EXPLORING THE ROLE OF MICRO RNAS AS KEY REGULATORS OF DIABETIC NEPHROPATHY-INDUCED CARDIOVASCULAR DISEASES

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Abstract

Diabetic nephropathy (DN) refers to the impairment of kidney function that occurs in patients with type 1 and type 2 diabetes mellitus. Diabetic Patients with kidney disease have an exceptionally high risk of developing cardiovascular complications. The hyperglycemic condition leads to the generation of oxidative stress, upregulation of the renin-angiotensin-aldosterone system, inflammation, initiation of the immune system, arterial stiffening, abnormal endothelial dysfunction, and nitric oxide metabolism. These changes lead to the dysregulation of various signaling cascades that ultimately causes cardiovascular diseases in a patient with diabetic nephropathy. There is a need to develop reliable strategies to prevent diabetic nephropathy before the progression of CVD. MicroRNAs are short non-coding nucleotide sequences that modulate gene expression through mRNA degradation or translational repression. We have accessed the gene target registry (GTR) for finding clinically tested genes involved in diabetic nephropathy-linked cardiovascular diseases. Bioinformatics tools including NCBI, miRanda, TargetScan, miRBase, and TarBase were used to identify different miRNAs targeting these genes. From the clinical data, we have identified that many genes expression is dysregulated which can be the direct target of miRNAs that targets them by binding at 8-mers sites. PPARG (miR-130-3p, miR-301a-3p, miR-451-3p), IL6 (miR-149-5p, miR-760), TLR4 (miR-140-5p), FTO (miR-150-5p), VDR (miR-4319, miR-125b-5p, miR-125a-5p), BDNF (miR-10b-5p, miR-10a-5p), MTHFR (miR-22-3p), VEGFA (miR-205-5p), and EDN1 (miR-1-3p, miR-206, miR-613). Conclusively, we predicted that different miRNAs targeting the genes involved in DN-linked cardiovascular diseases may pave a better path towards a miRNA-based therapeutic and diagnostic intervention for treating diabetic nephropathy-linked cardiovascular diseases.

Background

DN is typically linked with arterial hypertension and increased cardiovascular morbidity and mortality; consequences for people with type 1 (T1DM) or type 2 (T2DM) diabetes (Selby & Taal, 2020). Diabetic nephropathy may be a marker of vascular damage due to diabetes or may promote CVD through various mechanisms, such as blood pressure dysregulation, retention of uremic toxins, anemia, and altered mineral metabolism (Boer & Bakris, 2018). Micro RNAs are small non-coding RNAs that regulates about 60% of human genes at post transcriptional level Cell differentiation, growth and apoptosis are mainly regulated by micro RNAs (Seo et al., 2020), and its expression profiling needs further clinical applicability. MicroRNAs based therapeutics research is still at initial levels in case of DN. In case of DN some upregulated micro RNAs include miR-21, miR-34a-5p, miR-141, miR-503, miR-377, miR-130-3p, miR-205-5p, and miR-125b-5p (Tang et al., 2019)(Ishii et al., 2021). Some downregulted miRNAs includes miR-146a,miR-29a, miR-29b, miR-126, let-7, and miR-424 can also be used for detecting DN (Tang et al., 2019). Conclusively, majority of circulatory micro RNAs can be used as biomarker for DN diagnosis, and they also have therapeutic potential.

Objective

• To Investigate the role of micro RNAs in regulating the expression of different biomarkers involved in diagnosis and prognosis of DN linked CVD by Insilico tool

Materials & Methods

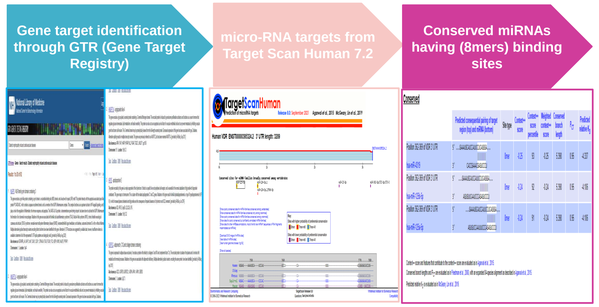

Figure 1: Identification of gene targets and prediction of microRNAs

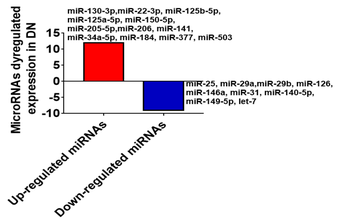

Figure 2: Upregulated and downregulated microRNAs expression in DN

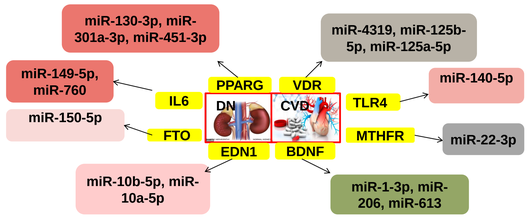

Figure 3: Gene targets regulated by microRNAs predicted by Target Scan

Discussion

MicroRNAs regulate the patho_x0002_physiology processes of DN by answering different signaling pathways and acting on different targets to inflammatory response, oxidative stress, immune response, fibrosis, and cell function(Tang et al., 2019).Deletions, translocations of genes or epigenetic aberrations disrupt functions of these microRNAs. Bioinformatic insilico analysis predicted several micro RNAs have 8nt binding sites, highest percentile score and conservation among many species. These micro RNAs have the potential to regulate many gene targets and can be potential candidate to understand the mechanistic regulation of disease progression. Furthermore, they can be used in diagnosis and therapeutic intervention against DN linked cardiovascular diseases .

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