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Interaction Between Insulin Sensitivity Status and Cex in control of Gene Expression in Human iPS Cell-Derived Myoblasts

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Insulin resistance is a major risk factor in the development of type 2 diabetes, metabolic syndrome, polycystic ovarian disease, and many other disorders. About 25% of people within the general non-diabetic population are insulin resistant, and this has been shown to increase the risk for type 2 diabetes and cardiovascular disease. The aim of this study was to uncover the nature of the cell autonomous differences in gene expression that contribute to differences in insulin sensitivity and disease risk using induced pluripotent stem cell (iPSC) derived from humans at both ends of the insulin sensitivity spectrum, i.e., top 20% of insulin resistance vs. top 20% of insulin sensitive.

We find that iPSCs differentiated into myoblasts (iMyos) from non-diabetic individuals in the highest quintile of insulin resistance (I-Res) show impaired insulin signaling, defective insulin-stimulated glucose uptake, and decreased glycogen synthase activity compared to iMyos from the insulin sensitive individuals (I-Sen), indicating these cells mirror in vitro the alterations seen in vivo. Transcriptomic analysis of these iMyos revealed a major effect of insulin resistance on gene expression, but an even larger, and unexpected, effect of sex of the donor on gene expression ex vivo. Thus, in cells from male donors, there were 184 significantly up-regulated and 167 significantly down-regulated genes in iMyos from I-Res vs I-Sen donors. The I-Res up-regulated genes were mostly related to the extracellular matrix organization and integrin signaling pathways, while the down-regulated genes belonged to immuno-regulatory pathways ($p<0.05$). Interestingly, in cells from females, distinct genes expression differences marked insulin resistance. Thus, iMyos from females showed up-regulation of 69 genes in the I-Res subgroup linked to cellular senescence and response to stress ($p<0.05$). In addition, and more strikingly, we also observed over 1500 sex-specific changes in gene expression that were independent of the insulin sensitivity status, with 766 genes significantly higher in cells from male donors and 786 genes higher in cells from female donors (FDR<0.2). Chromosomal positional analysis of the most sex-biased genes (FC>1.5) showed that only 7% of the differentially expressed genes were encoded by the X- or Y-chromosomes, while the remainder were spread across the autosomes. Furthermore, a comparison of the RNA sequencing data from these cell lines at the iPS cell and iMyos stage showed that X chromosome inactivation during the myoblast differentiation process was normal and that the sex-specific changes were not due to differences in X chromosome dosage in males and females but represent either persistent epigenetic changes and/or crosstalk between X and Y encoded genes and autosomal genes. Thus, insulin sensitivity status and

patient sex interact to produce changes in gene expression that can contribute to how insulin resistance and other diseases are manifest differently in men and women.

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