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Original article

Differential expression network analysis for diabetes mellitus type 2 based on expressed level of islet cells

Diabète de type 2 : analyse d'un réseau d'expression différentielle des îlots pancréatiques

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Abstract

Objective. – Diabetes mellitus type 2 (T2DM) is a metabolic disease that has become a pressing issue, with potential adverse impact on mental health. We aimed to explore the potential molecular mechanism of T2DM. *Material and methods.* – GSE38642 microarray data downloaded from gene expression omnibus was used to identify the differentially expressed genes (DEGs). Profiling of complex functionality (ProfCom) was used to analyze the complex function and mine T2DM signature genes. Finally, the differential expression network (DEN) was constructed. *Results.* – We identified 147 DEGs including 59 up- and 88 down-regulated genes. With increasing of degree, the specificity of functional description of DEGs was higher. GO term of "integral to membrane and immune response (not receptor activity) not regulation of immune response" in degree 4 was enriched by 6 DEGs, while the GO term of "immune response" in degree 1 was enriched by 12 DEGs. Two complex functions of integral to membrane an immune response and response to glucose stimulus were enriched by 11 T2DM signature genes including *ARG2, GLP1R, PFKFB2, PTPRN, ACSL5, CCR7, IL2RA, IL7R, IL1R2, IL1RL1 and CHST4*. Finally, DEN including 11 signature genes and 491 edges was obtained. *Conclusion.* – The identified DEGs especially 11 signature genes such as *PTPRN, GLP1R, CCR7* and *IL2RA* may play important roles in the pathogenesis of T2DM.

Keywords: Diabetes mellitus type 2; Differential expression network; Profiling of complex functionality

Résumé

Objectif. – Le diabète de type 2 (DT2) est une maladie métabolique nécessitant une prise en charge urgente, notamment du fait de possibles effets néfastes sur la santé mentale. Nous avons cherché à en explorer le mécanisme moléculaire potentiel. *Matériel et méthodes.* – À partir du téléchargement sur *gene expression omnibus* des données microréseau de GSE38642, nous avons identifié les gènes exprimés de manière différentielle (DEGs). Le profilage de fonctionnalité complexe (ProfCom) a été utilisé pour analyser la fonction complexe de ces signatures d'expression génique d'un diabète de type 2. Enfin, le réseau d'expression différentielle (DEN) a été construit. *Résultats.* – Nous avons identifié 147 DEGs dont 59 à régulation positive et 88 à régulation négative. Une augmentation de degré entraînait une meilleure spécificité de description fonctionnelle des DEGs. Le terme de *Gene Ontology* [ontologie de gènes] (GO) de « partie intégrante de la membrane et la réponse immunitaire, sans activité du récepteur, sans régulation de la réponse immunitaire » de degré 4 a été enrichi par 6 DEGs, tandis que le terme GO de « réponse immunitaire » de degré 1 a été enrichi par 12 DEGs. Deux fonctions complexes de partie intégrante de la membrane intégrale et la réponse immunitaire ainsi que la réponse à un stimulus glucosé ont été enrichies par des gènes de signature 11 de DT2 dont *ARG2*, *GLP1R*, *PFKFB2*, *PTPRN*, *ACSL5*, *CCR7*, *IL2RA*, *IL7R*, *IL1R2*, *IL1RL1* et *CHST4*. Enfin, un réseau d'expression différentielle a été obtenu avec une signature de 11 gènes et 491 allèles. *Conclusion.* – Les DEGs identifiés, en particulier ceux de signature 11 gènes tels *PTPRN*, *GLP1R*, *CCR7* et *IL2RA* peuvent jouer un rôle important dans la pathogenèse du DT2.

Mots clés : Diabète de type 2 ; Réseau d'expression différentielle ; Profilage des fonctionnalités complexes

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1. Introduction

Diabetes mellitus type 2 (T2DM) is a metabolic disorder, which is caused by relative lacking of insulin and hyperglycemia [1]. The typical symptoms of T2DM are increased thirst and hunger, frequent urination and weight loss [2]. Long-term T2DM induces various complications including heart disease, diabetic retinopathy, renal failure and strokes [3]. So far, treatment of T2DM mainly includes anti-diabetic medications treatment and insulin injections [4,5]. However, these treatment methods have not been found to improve long-term results, and even have side effects on visceral organs including kidney and liver [5,6]. Thereby, the molecular mechanism of T2DM was extensively researched.

