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COMMENTARY

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Adipose stromal cells promote the transition of colorectal cancer cells toward a mesenchymal-like phenotype

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ABSTRACT

Colon cancer progression is among the risks that increase with obesity. We have recently unveiled the molecular mechanism by which adipose tissue-released molecules, HGF and IL-6, make colorectal cancer (CRC) cells acquiring mesenchymal traits. Targeting of adipose-derived factors abrogate the metastatic potential of CRC stem cells (CR-CSCs) in obese patients.

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Author's comment

Although showing a slow decline in incidence, colorectal cancer (CRC) still represents the third most common cause of cancer-related death.[1] Despite the great effort dedicated to CRC research, which led to an improved survival rate in the last decades, the complex molecular machinery involved in the promotion of tumorigenesis and metastatic process is still not fully defined. In the last years, the role of tumor microenvironment (TME), including adipose tissue, the biggest endocrine organ, emerged as key player favoring the initiation and progression of tumor disease, due to the released factors that support a chronic inflammation. It has been demonstrated that obesity, whose prevalence is increasing worldwide, contributes to the increase of cancer incidence and to up to 20% of cancer-related deaths.[2] We have demonstrated that a small cell population, which share many biological features with normal stem cells, called cancer stem cells (CSCs), whose number and phenotype are finely regulated by the TME,[3–5] sustains the tumor growth. This cell subset has been found to be highly heterogeneous, whose heterogeneity influences the clinical outcome and response to chemo- and targeted-therapy. Guinney *et al*. have identified four transcriptional signatures that classify CRC into four consensus molecular subtypes (CMSs). Although each CMS has been associated with distinguishing features and clinical perspective, specifically CMS1, immune; CMS2, epithelial; CMS3, metabolic; CMS4, mesenchymal,[6] the effect of CRC TME on CMS plasticity is still unclear.

We demonstrated that HGF and IL-6 among the factors secreted by visceral adipose stromal cells (V-ASCs), expand the CRC stem cell (CR-CSC) compartment identified by the expression of CD44V6.[7] Interestingly, we noticed that $CD44V6^{+}$ cells release: *i)* some of the neurotrophins, as nerve growth factor (NGF) and Neurotrophin-3 (NT-3), favoring the recruitment and growth of neighboring V-ASCs, *ii)* and the Vascular-Endothelial Growth Factor (VEGF) that induces the endothelial transdifferentiation of V-ASCs, thus setting a favorable environment for cancer cell dissemination. Interestingly, the presence of V-ASCs, within the tumor, makes cancer cells acquire an invasive phenotype, in line with their reprogramming from CMS2 toward CMS4-like transcriptomic profile. V-ASCs microenvironmental factors foster the activation of Signal Transducer And Activator Of Transcription 3 (STAT3), which in turn downregulates miR-200a expression, thus leading to increased expression levels of Zinc finger E-box-binding homeobox 2 (ZEB2), a master epithelial–mesenchymal transition (EMT) regulator (Figure 1). Targeting STAT3 pathway abrogates the metastatic dissemination driven by V-ASCs.

Taken together, these findings reveal a new molecular mechanism by which visceral adipose tissue positively regulate the mesenchymal phenotype of CRC cells, by increasing their metastatic potential. In particular, adipose-derived factors, released in TME of obese patients, reprogram CMS2 CRC cells toward a hybrid epithelial/mesenchymal (CMS2/CMS4) cell phenotype, endowed with boosted tumorigenic and metastatic capacity. This observation is in line with the identification of CRC patients classified as mixed phenotype, which are characterized by a "hybrid" epithelial-mesenchymal (E/M) phenotype,[8,9] and an undefined clinical outcome. To note, the presence of a E/M state in cancer cells has been recently associated with the concomitant retainment of cancer stemness and tumor initiation abilities.[10]

If we will be able to define a specific molecular signature, aimed at the identification of obese CMS2 CRCs who might progress aggressively, we could identify eligible patients for an adjuvant therapy regimen.

Disclosure statement

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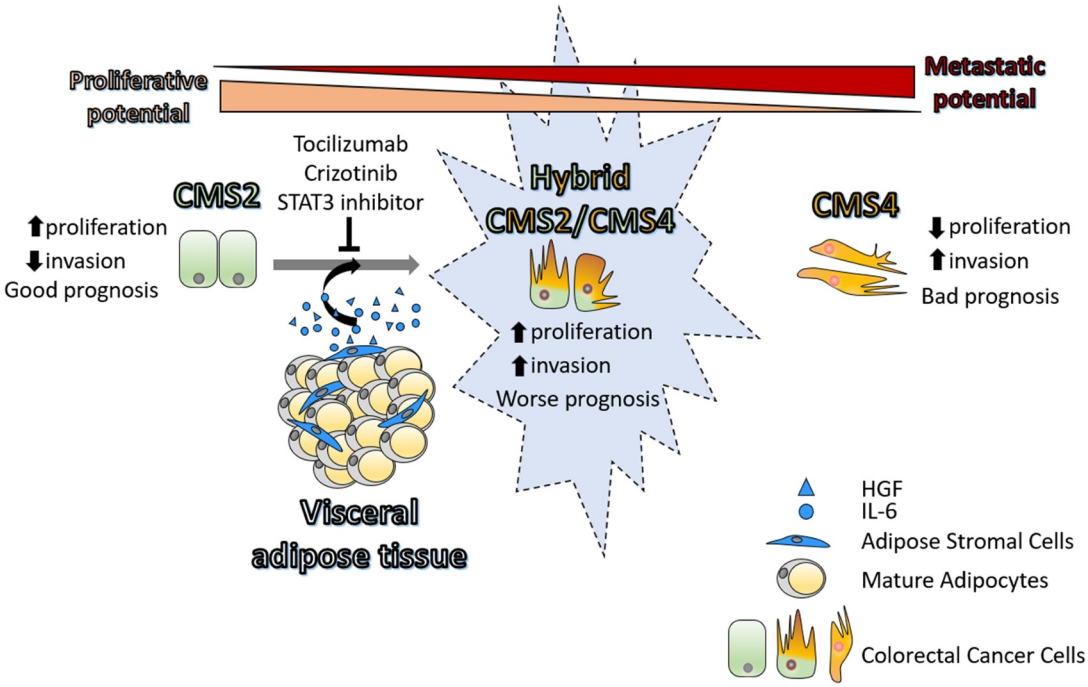

Figure 1. EMT-regulating crosstalk between adipose stromal cells and colorectal cancer cells in obese CRC patients. The paracrine activity of visceral adipose stromal cells (V-ASCs) boosts the proliferative and invasive capacity of nearby colorectal cancer (CRC) cells through the release of HGF and IL-6. These visceral adipokines drive the transition of epithelial (CMS2) CRC cells toward a highly aggressive hybrid epithelial/mesenchymal (CMS2/CMS4) subtype. Targeting of the pathways activated by microenvironmental adipokines restrain the metastatic potential of CRC cells.

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