

Paracrine adipocyte signaling promotes colorectal cancer growth in vitro



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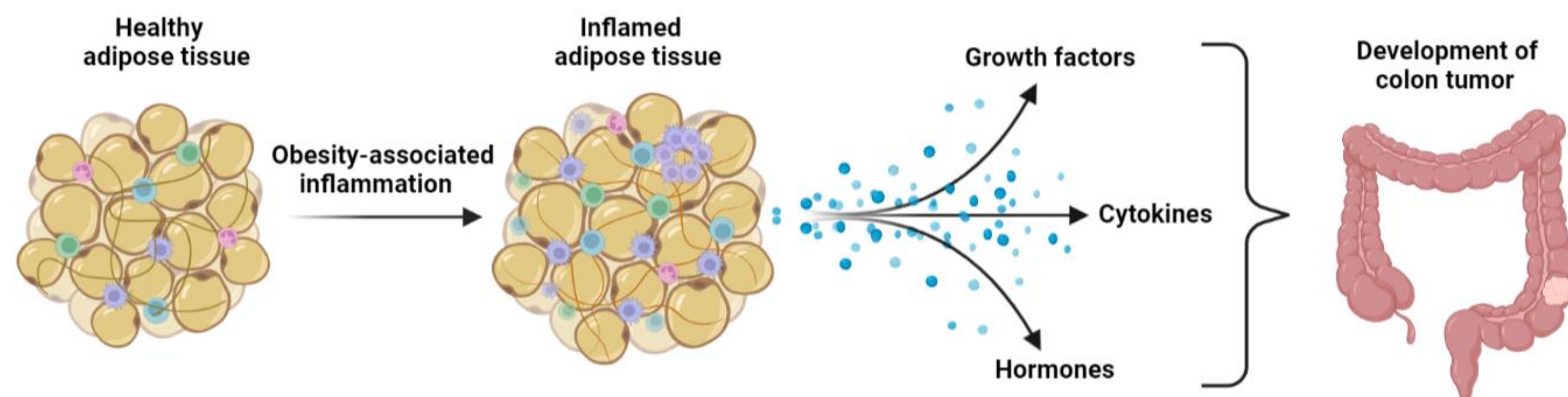
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Significance and Rationale

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

Introduction

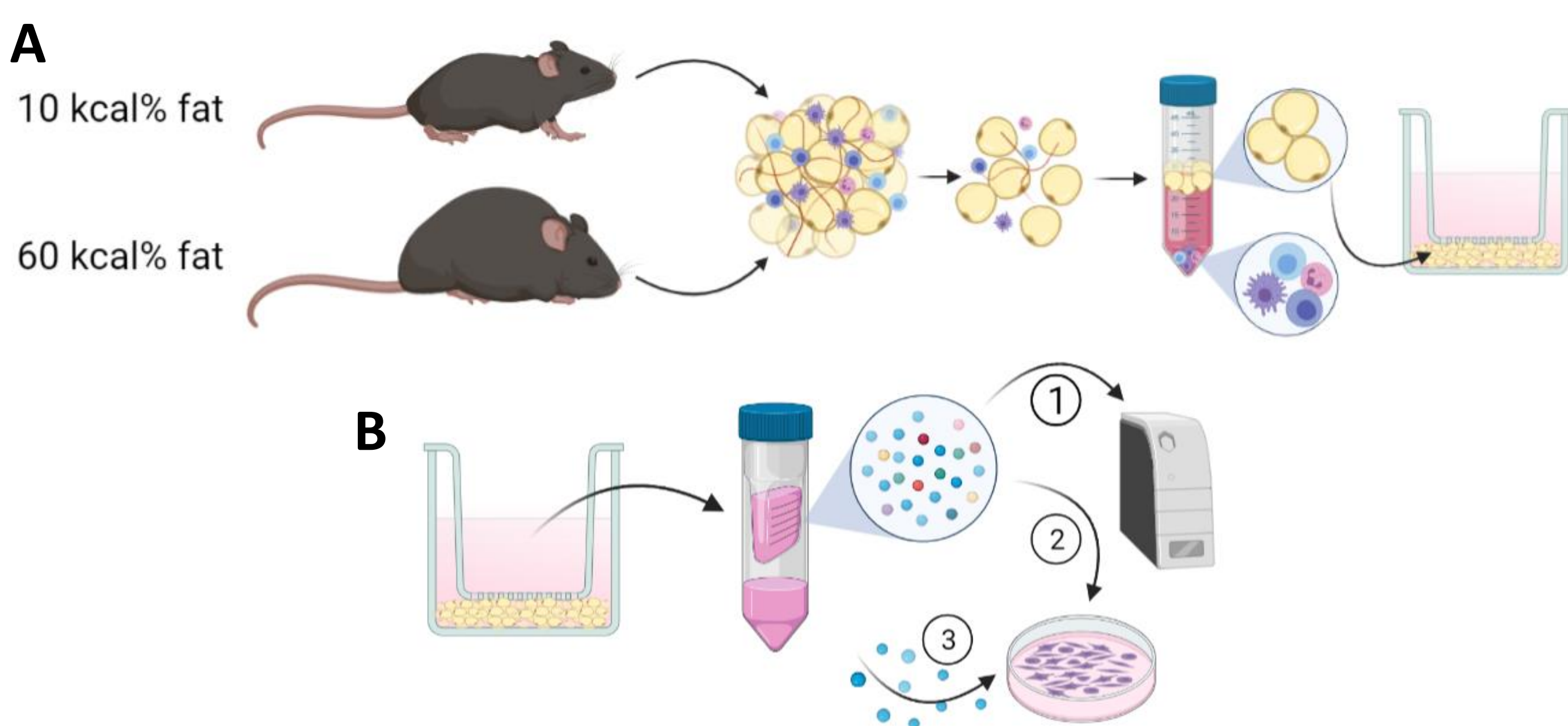
- The worldwide prevalence of obesity has nearly tripled over the last few decades and is characterized by the accumulation of excess white adipose tissue.
- Obesity promotes colorectal cancer incidence and progression.



