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Severe Hyperglycemia and Hyperlipidemia Alters Tumor Growth and Immune Profiles in Syngeneic Tumor Models

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Abstract/Introduction

Background and Objective: The global prevalence of obesity is increasing rapidly, causing the rise of obesity-associated diseases, such as diabetes, cardiovascular diseases, and cancers. It has been established that obesity increases the risks for various types of cancers. Over the past decades, studies have proposed that obesity promotes cancer progression through mechanisms like chronic low-grade inflammation, which alters immune responses and the tumor microenvironment, ultimately affecting tumor response to therapies. Previous studies in diet induced obese models showed T cells in the colorectal cancer are reduced in obesity. However, it is not clear how the tumor microenvironment is changed under both severe hyperglycemia and hyperlipidemia in different types of cancers.

This poster will highlight the changes of immune cell population in syngeneic tumor bearing mice with MC38 colorectal cancer in genetic obese models characterized by severe hyperglycemia and hyperlipidemia. Our study provides a detailed comparisons of how severe hyperglycemia and hyperlipidemia change the immune cells populations and tumor microenvironment in cancer. Notably, these changes observed in mice provide insights into why the risk of various cancer types increases differently under conditions of severe obesity. In addition, we also provide a platform for studies on cancer therapeutics in hyperglycemia and hyperlipidemia mouse models.

Method/Experimental design

db/db mice and C57BL/6 mice were fed with normal chow diet were used to examine syngeneic tumor growth kinetics. Gene expression changes in the tumors were evaluated by RNA profiling. Changes of immune cells populations in tumors were evaluated by FACS analysis.

Results

A. Body weight and blood glucose of db/db and C57BL6 mice

B. MC38 tumor growth curve

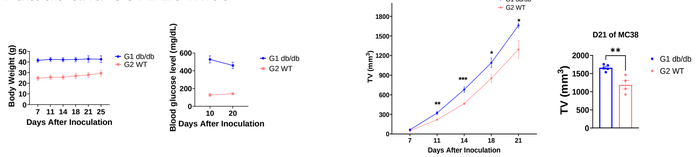
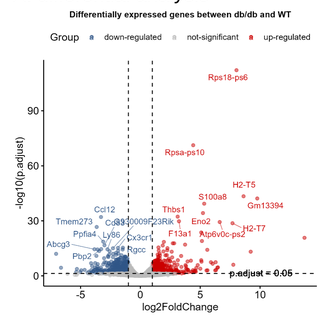


Figure 1. MC38 colorectal cancer grows faster in severe hyperglycemia and hyperlipidemia mice

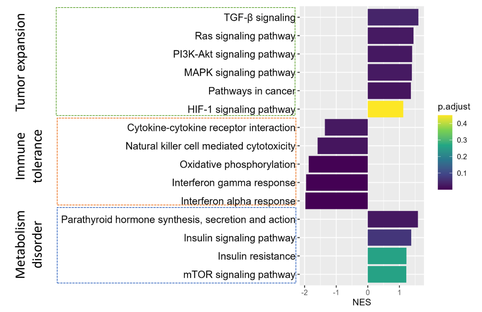
(A) body weight and blood glucose levels of db/db and WT C57BL6 mice. (B) MC38 tumor growth curve and the tumor volume on day 21 (D21) in db/db and C57BL6 mice.

