric vs Non-albuminuric)

- **Identification of significantly differentially expressed genes (DEGs)**
  4,680 (DPN) and 4,630 (DN)
- **Significantly enriched GO (Benjamini-Hochberg corrected p-value < 0.05)**



- **Extraction of the transcriptional regulatory network:**
  Differentially expressed genes as nodes are linked via NLP of PubMed abstracts at sentence level (Genomatix BiblioSphere)
  DPN (nerve): 2,935 nodes and 26,318 edges
  DN (kidney): 3,048 nodes and 32,045 edges



Network from DPN

Network from DN

TALE (align the networks to define the conserved network)

- **The shared network contains 91 nodes representing key hubs of cross-tissue conserved regulatory events.**
- **Well-known diabetes-related genes such as peroxisome proliferator-activated receptor gamma (PPARG) and leptin receptor (LEPR) are included.**
- **These shared genes will be further validated using animal models, proteomics, and metabolomics analyses.**
- **These genes will serve as a starting point to define therapeutic strategies targeting micro-vascular complication of DM independent of organ manifestation.**

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