Study Aim

To identify candidate mediators of paracrine signaling between adipocytes and colorectal cancer cells contributing to the obesity-cancer link.

Study Design

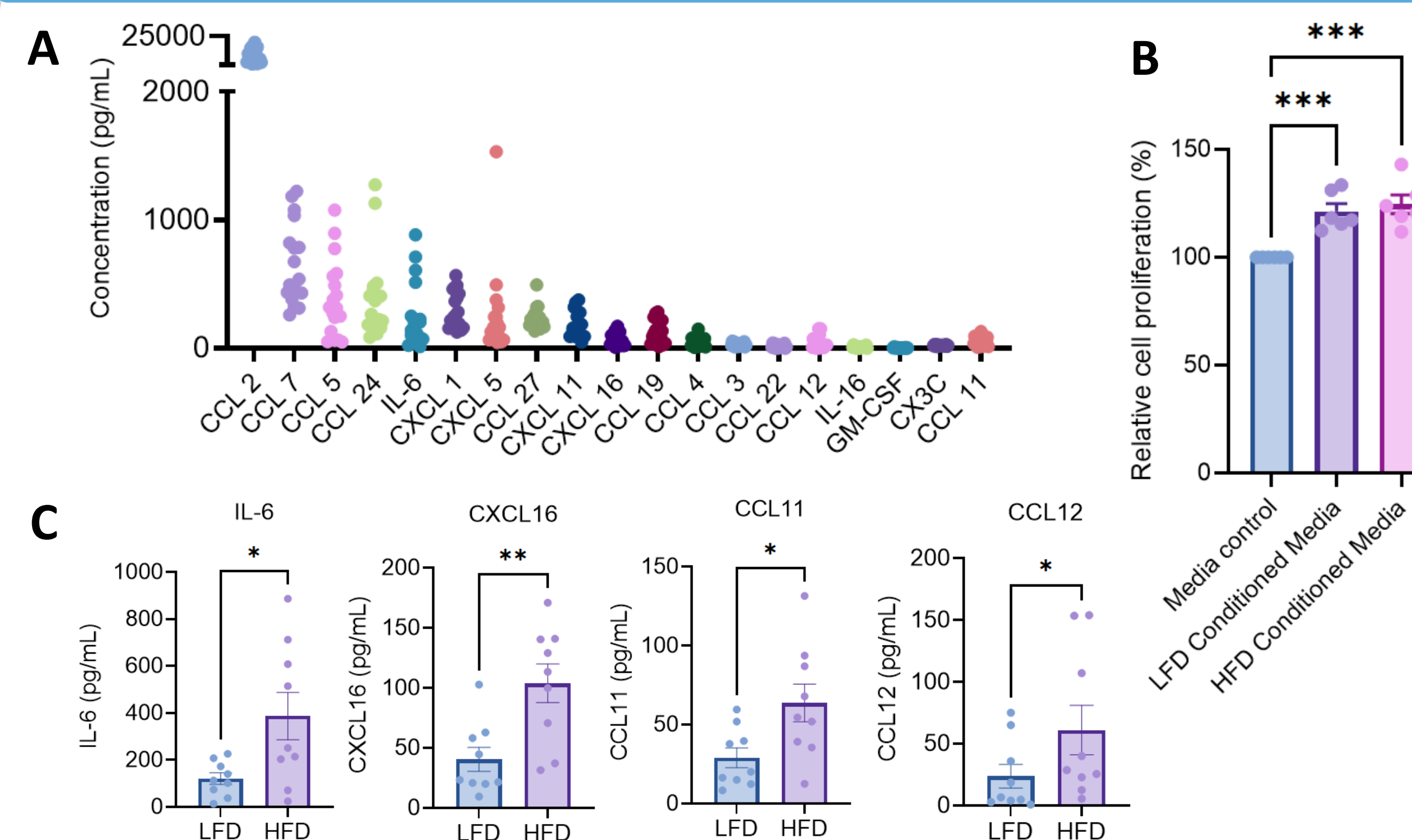


(A) Adipocytes were isolated from the adipose tissue of control (10 kcal% fat diet) and diet-induced obese (60 kcal% fat diet) mice. (B) Cytokines were quantified via Luminex (1), SW620 cells were cultured in adipocyte conditioned media (2) and then SW620 and MC38 cells were treated with recombinant cytokines of interest (3).

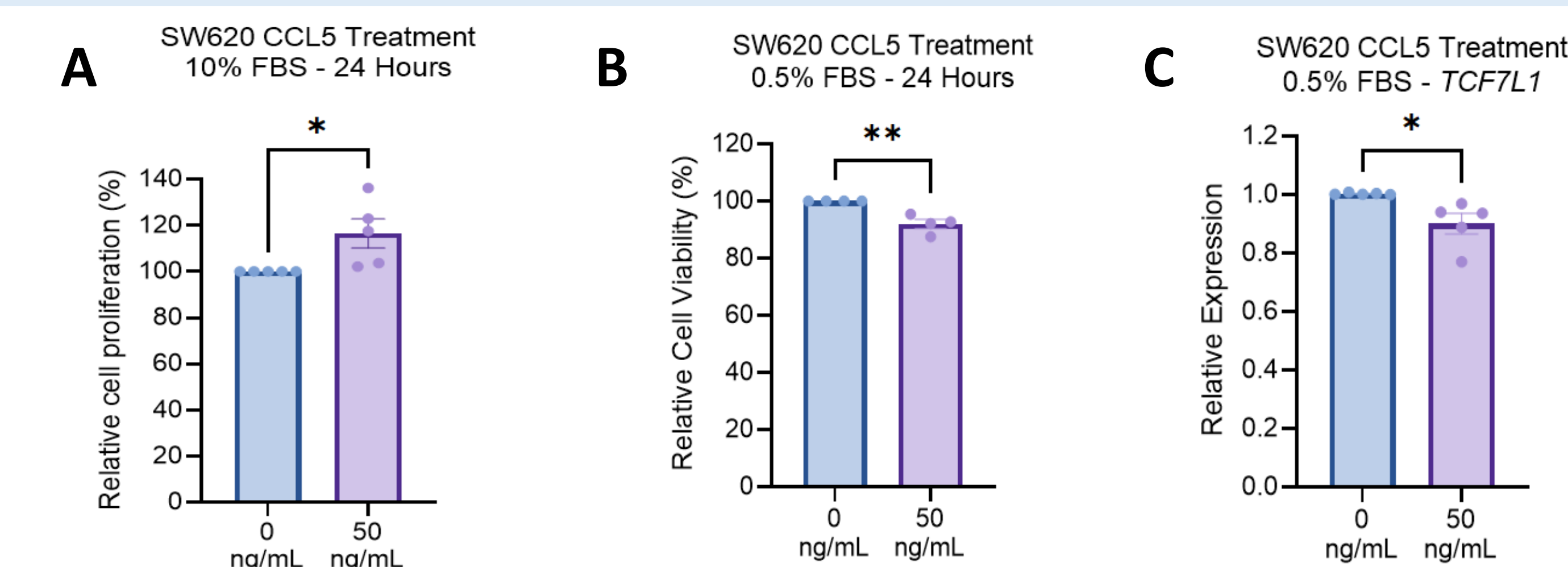
Methods

- Adipocyte Isolation:** Adipocytes were isolated from the gonadal fat pad of C57BL/6J male mice fed either a low-fat (10 kcal% fat; LFD) or high-fat (60 kcal% fat; HFD) diet and cultured for 24 hours.
- Cytokine Measurements:** Cytokine secretion was quantified using the Bio-Plex Pro mouse chemokine 33-plex panel.
- Cell Culture:** Human SW620 or murine MC38 colon cancer cells were grown for 24 hours in adipocyte conditioned media or without the addition of 20 ng/mL recombinant IL-6 or 50 ng/mL recombinant CCL5.
- Proliferation:** Proliferation was assessed using the MTT assay.
- Gene and protein expression:** Gene and protein expression were assessed via qPCR and western blotting, respectively.

