Adiponectin Induces Carcinogenic Macrophage Cytokine Expression – A Link to Early-Onset Colon Cancer

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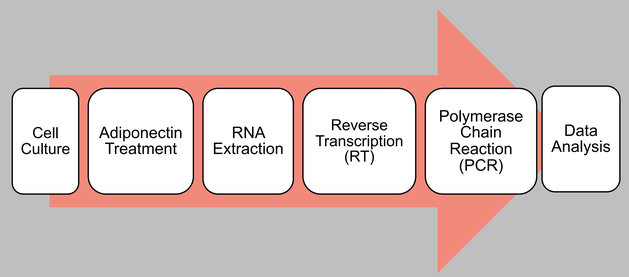
Introduction

- Early-onset colorectal cancer (EOCRC) is one of the three most common causes of cancer-related death among individuals <50 in the U.S.
- While the rate of CRC is dropping among individuals 65 and older, the incidence of EOCRC is increasing.
- Similarly, obesity rates continue to trend up in the U.S.
- EOCRC progression may be affected by inflammatory signals in the tumor microenvironment that are mediated through tumor-associated macrophages (TAMs).
- TAMs are polarized into either pro-inflammatory (M1) or anti-inflammatory (M2) subtypes with a higher M2/M1 ratio indicating worse prognosis in CRC.
- The adipose-derived hormone adiponectin protects against metabolic diseases through its anti-inflammatory influences, its effects on anti-inflammatory M2-like macrophages and their mediation of disease progression in CRC is poorly understood.

Hypothesis

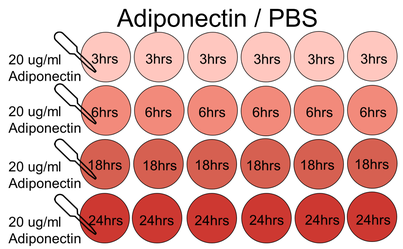
Adiponectin induces carcinogenic marker expression in M2-like TAMs, causing tumor promoting effects associated with worse clinical outcome in EOCRC.

Methods



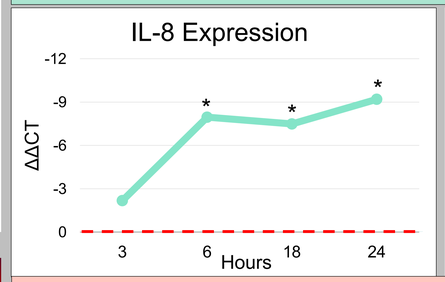
Methods

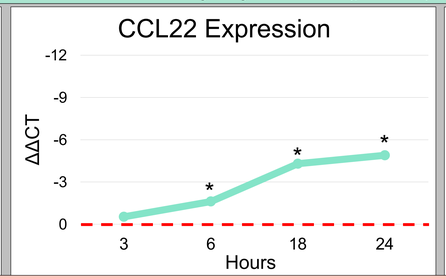
- Monocytes from the THP-1 cell line were seeded into 24-well cell culture plates and polarized into an M2-like macrophage phenotype within 14 days.
- M2 macrophages were treated with 20 ug/ml adiponectin and incubated for either 3, 6, 18, and 24 hours.
- RNA was extracted and converted to cDNA to perform qRT-PCR.
- Expression of pro- and anti-inflammatory cytokines, transcription factors NF-kB and PPARγ, and macrophage markers CD80 and CD206 were measured relative to the negative control.

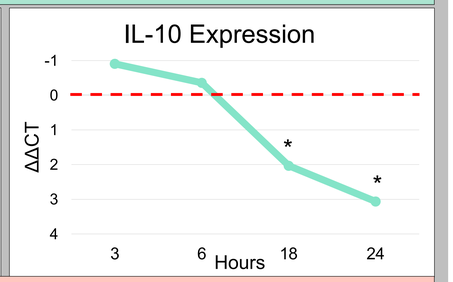


Results

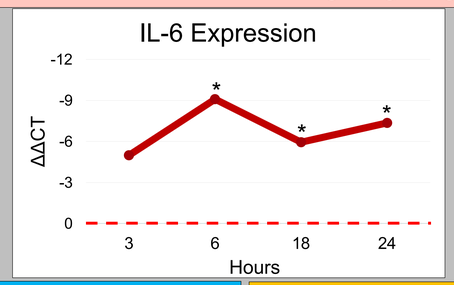
Anti-Inflammatory Cytokines ($p<0.05$)*

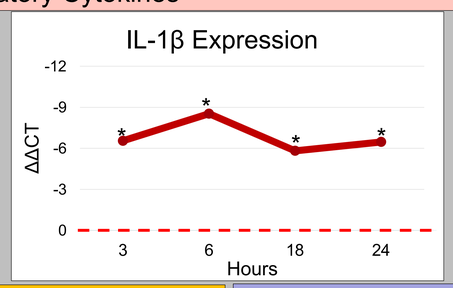




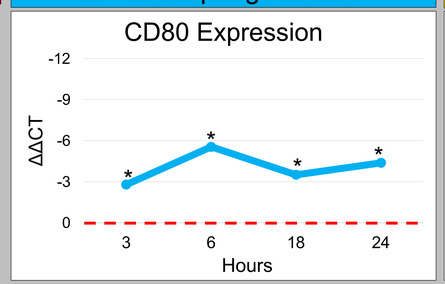


Pro-Inflammatory Cytokines

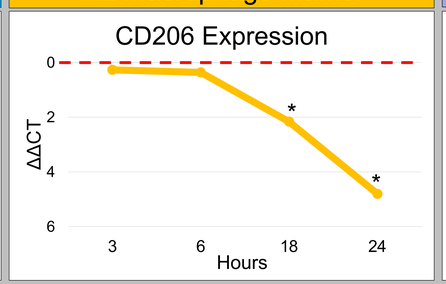




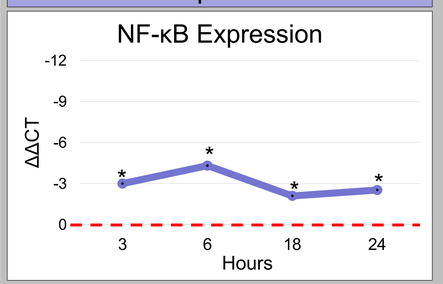
M1 Macrophage Marker



M2 Macrophage Marker



Transcription Factor



Results

- Following adiponectin treatment, M2-like macrophages showed an increase of the anti-inflammatory tumor-promoting cytokines C-C motif chemokine 22 and Interleukin (IL) 8 and a decrease of IL-10.
- Pro-inflammatory cytokines IL-6 and IL- 1β were increased in M2 macrophages
- Transcription factor Nuclear Factor-kB was upregulated at all time points.

Conclusions

- **Upregulation of the M1-like macrophage marker CD80 with simultaneous downregulation of the M2-like macrophage marker CD206 indicates a shift towards a pro-inflammatory phenotype in M2-like macrophages due to adiponectin treatment.**
- **Adiponectin induces carcinogenic pro- and anti-inflammatory cytokines in M2-like macrophages.**
- **The obesity-related hormone adiponectin has the potential to induce tumor-promoting effects through TAMs in patients with EOCRC.**

Future Endeavors

- Additional research is warranted to assess the effect of adiponectin on M0 macrophages or those which have not yet been differentiated into M1 or M2 macrophages.
- Next steps involve treating a colon cancer cell line with adiponectin to assess growth and proliferation.

Acknowledgements

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