Documents

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Acidosis-induced regulation of adipocyte G0S2 promotes crosstalk between adipocytes and breast cancer cells as well as tumor progression

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Abstract
Bidirectional interactions between cancer cells and their microenvironment govern tumor progression. Among the stromal cells in this microenvironment, adipocytes have been reported to upregulate cancer cell migration and invasion by producing fatty acids. Conversely, cancer cells alter adipocyte phenotype notably via increased lipolysis. We aimed to identify the mechanisms through which cancer cells trigger adipocyte lipolysis and evaluate the functional consequences on cancer progression. Here, we show that cancer cell-induced acidification of the extracellular medium strongly promotes preadipocyte lipolysis through a mechanism that does not involve lipophagy but requires adipose triglyceride lipase (ATGL) activity. This increased lipolysis is triggered mainly by attenuation of the G0/G1 switch gene 2 (G0S2)-induced inhibition of ATGL. G0S2-mediated regulation in preadipocytes affects their communication with breast cancer cells, modifying the phenotype of the cancer cells and increasing their resistance to chemotherapeutic agents in vitro. Furthermore, we demonstrate that the adipocyte-specific overexpression of G0S2 impairs mammary tumor growth and lung metastasis formation in vivo. Our results highlight the importance of acidosis in cancer cell-adipocyte crosstalk and identify G0S2 as the main regulator of cancer-induced lipolysis, regulating tumor establishment and spreading. © 2023 Elsevier B.V.

Author Keywords
Acidosis; Adipose triglyceride lipase (ATGL); G0/G1 switch gene 2 (G0S2); Lipolysis; Tumor microenvironment

Index Keywords
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