Previous study showed that insulin resistance (IR) and insulin-secretion deficiency were the main characters of T2DM pathogenesis [7]. In molecular mechanism, promoted IR has confirmed to be caused by macrophage polarization which transited from an alternative M2 activation state regulated by *PPARs* and *STAT6* to a classical M1 activation state induced by *AP1, NF-κB*, and other transcription factors [8]. Moreover, the mechanism of IR included various theories including, as oxidative stress, endoplasmic reticulum stress, inflammatory response and mitochondrial dysfunction [9,10]. Among of these, TNF-α, a factor of proinflammatory response and stress-induced cytokines, induced ser-phosphorylation of inflammatory response substrate, and further inhibited phosphorylation of Tyr and signal transduction of insulin, finally induced IR [11]. Similarly, activated IKK-β directly effected on signal molecules including insulin receptor, insulin receptor substrate, and then catalyzed the phosphorylation of Ser/Thr residues in specific sites, thereby inhibited Tyr residues phosphorylation of signal molecule, finally induced IR [12,13]. Furthermore, many pathways including innate immune, activation of the unfolded protein response and accumulation of ectopic lip metabolites, have confirmed to be related with the pathogenesis of IR [14]. In addition, insulin-secretion deficiency was mainly caused by disorders of glucose transport and non-enzymatic glycosylation of protein. Therein, *GLUT2*, encoded by *SLC2A2*, is a glucose transporter with high capacity [15]. In the environment of high glucose, decreased *GLUT2* expression of islet cells leads to insulin-secretion deficiency [16]. Besides, aminoguanidine can promote the insulin secretion and biosynthesis by inhibiting of advanced glycation end products [17]. However, there is still dearth of information from islets tissue because it's difficult to obtain the tissue.

In this present study, expression profile microarray of islets tissue was used to analyze the pathogenesis of T2DM. We downloaded GSE38642 and screened differentially expressed genes (DEGs) for T2DM signature genes mining and functional enrichment analysis. Moreover, differential expression network of T2DM signature genes was constructed.

2. Materials and methods

2.1. Microarray data

The transcription profile GSE38642 was downloaded from Gene Expression Omnibus (GEO, http://www.ncbi.nlm.nih.gov/geo/) database, including 54 non-diabetic and 9 diabetic islets samples [18]. The platform of this profile was Affymetrix Human Gene 1.0 ST Array. These 63 islet samples were obtained from cadaver donors and provided by the Nordic Islet Transplantation Programme (www.nordicislets.org), Uppsala University. The raw data was downloaded for further analysis.

2.2. Data preprocessing and differentially expressed genes (DEGs) screening

The raw data was preprocessed by Affy package (R/Bioconductor) of R language following the three steps: background adjustment, quantile normalization and finally summarization, and logarithmic transformation [19]. Then the expression matrix with probe level was transformed to matrix with gene level based on annotation files. Multiple Linear Regression limma [20] was applied for DEGs analysis. The threshold of DEGs was $P < 0.001$.

2.3. Functional enrichment and T2DM signature genes mining

Profiling of complex functionality (ProfCom) [21] is a functional annotation method for screened gene list. Compared with normal enrichment methods, such as geometric distribution and Chi-squared testing, ProfCom could process functional enrichment analysis of "complex function". Complex functions could combine individual terms by Boolean computation (and, or, not) on the basis of GO terms [22]. The number of integrated GO terms was defined as degree. The described specificity of enriched results has a positive correlation with degree. In this study, ProfCom was used for DEGs functional enrichment analysis and T2DM signature genes mining through online tool of BioProfiling.de (http://www.bioprofiling.de/) [23].

2.4. Differential expression network (DEN) construction

DEN was constructed based on the study of Sun et al. [24] as follows:

- signature genes protein-protein international (sg.ppi) network was extracted from PPI network of STRING V9.1;
- comprehensive expression values was used for spearman correlation test of each pair in the state of T2DM and non-T2DM;
- Benjamini and Hochberg (BH) method was used for the correction of P-value, and corrected p-value < 0.05 was the