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"Differential Gene Expression Analysis of Tumors in Lean and Obese Mice with Triple-Negative Breast Cancer"

Triple-negative breast cancer (TNBC) is one of the four subtypes of breast cancer and is characterized by the absence of estrogen receptors, progesterone receptors, and human epidermal growth factor receptor 2 expression. Compared to other invasive breast cancers, TNBC generally grows faster and has fewer options for treatments, tending to lead to worse outcomes. Patients with higher BMI have been shown to be at a higher risk of TNBC as well as having higher tumor grades and sizes. The goal of this study is to use a mice model to study differential gene expression between TNBC tumors in lean and obese mice and to determine the molecular signatures of lean and obese TNBC. In the future, we will identify if the - similar molecular signatures can be observed in TNBC patients to determine actionable biomarkers. .

FVB (female) mice were in control or Western diet (Envigo) to induce obesity. After four months, the mice were injected with syngeneic TNBC C0321 cells into their mammary fat pad, and growth of the tumor was tracked for three weeks. RNA was then extracted from a tumor sample using Qiagen DNA/RNA All Prep Kit and used to prepare genomic sequences with Illumina's mRNA Stranded Library Preparation kit. Libraries were quantified by Qubit and sequenced on the Illumina NextSeq500. Following sequencing, the FASTQ files were uploaded to Partek Flow for QC and analysis, using Bowtie 2 v2.2.5 to remove contaminants and STAR v2.7.3a for alignment to mice genome mm10. Reads were quantified with RefSeq Transcripts 99 (released 2021-08-02). Non-normalized read counts were used to generate a differential gene expression analysis using DESeq2 in R with filtering with an average of 10 reads per sample. The output was visualized in R and significantly differentially expressed genes were entered into gene ontology to identify any potential differentially expressed pathway.

Of the 26,202 genes analyzed in the alignment to mm10, 13992 genes reported an average of 10 counts. From the differential gene expression analysis using DESeq2, 7 genes were identified as statistically significant differential expression (padj<0.05). The genes *Hspa1b* and *Hspa1a* were down-regulated and the genes *Gm7030*, *Slc2a4*, *Shisa4*, *Slc38a3*, and *Vsig8* were up-regulated in the obese mice. Gene ontology did not identify any differentially expressed pathways from either the up-regulated or down-regulated genes respectively.

This experiment identified some gene candidates that may be playing a role in pathway dysfunction allowing for a more favorable environment for tumor growth. However, this would need to be further investigated. Another finding was that the tumor inside of the lean mice had a very high variation in gene expression to all other mice in this study based on a PCA plot. This may be a result of heterogeneity that may have occurred at random or may indicate differences in tumor and host interactions. Overall, this experiment has identified next directions in investigating TNBC in patients with higher BMI based on differential gene expression of the tumor.