The genomic profile of type 2 diabetes patients has two tissue specific subtypes: pancreatic islets and non-pancreatic islets

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Background and Motivations

Diabetes mellitus (simply, diabetes) is a group of metabolic diseases in which a person has high blood sugar, because the body does not produce enough insulin (type 1, T1D), or the body cannot effectively use the insulin it produces (type 2, T2D), or when a pregnant woman without a previous diagnosis of diabetes develops hyperglycaemia (gestational). Symptoms of gestational diabetes are similar to type 2 diabetes, and may precede development of the latter.

The World Health Organization (WHO) estimates that 347 million people worldwide have diabetes as of March, 2013, and projects that diabetes will be the 7th leading cause of death by 2030 [1]. T2D is rapidly becoming a global pandemic and is projected to afflict more than 300 million individuals worldwide by the year 2025, with most of the increase occurring in India and Asia [2]. Here we focus on T2D and try to explore more clearly mechanisms or pathophysiology of T2D.

Materials & Methods

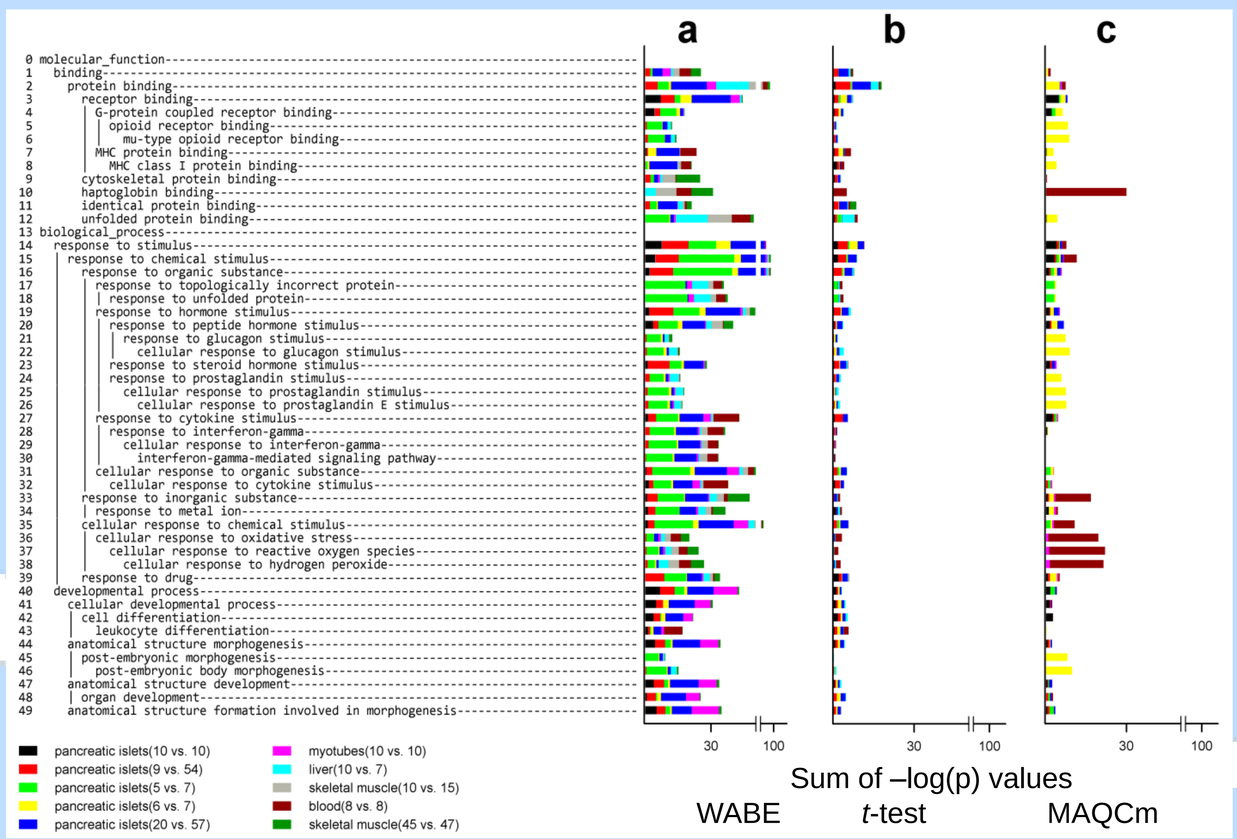
We obtained gene expression microarray data on T2D patients and normal controls from EuroDia database, a collection of gene expression measurements on beta-cells of human, mouse and rat [3], and from Gene Expression Omnibus (GEO) database. The 10 microarray datasets collected for this study were derived from different human tissues including pancreatic islets, skeletal muscle, liver tissue, etc. (Table 1)

For analysis we used the tool Weighing Arrays By Error (WABE), an algorithm based on z-statistics tests for analyzing large sets of microarray data to analysis these ten microarray datasets [4]. Unlike standard methods including SAM and ANOVA, WABE respects molecular heterogeneity and uses in-array errors for deriving statistical weights of measured gene expression intensities; it has been shown to be a powerful tool for detecting differentially expressed gene sets representing GO terms. For the present case we used WABE with an FDR cutoff of 0.5.

Table 1. Gene expression microarray data on T2D patients and normal controls.

