Tumor associated macrophage heterogeneity contributes to improved anti-PD1 efficacy in obese MC38 tumor bearing mice

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Introduction

- Obesity-induced chronic inflammation can result in T cell exhaustion characterized as increased immune checkpoint expression including PD1.
- Obesity driven T cell exhaustion has been suggested to contribute to improved efficacy found in obese cancer patients however a clear mechanism has yet to be established.
- Macrophages are also greatly affected by obesity and due to their prevalence in the tumor microenvironment may contribute to immune therapy response
- We sought to better understand how obesity alters tumor infiltrating immune cells to improve PD1 efficacy

Experimental Design

- Purified low fat diet or 45% high fat diet (research diets) administered at 6 weeks of age and continued for 25-28 weeks before initiation of MC38 tumor model
- Mice fasted for 5 hours prior to blood glucose measurement via tail sampling using a glucometer
- Fast ing blood glucose measured using calipers following 3P MC38 cell injection on Day 0
- Tumor diameter measured using calipers following 10^5 MC38 cell injection on Day 0
- Tumor mass on day 19 post MC38 injection
- Infiltration of TAMs within tumors assessed via flow cytometry, displayed as percent of CD45+/CD11b+/Ly6G-/Ly6C-

Figure 1. High fat diet feeding results in an obese phenotype

Figure 2. Obesity accelerates tumor growth and aPD1 treatment attenuates obesity-enhance growth

Figure 3. T cell exhaustion does not contribute to obesity-enhanced tumor growth

Figure 4. Tumor Associated Macrophage and CD206 expression consistent with tumor mass

Figure 5: Obesity and aPD1 treatment result in heterogeneity within macrophage assigned clusters

Conclusions and Future Directions

- Obesity accelerated MC38 tumor growth and anti-PD1 treatment was effective at attenuating growth only within obese mice
- TAM presence and CD206 expression contributes to improved aPD1 efficacy rather than T cell exhaustion
- Macrophage heterogeneity within diet and aPD1 treatment suggests that TAM subsets may improve immune checkpoint efficacy
- Further analysis of scRNAseq data to identify specific genes or metabolic pathways that drive this obesity enhanced tumor growth or improved aPD1 efficacy

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