Crosstalk between Platelets, Immune Cells, and the Glomerulus is Shown by Bioinformatics Analysis, and it May Be a Key Factor in the Development of Diabetic Nephropathy

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Abstract

End Stage Renal Disease (ESRD) is primarily brought on by Diabetic Nephropathy (DN) (ESRD). One of the main pathogenic alterations in DN is glomerulus injury. We used the Gene Expression Omnibus (GEO) database up to December 2020 to identify the gene expression changes in the glomerulus related to DN development. For additional bioinformatics investigation, eleven gene expression datasets pertaining to the human DN glomerulus and its control were retrieved. All expression data was extracted using the R language and Shambhala then cross platform normalised them. By using student's t-test together with false discovery rate and fold change, Differentially Expressed Genes (DEGs) were found. The Database for Annotation, Visualization and Integrated Discovery (DAVID) conducted additional analysis on DEGs to End Stage Renal Disease (ESRD) is primarily brought on by Diabetic Nephropathy (DN) (ESRD). One of the main pathogenic alterations in DN is glomerulus injury. We used the Gene Expression Omnibus (GEO) database up to December 2020 to identify the gene expression changes in the glomerulus related to DN development. For additional bioinformatics investigation, eleven gene expression datasets pertaining to the human DN glomerulus and its control were retrieved. All expression data was extracted using the R language and Shambhala then cross platform normalised them. By using student's t-test together with False Discovery Rate (FDR) (P 0.05) and Fold Change (FC) of 1.5, Differentially Expressed Genes (DEGs) were found. The Database for Annotation, Visualization, and Integrated Discovery (DAVID) conducted additional analysis on DEGs to gain a fresh understanding of DN pathogenesis.

Keywords: Diabetic nephropathy • False discovery rate • bioinformatics investigation • pathogenic alterations

Introduction

One of the most severe chronic microvascular consequences of diabetes and the main factor contributing to end stage renal impairment is Diabetic Nephropathy (DN). One of the main pathogenic alterations in DN is glomerulus injury. It is understood that glomerular pathology alterations, including glomerular mesangium growth, Glomerular Basement Membrane (GBM) thickness and podocytes loss, all contribute to the advancement of DN. Proteinuria and glomerulosclerosis are brought on by these alterations, which harm glomerular filtration. The Glomerular Filtration Rate (GFR) may eventually decline as a result and end stage renal disease may ensue. The leading cause of dialysis or kidney transplantation today is DN, which places a significant burden on worldwide public health. Only sodium glucose co-transporter 2 and the Renin Angiotensin Aldosterone System (RAAS) are currently the targets of medications. Inhibitors of (SGLT2) to cure DN (5-7) therefore, it is critical to investigate the recently discovered molecular mechanism of DN and offer a fresh approach to the disease's detection and management.

Transcriptomic analysis is a potent approach used to investigate numerous diseases, including DN and find new targets. The transcriptome approach has been extensively used and has produced some novel targets and mechanisms for DN. The transcriptomic approach does, however, have significant drawbacks. Due to their high prices, this procedure can only employ a single race sample and a small number of samples. Moreover, the majority of transcriptome techniques have low stability because of their high measurement error. Gene screening performed using various transcriptome research techniques thus varies and occasionally even conflicts. Multiple transcriptome approaches can be combined using bioinformatics tools to boost statistical power. Consequently, it is possible to get several stable differentially expressed genes from limited population samples. Using bioinformatics numerous studies have examined the transcriptomic data already available and some significant findings have been made. Researchers, Tang, et al. discovered that NTNG1 and HGF were promising DN biomarkers with excellent specificity and sensitivity after analysing glomerulus and renal tubule tissue transcription omics data. According to Wang, et al. changes in the methylation status of core regulatory genes may play a role in the pathogenesis of DN. The glomerulus in DN kidney tissue primarily causes changes in cell connectivity and tissue cell modification, whereas renal tubular tissue primarily causes abnormalities in energy metabolism. We are aware of very few studies that have examined all human glomerulus transcriptomic datasets using bioinformatics technologies in order to identify new potential biomarkers and the pathogenesis of DN. Therefore, doing it will be quite appealing.

Description

Meta-analysis and cross platform normalisation are two key components of bioinformatics tools that combine the data from numerous different transcriptome investigations. Using one of three forms of statistics p-value, effect size or ranking gene lists the meta-analysis approach first analyses each experiment independently. All platform transcriptomic data is treated as a single dataset during cross platform normalisation. With this method, biological distinctions between conditions are preserved while removing artifactual variations amongst transcriptome investigations. For "separate statistics," cross platform normalisation is thought to perform better than meta-analysis and "averaging is frequently less powerful than simply computing statistics from aggregated data."

Our goal is to thoroughly evaluate the transcriptome profiles of all available glomerular datasets from DN patients in the GEO database in order to comprehend the pathophysiology of DN. In this investigation, we first retrieved the raw transcriptome data from the glomerular tissues of all DN patients and their controls. Then, using bioconductor tools (DEGs), we performed cross platform normalisation (Shambhala method), a static test screening and the identification of differentially expressed genes. We enhanced the Gene Ontology (GO) DEGs and the Kyoto Encyclopaedia of Genes and Genomes (KEGG) pathways using the Database for Annotation, Visualization and Integrated Discovery (DAVID).

To filter core genes, we built a Protein Protein Interaction (PPI) network and modules. We also investigated immune cell infiltration in the DN glomerulus using CIBERSORTx.

Conclusion

In conclusion, we identified three key genes that may contribute to the pathogenesis of DN (LYZ, LUM and THBS2). Additionally, our additional bioinformatics study revealed that platelets, immune cells and the glomerulus might all be in a positive feedback loop. And even after the initial high glucose damages have been repaired, this feedback may continue to harm the glomerulus. These discoveries might offer fresh perspectives on the pathophysiology and management of DN. But more research is required because this finding lacked experimental validation.

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