IL-6 Stimulation of the JAK2-STAT3 Signaling Pathway on Colon Cancer Growth

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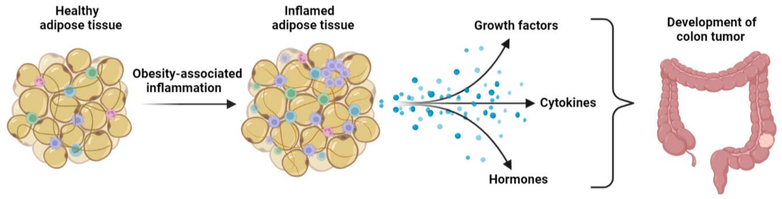
Rationale and Significance

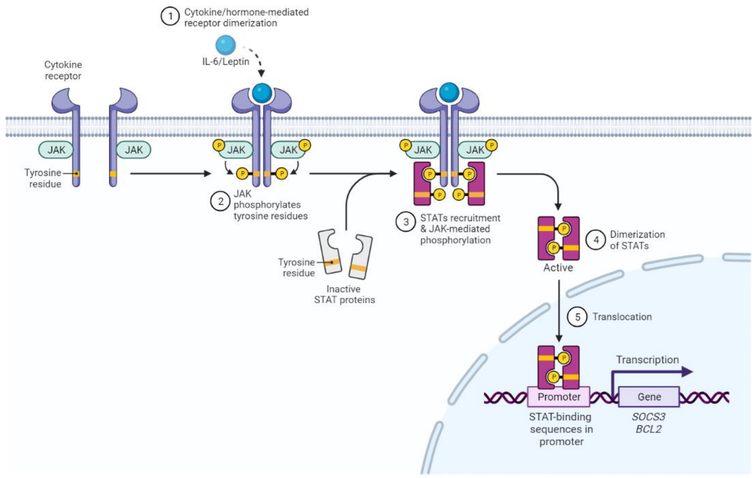
- Obesity-associated inflammation and the altered secretome of obesity-associated adipose tissue correlate with colorectal tumorigenesis and tumor proliferation.
- Understanding pro-inflammatory pathways involved in colon cancer could open future clinical avenues to mitigate cancer progression through pharmaceutically targeting genes or proteins in these pathways.

Introduction

- Obesity promotes colorectal cancer incidence and progression.



- The JAK-STAT pathway is involved in a variety of critical cell processes such as adipogenesis, apoptosis, hematopoiesis, inflammation, and cancer.



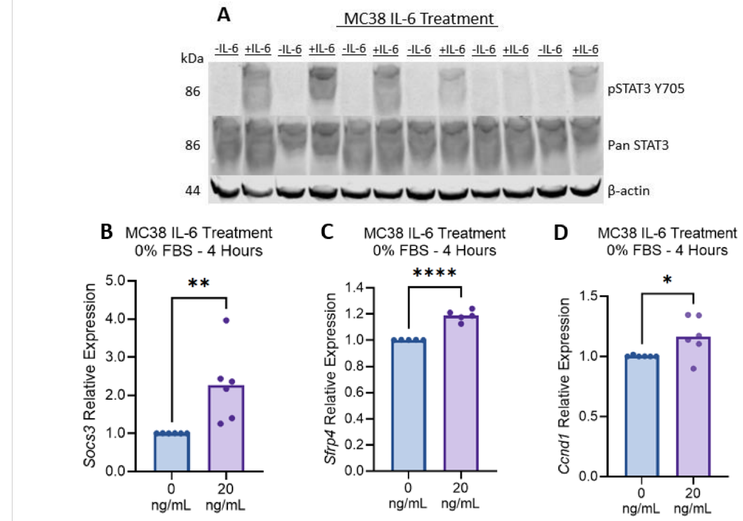
Study Aim

- To determine whether *in vitro* activation of the JAK-STAT pathway by recombinant IL-6 influences the pro-cancer Wnt/β-catenin pathway and/or EMT process.
- Evaluate whether the effects of IL-6 can be mitigated through the JAK-STAT inhibitor Stattic.