No.	Tissue Type	GEO or Group	Platform	T2D vs. Control
1	pancreatic islets	GSE20966	Affy Human X3P Array	10 vs. 10
2	pancreatic islets	GSE38642	Affy HuGene 1.0 st Array	9 vs. 54
3	pancreatic islets	Jenny E. Gunton	Affy HG-U133A Array	5 vs. 7
4	pancreatic islets	GSE25724	Affy HG-U133A Array	6 vs. 7
5	pancreatic islets	GSE41762	Affy HuGene 1.0 st Array	20 vs. 57
6	myotubes	GSE12643	Affy HG U95A v2 Array	10 vs. 10
7	liver	GSE23343	Affy HG-U133 plus 2.0 Array	10 vs. 7
8	skeletal muscle	GSE25462	Affy HG-U133 plus 2.0 Array	10 vs. 15
9	blood	GSE15932	Affy HG-U133 plus 2.0 Array	8 vs. 8
10	skeletal muscle	GSE18732	Affy HG-U133 plus 2.0 Array	45 vs. 47

Figure 1. Methodology comparison between: *a*, WABE; *b*, *t*-test; and *c*, MAQCm.

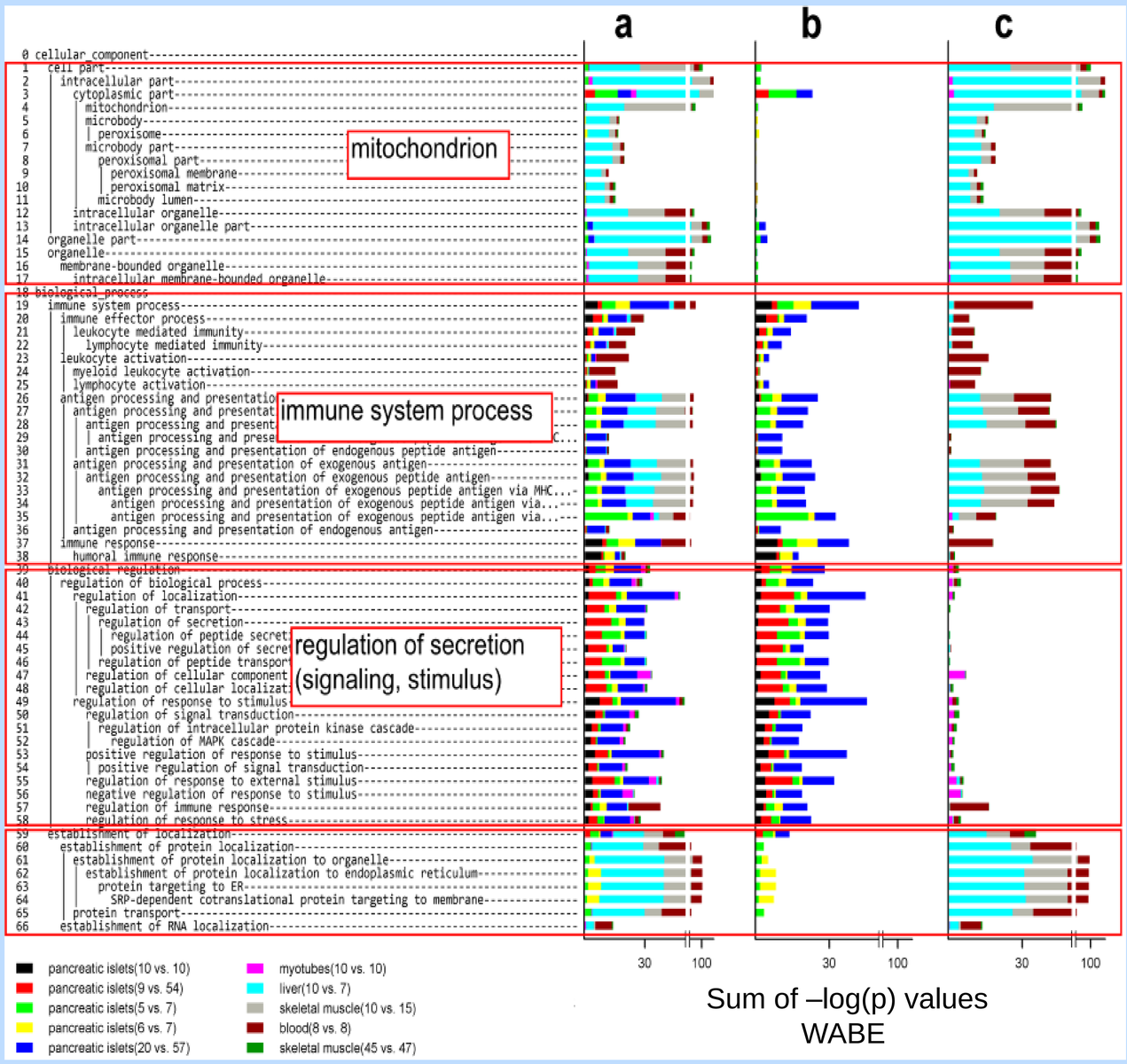


Results

We compared differentially expressed GO terms obtained from WABE, the standard method based on *t*-test statistics (*t*-test), and the widely used method based on a hybrid of *t*-test statistics and fold-change [5], and found that WABE yielded much richer results (Figure 1).

We observed significant tissue specific differentially expressed GO terms among T2D patients (Figure 2). These results separated tissues into two groups, pancreatic islets group (PIG) and non-pancreatic islets group (NPG), including skeletal muscle (the largest set), liver, blood and myotube. GO terms that were expressed higher in PIG included response to stimulus and regulation of secretion. Those higher in NPG included expression of mitochondrion, protein complex organization, and catabolic process. GO terms high in both groups included metabolic process and immune system process [6]. Mitochondrial dysfunction has been reported as a cause for T2D [7].

Figure 2. Significant tissue specific differentially expressed GO terms among T2D patients by WABE. *a*, all tissues; *b*, pancreatic islets group (PIG); *c*, non-pancreatic islets group (NPG).



Conclusion

That T2D has two gene expression subtypes with distinct tissue specificities should have important implications in diagnostic and treatment of diabetes, including the design of targeted drug delivery.

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