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Stearoyl-CoA desaturase 1 and paracrine signal involvement in the promotion of breast cancer cell migration induced by cancer-associated fibroblasts

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Despite the acknowledged impact of the tumor stroma on breast cancer development and progression, the molecular basis of such effects remain partially unexplained. We previously reported that breast cancer-associated fibroblasts (CAFs) induced epithelial-mesenchymal transition and an increase in cell membrane fluidity and migration speed in poorly (MCF-7) and highly invasive (MDA-MB-231) breast cancer cells. More recently, in order to better define the mechanisms responsible for the CAF-promoted tumor cell migration, we investigated the role of Stearoyl-CoA desaturase 1 (SCD1), the main enzyme regulating membrane fluidity, and demonstrated its CAF-triggered up-regulation as well as its crucial role in the migratory ability of the above tumor cells. Besides SCD1 induction, a CAF-promoted enhancement in the protein level and/or activity of the SCD1 transcription factor, the sterol regulatory element-binding protein 1 (SREBP1), was observed. Moreover, the influence of stroma-derived signals in cancer cell migration speed was proved by cell tracking analysis in the presence of neutralizing antibodies to hepatocyte growth factor, transforming growth factor-β or basic fibroblast growth factor, where a marked reduction or abolishment of the fibroblast-triggered increase in cancer cell migration speed was observed.

In the last part of this study, in order to verify if soluble CAF-derived factors stimulate breast cancer cell migration in a SCD1-dependent manner, tumor cells were exposed to CAF-conditioned medium (CM) and their migration evaluated by *scratch* assay in the presence of a small molecule inhibitor of SCD1. Moreover, to assess if the induction of SCD1 expression by CAFs might occur *via* SREBP1, the desaturase levels were also determined in SREBP1-inhibited tumor cells.

These latest investigations indicate that SCD1 contributes to the promotion of breast cancer cell migration by CAF-derived soluble factors, since the desaturase inhibition completely suppressed the stimulatory effect of CAF-CM on tumor cell migration. SREBP1 inhibition impaired CAF-mediated up-regulation of SCD1 in poorly invasive but not in highly invasive tumor cells, in which SREBP1-independent mechanisms may account for the enhancement of SCD1 levels.

These results provide further insights in understanding the role of CAFs in promoting tumor cell migration, which may help to design new stroma-based therapeutic strategies.

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