Results

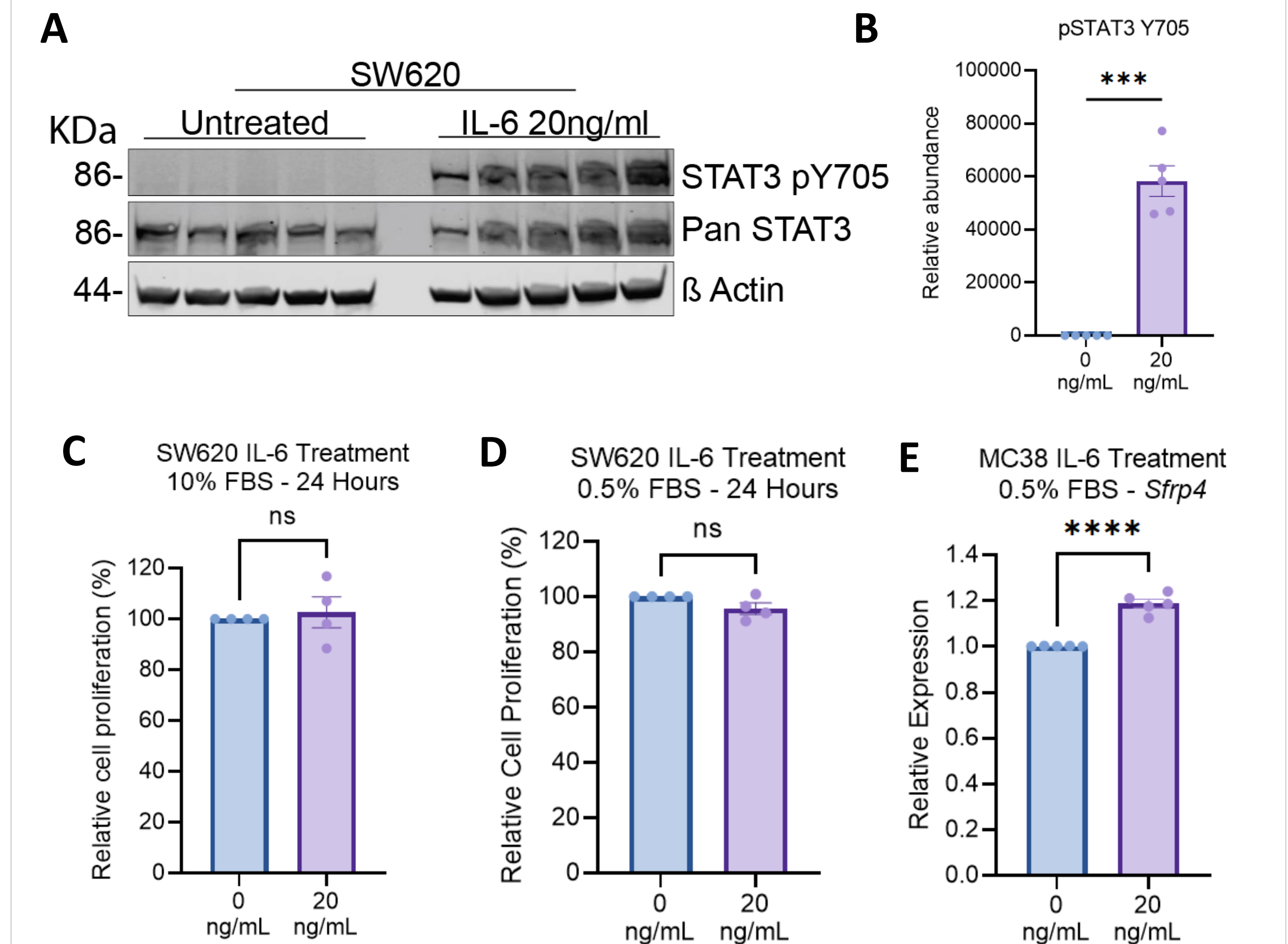


Adipocytes secrete cytokines and they secrete more cytokines in an obese environment. (A) Detected cytokines (of 33 assayed) in adipocyte conditioned media. (B) Relative proliferation of SW620 cells cultured in either media or conditioned media of adipocytes isolated from either control (low-fat diet; LFD) or obese (high-fat diet; HFD) mice. (C) Cytokines secreted at significantly elevated levels in conditioned media of adipocytes isolated from HFD relative to LFD mice. One-way ANOVA panel B, paired t-tests panel C; * $p < 0.05$, *** $p < 0.001$.