Results

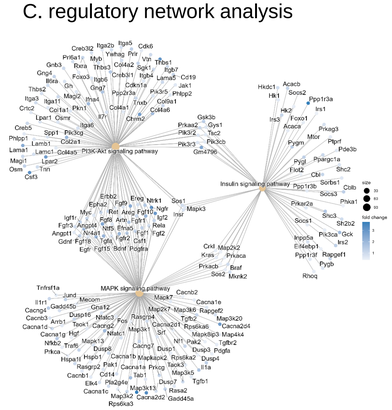
A. differential analysis



B. functional enrichment analysis



C. regulatory network analysis



D. tumor purity estimation

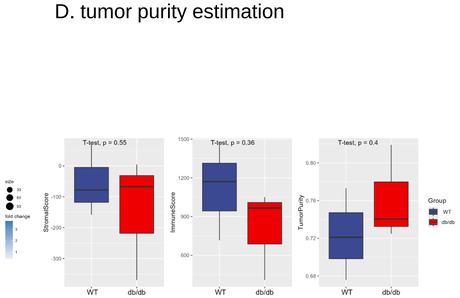
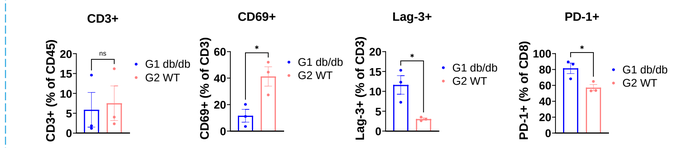


Figure 2. MC38 tumors in db/db have differentiated gene expression profiles, signal pathways and tumor purity, promoting tumor progression, comparing to the C57BL6 mice.

MC38 tumors were collected on D21 from db/db and C57BL6 mice, (A) differential analysis, (B) functional enrichment analysis, (C) regulatory network analysis, and (D) tumor purity estimation analysis of the RNA profiling results of the MC38 tumors. A significantly differentiated gene expression profile was detected in tumor from db/db mice(A). Pathways promoting tumor expansion were elevated while the pathways promoting immune response were reduced (B). One example of how differentiated signal pathways were connected in db/db mice is presented (C). Tumor purities was significantly reduced in db/db mice (D). All these changes in the tumors from db/db mice is consistent with the observed increased tumor growth.

A. FACS on T cells



B. FACS on Myeloid cells

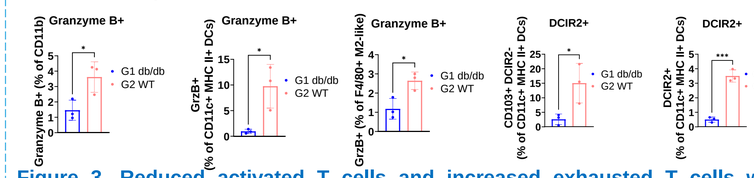


Figure 3. Reduced activated T cells and increased exhausted T cells were observed in the MC38 tumors from db/db mice. Reduced Granzym B expression and DCIR2 expression was observed in the myeloid cells.

FACS analysis on tumor infiltrated T cells (A) and Myeloid (B).

Conclusions/Summary

MC38 colorectal cancer grow faster in db/db mice with servere hyperglycemia and hyperlipidemia than the WT C57BL6 mice. RNA profiling revealed the gene expression profile in the tumor favors tumor expansion, and FACS analysis of the tumor infiltrated lymphocyte showed more exhausted T cells and less granzyme B expression in myeloid cells in db/db mice. All these changes in db/db mice are consistent with the observed increased tumor growth in the severe hyperglycemia and hyperlipidemia condition.

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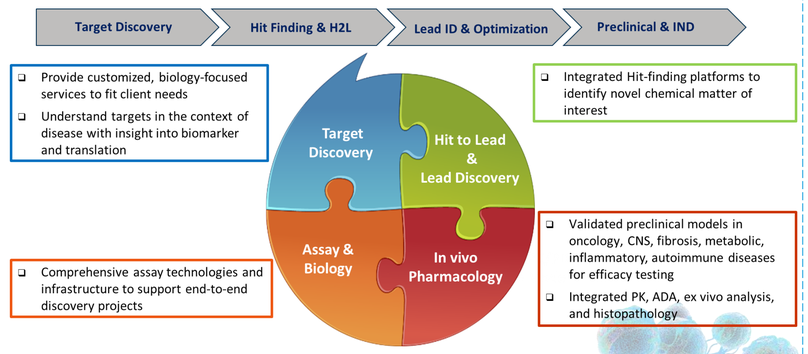

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