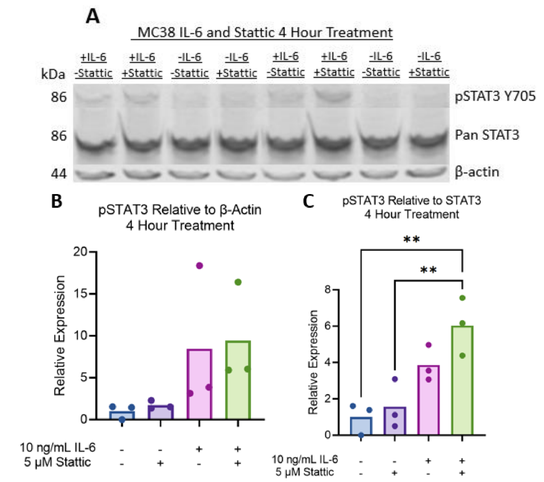
Methods

- Cell Culture: Murine MC38 colon cancer cells were treated with IL-6 or IL-6 + Stattic for 4 hours in 0% FBS media or 24 hours in 2% FBS media.
- Gene and protein expression: Gene and protein expression were assessed via qPCR and western blotting, respectively.

Results

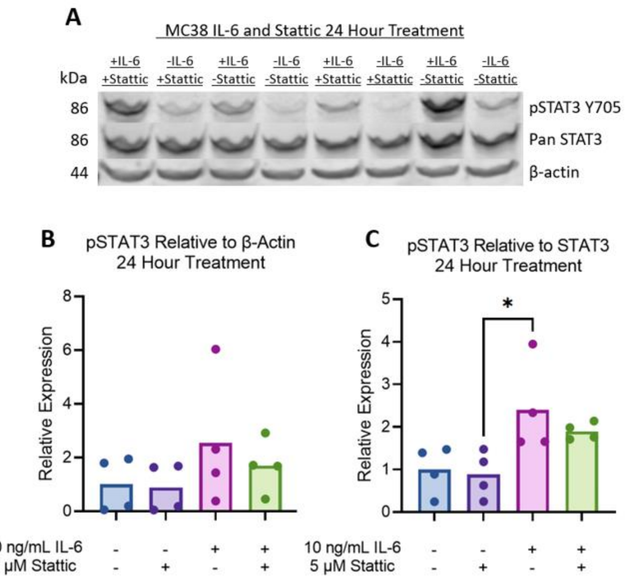


Protein and gene expression analysis of IL-6 stimulation for 4 hours in MC38 cells. (A) Western blot of pSTAT3 for MC38 cells with or without 20 ng/mL recombinant IL-6 treatment. mRNA expression of **(B)** Socs3, **(C)** Sfrp4, and **(D)** Ccnd1 in MC38 cells treated with IL-6 in 0% FBS media for four hours (n=6). Mean; unpaired t-tests with Welch's correction **(B-D)**; *p<0.05, **p<0.01, ****p<0.0001.



Protein analysis of MC38 cells treated with IL-6 and Stattic for 4 hours (A) Western blot of MC38 cells cultured in DMEM 0% FBS media with or without 10 ng/mL IL-6 and 5 μM Stattic (n=4). Quantification of **(B)** pSTAT3 relative to β-actin (n=4) and **(C)** pSTAT3 relative to STAT3 (n=3). Mean; one-way ANOVA with Tukey post-hoc test; **p<0.01.

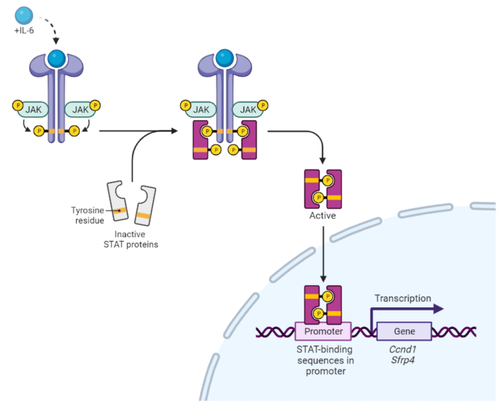
Results



Protein analysis of MC38 cells treated with IL-6 and Stattic for 24 hours (A) Western blot of MC38 cells cultured in DMEM 2% FBS media with or without 10 ng/mL IL-6 and 5 μM Stattic (n=4). Quantification of **(B)** pSTAT3 relative to β-actin (n=4) and **(C)** pSTAT3 relative to STAT3 (n=4). Mean; one-way ANOVA with Tukey post-hoc test; *p<0.05.

Conclusion

- IL-6 production from obesity-associated adipocytes activates the JAK-STAT signaling pathway to increase *Sfrp4* and *Ccnd1* expression, which are modulators/targets of the Wnt/β-catenin pathway and EMT process.



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