CCL5 suppresses proliferation and a transcription factor in the Wnt signaling pathway when growth factors are limited. Relative proliferation of SW620 cells when treated with recombinant CCL5 and cultured with (A) 10% FBS and (B) 0.5% FBS. (C) mRNA expression of *TCF7L1*. Unpaired t-tests; * $p < 0.05$, ** $p < 0.01$.

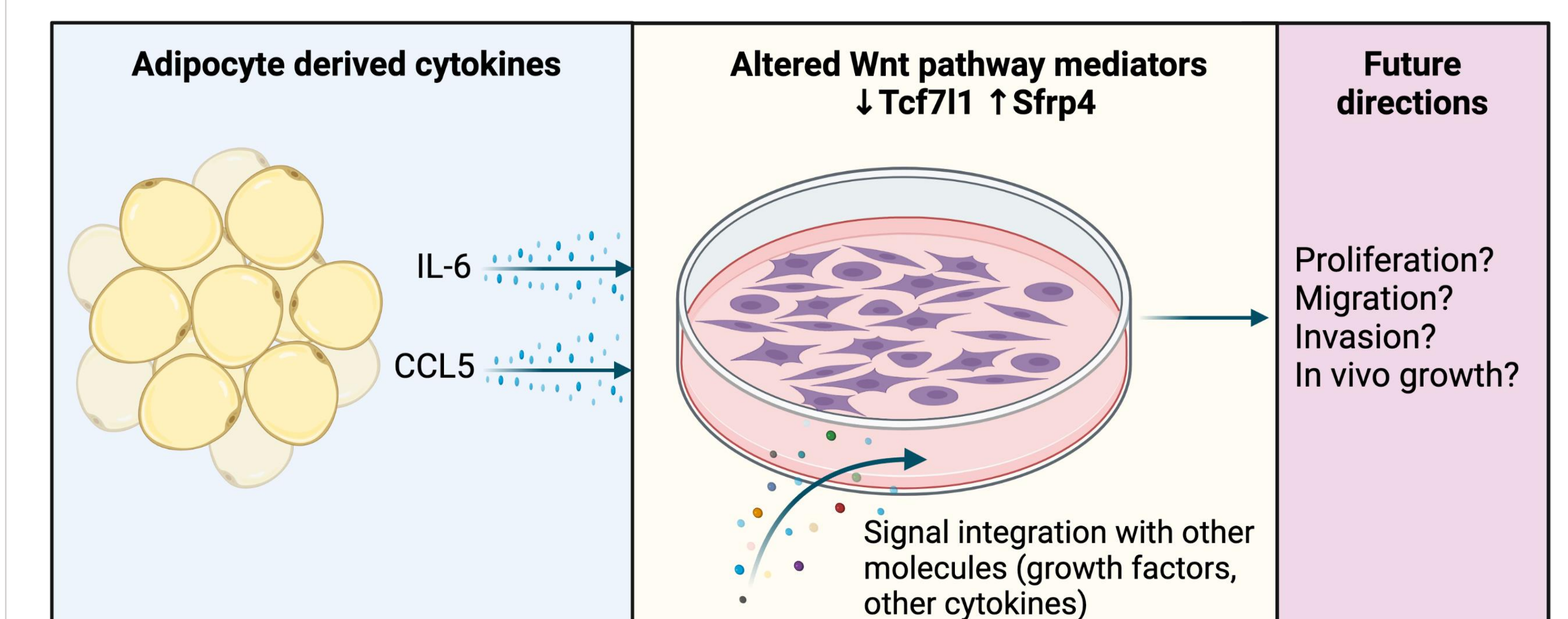
Results



IL-6 does not alter proliferation but does increase *Sfrp4* expression, a known mediator of Wnt signaling, when growth factors are limiting. (A) Western blot and (B) corresponding quantification of pSTAT3 for SW620 cells with or without IL-6 treatment. Relative proliferation of IL-6 untreated or treated SW620 cells cultured with (C) 10% FBS or (D) 0.5% FBS. (E) mRNA expression of *Sfrp4*. Unpaired t-tests; *** $p < 0.001$, **** $p < 0.0001$.

Conclusion

- Tumor-promoting paracrine signaling from adipose tissue may potentiate colon cancer growth in part via adipocyte-derived cytokine production.



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