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.

RESULTS

Network from DPN

• 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
  - DPN (nerve): 2,935 nodes and 26,318 edges
  - DN (kidney): 3,048 nodes and 32,045 edges

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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