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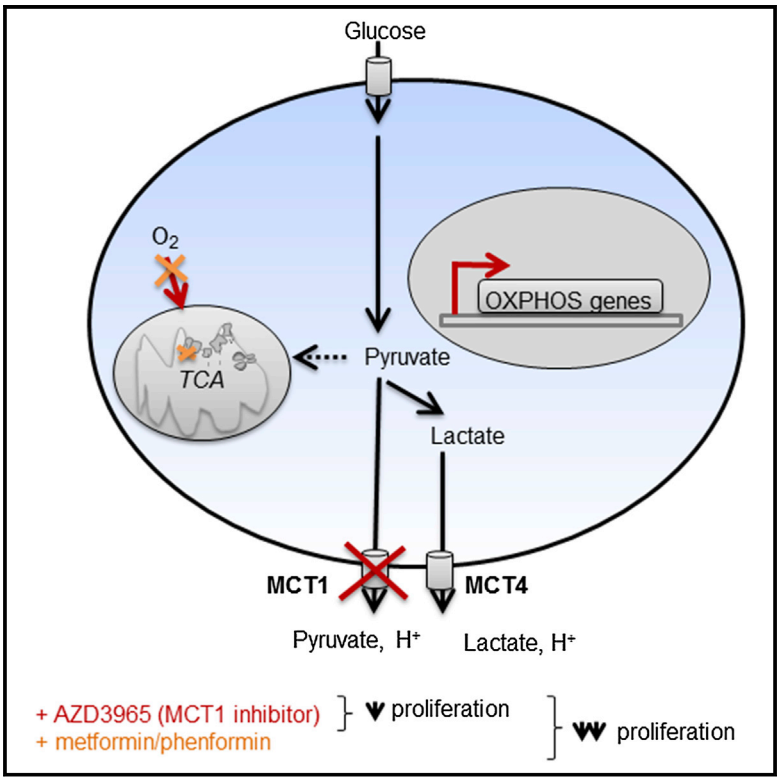
Report

MCT1 Modulates Cancer Cell Pyruvate Export and Growth of Tumors that Co-express MCT1 and MCT4

Graphical Abstract



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In Brief

Hong et al. show a lactate-transport-independent role for MCT1 in promoting proliferation of glycolytic breast cancer cells that co-express MCT1 and MCT4. Their results suggest a key role for MCT1 in mediating tumor pyruvate export, which has important implications for use of MCT1 inhibitors in the clinic.

Highlights

- MCT1 levels correlate with glycolytic metabolism and malignancy in breast cancer
- Cancer cells adapt to MCT1 loss-of-function by increasing oxidative metabolism
- MCT1 inhibition reduces pyruvate but not lactate export in cancer cells with MCT1/MCT4
- MCT1 inhibition of cancer cells with MCT1/MCT4 reduces proliferation and tumor growth

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MCT1 Modulates Cancer Cell Pyruvate Export and Growth of Tumors that Co-express MCT1 and MCT4

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SUMMARY

Monocarboxylate transporter 1 (MCT1) inhibition is thought to block tumor growth through disruption of lactate transport and glycolysis. Here, we show MCT1 inhibition impairs proliferation of glycolytic breast cancer cells co-expressing MCT1 and MCT4 via disruption of pyruvate rather than lactate export. MCT1 expression is elevated in glycolytic breast tumors, and high MCT1 expression predicts poor prognosis in breast and lung cancer patients. Acute MCT1 inhibition reduces pyruvate export but does not consistently alter lactate transport or glycolytic flux in breast cancer cells that co-express MCT1 and MCT4. Despite the lack of glycolysis impairment, MCT1 loss-of-function decreases breast cancer cell proliferation and blocks growth of mammary fat pad xenograft tumors. Our data suggest MCT1 expression is elevated in glycolytic cancers to promote pyruvate export that when inhibited, enhances oxidative metabolism and reduces proliferation. This study presents an alternative molecular consequence of MCT1 inhibitors, further supporting their use as anti-cancer therapeutics.

INTRODUCTION

Given that glycolytic metabolism contributes to tumor growth in many cancers, efforts have been made to block tumor glycolysis by inhibiting the monocarboxylate transporters (MCTs) that regulate cancer cell lactate export. The MCT family includes 14 members, but only MCT1-4 have been demonstrated to mediate proton-linked bi-directional transport of monocarboxylates such as lactate, pyruvate, and ketone bodies across the plasma membrane (Halestrap and Meredith, 2004). Tumor lactate export is thought to be primarily mediated by MCT1 and MCT4, since these are the family members most commonly upregulated in cancers (Halestrap and Meredith, 2004; Halestrap and Wilson, 2012). SLC16A1, the gene that encodes MCT1, was recently reported to be a MYC transcriptional target essential for lactate transport and glycolytic flux of certain cancer cell lines (Doherty et al., 2014). MCT1 inhibition induces cell death in Burkitt lymphoma cells and MCF7 breast cancer cells through disruption of lactate export, glycolysis, and glutathione synthesis (Doherty et al., 2014). Consistently, small molecule inhibitors of MCT1 block activation of T cells reliant on increased glycolysis for proliferation through abrogation of lactate export (Guile et al., 2006; Murray et al., 2005). AZD3965 is a MCT1 inhibitor that is currently undergoing phase I evaluation in the United Kingdom for patients with solid tumors, prostate cancer, gastric cancer, and diffuse large cell B lymphoma (Polański et al., 2014). Multiple studies,