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Abstract 233: Tumor-associated carbonic anhydrase IX maintains cellular proliferation by regulating tumor metabolism: a novel link revealed by proteomics FREE

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Abstract

Tumor hypoxia is a critical microenvironmental stress occurring in virtually all types of solid tumors. Survival of cancer cells is dependent upon their ability to adapt to these limiting conditions. Hypoxia-induced carbonic anhydrase IX (CA IX) plays a crucial adaptive role in response to hypoxic and acidic microenvironments by catalytically hydrating extracellular CO_2 to produce bicarbonate ions that maintain intracellular pH (pHi). In order to determine how CAIX function impacts other cellular processes, we used proteomic profiling to identify changes in response to transient CA IX knockdown in hypoxia. We discovered a significant reduction of key glycolytic enzyme levels with a most prominent decrease in lactate dehydrogenase (LDH). Our data shows that in addition to participating in cellular regulation of pHi, CA IX significantly stimulates glycolytic flux, lactate production and rate of proliferation in hypoxia. Because LDH activity contributes to pHi regulation by consuming cytoplasmic protons in the process of NADH regeneration, CA IX knockdown-mediated LDH suppression may further compromise the pHi regulating ability in hypoxia. Interestingly, addition of the alternative LDH substrate alpha-ketobutyrate compensates for reduced lactate production and restores pHi and proliferation in CA IX-deficient cells. These findings suggest that CA IX confers adaptive plasticity and supports proliferation of cancer cells both directly and

indirectly - through its effect as a pHi regulator and by maintaining glycolysis-permissive intracellular environment, respectively. Because CA IX expression is limited almost exclusively to tumors, our findings highlight the role as well as provide mechanistic insight for the utility of CA IX as an anti-cancer target and suggests that highly glycolytic tumors might be particularly vulnerable to CA IX-targeted therapy.

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