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A transcriptional signature of "exercise resistance" in skeletal muscle of individuals with type 2 diabetes mellitus ☆

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ABSTRACT

Aims/Hypothesis. Exercise benefits most, but not all, individuals with type 2 diabetes mellitus (T2DM). The aim of this study was to determine whether a proportion of individuals with T2DM would fail to demonstrate exercise-induced metabolic improvements. We hypothesized that this lack of response would be related to their skeletal muscle transcriptional profile.

Methods. 42 participants with T2DM from the previously reported HART-D study underwent a 9-month supervised exercise intervention. We performed a principal components analysis to distinguish Responders from Non-Responders (n = 9 each) based on: decreases in (1) HbA_{1c}, (2) %fat (3) BMI and (4) increase in skeletal muscle mtDNA. mRNA expression patterns in muscle tissue at baseline were assessed by microarray and qRT-PCR analysis in both groups.

Results. Of 186 genes identified by microarray analysis, 70% were up-regulated in Responders and down-regulated in Non-Responders. Several genes involved in substrate metabolism and mitochondrial biogenesis were significantly different (fold-change > 1.5, $p < 0.05$) between the groups at baseline, indicating a blunted oxidative capacity at baseline in Non-Responders.

Conclusions/Interpretations. These data suggest that a unique baseline expression pattern of genes involved in muscle fuel metabolism may predict an individual's lack of exercise response in metabolic outcomes, thus allowing exercise interventions to be targeted to these individuals and aid in the identification of novel approaches to treat Non-Responders in the future.

1. Introduction

As many as 40% of Americans will have T2DM within their lifetime [1]. Exercise benefits most individuals with T2DM; however, some people derive significantly less metabolic benefit. We and others have found that ~15–20% of individuals fail to increase muscle mitochondrial density and improve their glucose homeostasis and insulin sensitivity

Abbreviations: AT, aerobic training; IPA, ingenuity pathway analysis; PCA, principal components analysis; RT, resistance training; SEM, structural equation model; T2DM, type 2 diabetes mellitus.

☆ Disclosure Statement: The authors have nothing to disclose.

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after supervised exercise interventions [2–4]. Recent findings have shown that a genetic predisposition to diabetes can modify ATP flux responses, whereby a single nucleotide polymorphism in a mitochondrial Complex I subunit gene reduces the ability to improve *in vivo* mitochondrial function with exercise [5]. Furthermore, VO_2max responses to endurance exercise training can be predicted by a 29-gene RNA expression signature in the pre-trained muscle [6], while transcriptional data have demonstrated that individuals with insulin resistance have a reduced response of nuclear-encoded mitochondrial genes to acute

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Clinical Characteristics	Responder	Non-Responder	P value
Age (y)	57.0 ± 3.35	55.7 ± 2.13	NS
Sex (M/F)	4/5	5/4	NS
Height (cm)	168.04 ± 2.85	171.0 ± 1.83	NS
Δ%HbA1c	-12.92 ± 3.38	3.16 ± 1.93	p=0.0008
Δ%Body fat	-6.76 ± 2.3	-0.17 ± 1.27	p=0.0258
ΔBMI	-3.31 ± 1.14	0.77 ± 0.56	p=0.0052
Δ%mtDNA	50.68 ± 12.76	-23.39 ± 10.87	p=0.0004

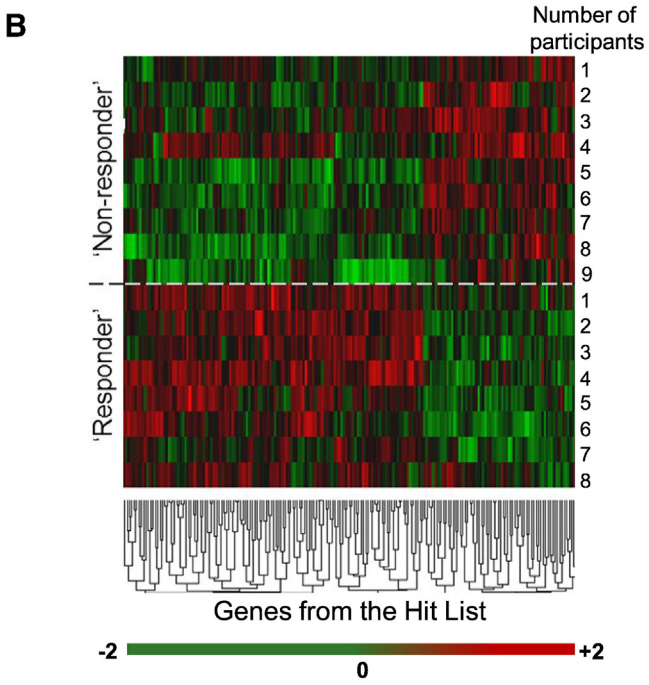

Fig. 1 – (A) Changes in metabolic parameters following nine months of supervised exercise and clinical characteristics. The changes (or lack thereof) in HbA_{1c}, %body fat, BMI and mtDNA content were used in PCA analysis to distinguish Responders from Non-Responders. Data are presented as mean ± SEM. (B) Unsupervised cluster analysis of Illumina transcription arrays in muscle tissue mRNA at baseline generated a 'hit list' of 186 genes. Each color represents the log2 ratio of the (Responder gene expression/Non-Responder gene expression) of a particular gene in each participant. The fold change cut-off value was 1.3. False Discovery Rate (FDR) was 0.05. Each column shows data from a specific gene and each row shows data from a single participant. (Data from one Responder were not included due to poor quality.) Green indicates down-regulation and red indicates up-regulation. The values in the heat map range between −2 and +2. Expression ratios range from −2.3-fold in one direction to 3.6-fold in the other. The dendrogram reflects the degree of correlation of the genes assessed by the hierarchical clustering. (C) Subset of genes involved in substrate metabolism and mitochondrial function from the 'hit list'. Functions were determined with Ingenuity Pathway Analysis (IPA) and available gene ontology. Of 186 genes, 48 genes were classified as hypothetical/pseudogenes or small nucleolar RNAs (data not shown). 33 genes from the 'hit list' were functionally classified as being involved in substrate metabolism and mitochondrial function. * indicates genes validated by qRT-PCR.

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