Obesity Research & Clinical Practice (2017) xxx, xxx–xxx

ORIGINAL ARTICLE

Gene expression profiles in whole blood and associations with metabolic dysregulation in obesity

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Received 21 April 2017; received in revised form 3 July 2017; accepted 5 July 2017

KEYWORDS
Metabolic syndrome;
Obesity;
Gene expression;
Pathway analysis

Summary
Background: Gene expression data provides one tool to gain further insight into the complex biological interactions linking obesity and metabolic disease. This study examined associations between blood gene expression profiles and metabolic disease in obesity.
Methods: Whole blood gene expression profiles, performed using the Illumina HT-12v4 Human Expression Beadchip, were compared between (i) individuals with obesity (O) or lean (L) individuals (n = 21 each), (ii) individuals with (M) or without (H) Metabolic Syndrome (n = 11 each) matched on age and gender. Enrichment of differentially expressed genes (DEG) into biological pathways was assessed using Ingenuity Pathway Analysis. Association between sets of genes from biological pathways considered functionally relevant and Metabolic Syndrome were further assessed using an area under the curve (AUC) and cross-validated classification rate (CR).
Results: For OvL, only 50 genes were significantly differentially expressed based on the selected differential expression threshold (1.2-fold, $p < 0.05$). For MvH, 582 genes were significantly differentially expressed (1.2-fold, $p < 0.05$) and pathway analysis revealed enrichment of DEG into a diverse set of pathways including immune/inflammatory control, insulin signalling and mitochondrial function pathways. Gene sets from the mTOR signalling pathways demonstrated the strongest association with Metabolic Syndrome ($p = 8.1 \times 10^{-8}$; AUC: 0.909, CR: 72.7%).

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http://dx.doi.org/10.1016/j.orcp.2017.07.001

Please cite this article in press as: Cox AJ, et al. Gene expression profiles in whole blood and associations with metabolic dysregulation in obesity. Obes Res Clin Pract (2017), http://dx.doi.org/10.1016/j.orcp.2017.07.001

Conclusions: These results support the use of expression profiling in whole blood in the absence of more specific tissue types for investigations of metabolic disease. Using a pathway analysis approach it was possible to identify an enrichment of DEG into biological pathways that could be targeted for in vitro follow-up.

Introduction

The aetiology of obesity is complex and includes both biological and environmental factors with prevalence estimates suggesting that in some Western nations over 60% of the adult population are now considered to be overweight or suffering from obesity [1]. Accordingly, the associated burden of disease poses significant societal and economic implications [2]. Efforts to better manage risk for adverse outcomes associated with obesity increasingly include consideration of the biological pathways linking obesity and metabolic disease. Inflammation is one mechanism that has been implicated as underpinning risk for obesity-associated disease and the potential for cross-talk between immune/inflammatory and metabolic signalling pathways may underpin risk for disease. Gene expression data provides one tool to gain further insight into these complex biological interactions.

Use of biologically relevant tissues in gene expression studies to directly characterise the specific cellular mechanisms underpinning disease has been easy to justify. For example, adipose tissue [3—5] and muscle biopsy samples [6,7] have been frequently used to assess both genome-wide and targeted gene expression patterns in obesity and type 2 diabetes, predicated on the basis that these two tissue types represent major depots for energy storage and utilisation. Results from several of these studies support the differential expression of individual genes or groups of genes involved in immune and inflammatory pathways in metabolic disease phenotypes [3,4,8]. This data lends further support to the role of immune and inflammatory control in the development of metabolic disease.

Beyond assessment of gene expression in biologically relevant tissues, alternative approaches to gene expression profiling have also been considered. Whole blood or isolated blood cells subsets have been utilised to avoid the challenges associated with obtaining tissue biopsy samples. Differential gene expression patterns related to body mass have been reported using these less invasive sample types [9,10], as well as in individuals with or without specific disease phenotypes such as Metabolic Syndrome (MetS) and type 2 diabetes (T2D) [11—14]. To date, most studies have reported modest fold-changes for individual transcripts, generally <4-fold [11—13]. However, enrichment of differentially expressed genes into biological pathways has allowed for further consideration of the mechanisms linking obesity and metabolic disease.

This study aims to extend the current understanding of the biological pathways that may underpin obesity and metabolic disease by performing whole genome gene expression profiling using whole blood samples from (i) individuals with obesity or lean individuals and (ii) individuals with or without MetS. It is hypothesised that patterns of gene expression will be different between individuals with excess body mass or evidence of metabolic disease compared to control groups.

Materials and methods

Study design and subjects

This study was designed as a cross-sectional study to compare whole blood gene expression patterns in: (i) individuals with obesity (n = 21) or individuals with healthy body mass (n = 21) based on body mass index (BMI) criteria (obese >30 kg/m^2; healthy body weight <25 kg/m^2); (ii) individuals with (n = 11) or without (n = 11) MetS. The Griffith University Human Research Ethics Committee (EC00162) provided ethical approval for this study (approval#: MED/32/13/HREC), all study procedures were carried out in accordance with the Declaration of Helsinki, and all subjects provided written informed consent prior to participation.

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