# Review of: "Adipose stem cell niche reprograms the colorectal cancer stem cell metastatic machinery"

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The contribution of local adipose tissue stem cells towards obesity related comorbidities has expanded again. Recent findings demonstrate adipose derived cytokines provide critical paracrine signals on other tissue microenvironments, including cascades that impact the programming and progression colorectal cancer (CRC). In the current results published in Nature Communications, *Franco et al.*[1], used adipose stromal cells (ASCs) and CRC sphere cells (CR-CSphCs) from human patients to examine this previously unknown mechanism. Specifically, the investigators were focused on the interplay between adipose precursor cells and CRC tumor cells in patients, hence highlighting a possible opportunity for pharmacotherapies that block STAT3 and impair metastasis in CRC patients.

CRC is the third most common cancer and appears to be influenced by obesity, along with several other cancer types. Over the last several decades, researchers and clinicians have been focused on understanding CRC related metastasis and the role of tumor microenvironment (TME) in CRC metastasis and associated molecular mechanism by which the TME regulates metastasis. However, mechanistic links between obesity and the programming and progression of CRC risk remained undetermined.

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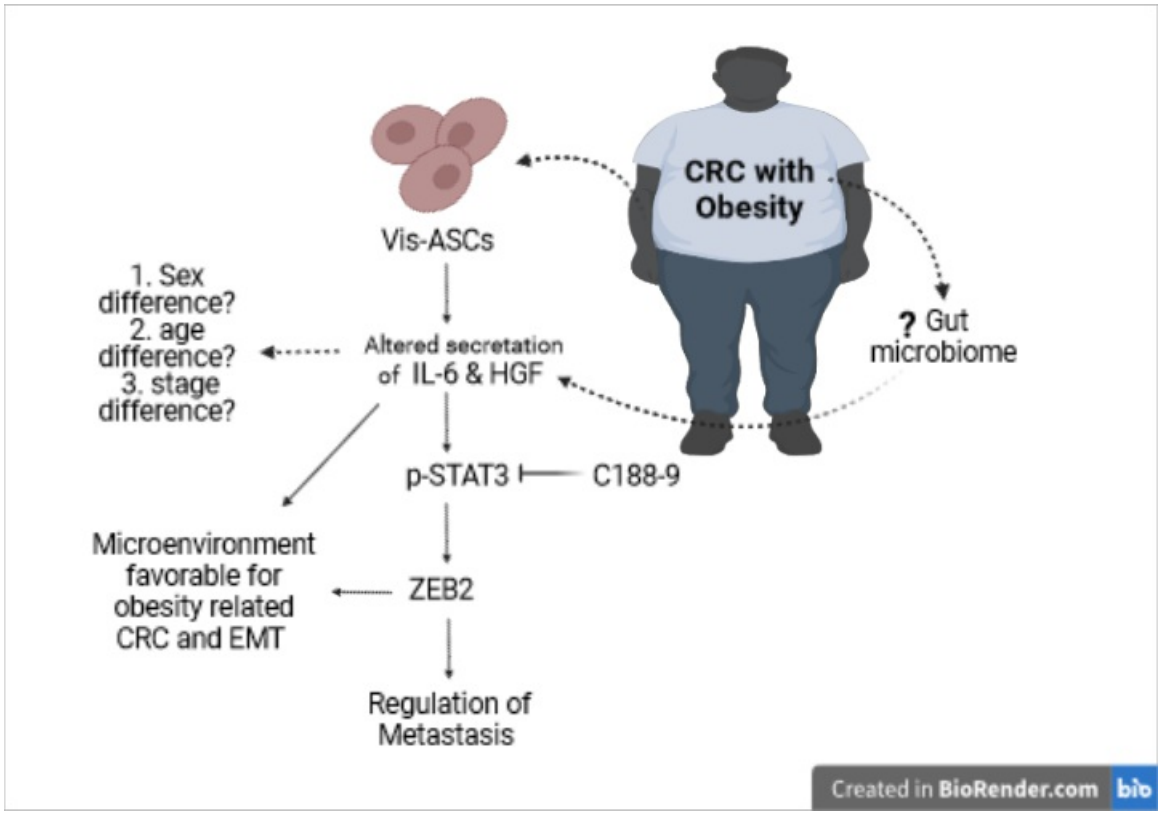


