



Figure 1. CTGF-mediated autophagy-senescence transition in tumor stroma promotes anabolic tumor growth and metastasis. Cancer cells secrete oxidative stress factors (H₂O₂) that induce autophagy in cancer-associated fibroblasts. Additionally, caveolin-1 (cav-1) loss leads to activation of connective tissue growth factor (CTGF) and HIF-1 α that mediate autophagy and senescence in these stromal cells. This is called the autophagy-senescence transition (AST). AST leads to mitophagy and elevated glycolysis in cancer-associated fibroblasts. Aerobic glycolysis results in the elevated production of several nutrients (pyruvate, ketone bodies and L-lactate), which can be utilized by cancer cells for tumor growth and metastasis.

stress. CTGF overexpression in fibroblasts also promoted tumor growth when co-injected with breast cancer cells in mice (Fig. 1), independent of angiogenesis. As expected, CTGF overexpression in breast cancer cells inhibited tumor growth. CTGF is known to be involved in extracellular matrix synthesis; however, the effects of CTGF overexpression in fibroblasts and tumor cells were found to be independent of this function.⁶

Overall, the authors have identified a novel mechanism by which CTGF promotes AST and aerobic glycolysis in cancer-associated fibroblasts. In turn, the stromal cells stimulate anabolic tumor growth and metastasis. The authors also genetically validate the two-compartment model of cancer metabolism, whereby autophagy genes and CTGF have differential effects in stromal cells and tumor cells. The current studies have several implications for cancer therapy. The finding that HIF-1

activation is necessary for the induction of autophagy and senescence downstream of caveolin-1 loss and CTGF activation in stromal fibroblasts is intriguing. Activation of HIF-1 in the hypoxic tumor microenvironment is known to promote tumor cell growth, survival and therapeutic resistance.⁸ Therefore, targeting HIF-1 has the potential to block tumor progression through dual inhibitory effects on hypoxic cancer cell growth and survival as well as the induction of autophagy in stromal fibroblasts. CTGF and AST in the tumor stroma could serve as biomarkers for predicting clinical outcome, therapy response and metastasis. The two-compartment model of tumor metabolism raises further questions regarding the use of antioxidants and autophagy inhibitors/inducers for cancer therapy. The use of these agents in the clinic should be carefully evaluated considering their differential effects on stromal cells and cancer cells.

References

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