Figure 1: **Visceral adipose stromal cells (vASCs) secreted factors regulate tumor microenvironment stimulating EMT, and metastasis in obesity associated CRC**. Secretion of IL-6 and HGF by vASCs and activation of STAT3 (which can be blocked by inhibitor C188-9) and ZEB2 to regulate metastasis in CRC. Involvement of vASCs in different age groups, sex, stages of CRC and the role of gut microbiome in the regulation of cytokines may be critical during CRC metastasis.

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Adipose tissue derived precursor cells self-renew and differentiate into many mesenchymal stem cell lineages including adipocytes, chondrocytes, myocytes, and osteoblasts. These cells function locally in addition to providing endocrine and immune signals, through the secretion of hormones, cytokines, and chemokines that modulates cellular behavior and growth in tumor microenvironments (TMEs) of surrounding tissues. In other research performed in mice, *Liu et al.* suggest that obesity induced inflammatory cytokines, including TNF-α, which induced the phosphorylation of GSK3β and activates WNT signaling pathways key in elevating colorectal cancer risk. However, the role of cytokines in specifically driving mesenchymal characteristics and metastasis remained unknown.[2]

In the current Nature Communications article, *Franco et al.*[1], show that ASCs, and visceral ASCs (vASCs) from CRC obese patients to a greater degree, secrete inflammatory cytokine IL-6 and hepatocyte growth factor (HGF), which likely regulate cancer cell clonogenicity and enhanced cell invasion in CRC metastasis. These signals drove cell behavior through STAT3 and upregulating *CXCR4, SLUG, TWIST*, and *ZEB1/2*, stimulating epithelial to mesenchymal transition in human CRC sphere cells. Hence IL-6 and HGF secreted by ASCs appear to be key components for tumor progression in CRC patients and provide a cogent explanation for the link between obesity and CRC metastasis. Their study also highlighted that *ZEB2*

expression increased CD44 cells containing variant exon v6 (CD44v6), which are specifically linked to CRC progression and metastasis.[3] IL-6 and HGF promote proliferative capacity and influences CD44v6- progenitors into CD44v6+ cells. CD44v6 + CRC progenitor cells increase their metastatic potential by secreting nerve growth factor (NGF) and recruiting ASCs. In the TME, CD44v6+ cells secrete elevated level sof VEGF, which in turn bind VEGFR on ASCs enhancing proliferation and angiogenesis. Cytokines in ASC conditioned media are sufficient to drive CRC ZEB1/2 expression at both at mRNA and protein levels, as well as miR-200 which influence extracellular matrix interactions. Importantly, experimental blockade of IL6/HGF in vASCs conditioned media inhibited the progression of metastatic behavior of CRC, the key finding of the work.

Despite challenges in the field, the work of *Franco et al*[1]*.* has addressed a critical gap in understanding obesity linked CRC progression through their use of human ASC and CRC sphere cells. Although this study was performed with human tissues, it remains unclear whether sex related differences can also be determined through similar studies. Sex related differences in CRC patients may drive disproportionate affect the risk of onset, progression, and mortality in males.[4] Other opportunities include deeper understanding for these novel mechanisms based on patient age and stage of disease.

In addition to the current signaling mechanisms studied, other work suggests the gut microbiome of obese subjects is linked to CRC.[5,6] Patients with obesity and other metabolic disease display an altered gut microbiota community that associated with inflammatory cytokines linked to CRC progression.[7] As we proceed in the era of personalized medicine, further insights are needed to hone in on the inflammatory and signaling interactions between host stem cell precursors, immune cell populations and the microbiome in shaping TME cell behavior and cancer risks. Along these lines, investigating the dependencies of CRC-ASCs-Gut microbiome axis in future humans and animal studies may provide additional personalized risk assessment, improve treatment approaches, and reveal new therapeutic options in the setting of CRC.

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