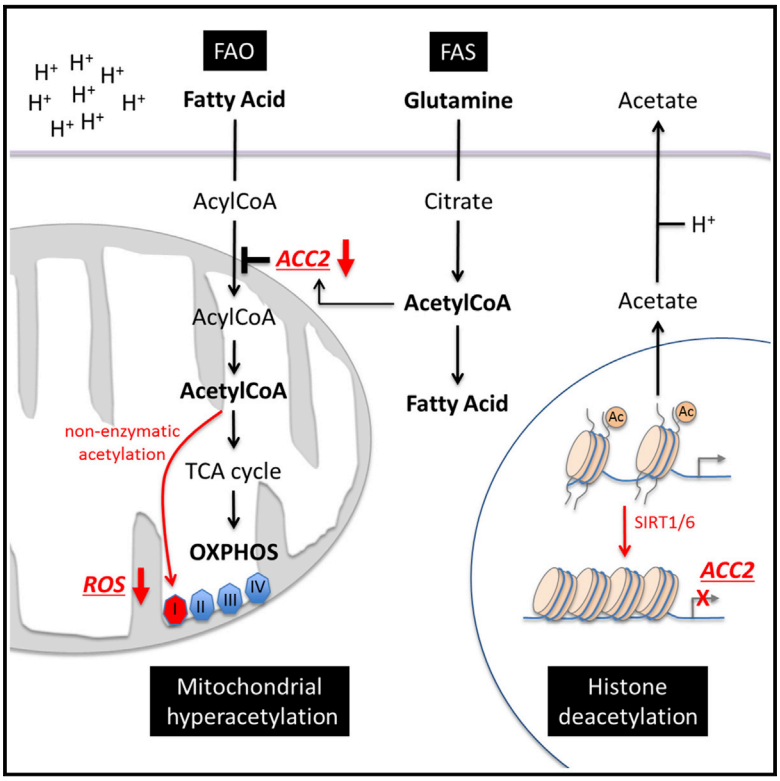
Article

Cell Metabolism

Acidosis Drives the Reprogramming of Fatty Acid Metabolism in Cancer Cells through Changes in Mitochondrial and Histone Acetylation

Graphical Abstract



Highlights

- Chronic tumor acidosis induces metabolic rewiring toward fatty acid oxidation
- Acidosis-induced mitochondrial hyperacetylation restrains complex I activity
- Histone deacetylation-mediated ACC2 repression allows FAO and FAS concomitance
- Fatty acid metabolism is a promising target to tackle the tumor acidic compartment

Authors

Cyril Corbet, Adán Pinto, Ruben Martherus, João Pedro Santiago de Jesus, Florence Polet, Olivier Feron

Correspondence

olivier.feron@uclouvain.be

In Brief

Like hypoxia, acidosis is nowadays recognized as a hallmark of many tumors. Corbet et al. show that acidic pH profoundly reprograms the metabolism of cancer cells toward fatty acid oxidation. Associated changes in the acetylome further tune this rewiring by clamping mitochondrial complex I activity and downregulating acetyl-CoA carboxylase ACC2.

Corbet et al., 2016, Cell Metabolism *24*, 311–323
August 9, 2016
http://dx.doi.org/10.1016/j.cmet.2016.07.003

Cell Metabolism
Article

Acidosis Drives the Reprogramming of Fatty Acid Metabolism in Cancer Cells through Changes in Mitochondrial and Histone Acetylation

Cyril Corbet,[1] Adán Pinto,[1] Ruben Martherus,[1] João Pedro Santiago de Jesus,[1] Florence Polet,[1] and Olivier Feron[1,*]
[1]Pole of Pharmacology and Therapeutics (FATH), Institut de Recherche Expérimentale et Clinique (IREC), UCLouvain, 53 Avenue Mounier B1.53.09, 1200 Brussels, Belgium
*Correspondence: olivier.feron@uclouvain.be
http://dx.doi.org/10.1016/j.cmet.2016.07.003

SUMMARY

Bioenergetic preferences of cancer cells foster tumor acidosis that in turn leads to dramatic reduction in glycolysis and glucose-derived acetyl-coenzyme A (acetyl-CoA). Here, we show that the main source of this critical two-carbon intermediate becomes fatty acid (FA) oxidation in acidic pH-adapted cancer cells. FA-derived acetyl-CoA not only fuels the tricarboxylic acid (TCA) cycle and supports tumor cell respiration under acidosis, but also contributes to non-enzymatic mitochondrial protein hyperacetylation, thereby restraining complex I activity and ROS production. Also, while oxidative metabolism of glutamine supports the canonical TCA cycle in acidic conditions, reductive carboxylation of glutamine-derived α-ketoglutarate sustains FA synthesis. Concomitance of FA oxidation and synthesis is enabled upon sirtuin-mediated histone deacetylation and consecutive downregulation of acetyl-CoA carboxylase ACC2 making mitochondrial fatty acyl-CoA degradation compatible with cytosolic lipogenesis. Perturbations of these regulatory processes lead to tumor growth inhibitory effects further identifying FA metabolism as a critical determinant of tumor cell proliferation under acidosis.

INTRODUCTION

Rewiring of cellular metabolism is crucial for sustaining the increased growth and proliferation of tumor cells. Acetyl-coenzyme A (acetyl-CoA) occupies a critical position within tumor metabolic processes as a biosynthetic intermediate but also as a key determinant of protein acetylation (Choudhary et al., 2014). While acetyl-CoA mostly derives from pyruvate or fatty acid oxidation in the mitochondria (Pietrocola et al., 2015), acetyl-CoA may also be directly generated in the tumor cell cytosol under certain circumstances (Corbet and Feron, 2015). Tumor cells may indeed produce acetyl-CoA from reductive carboxylation of glutamine-derived α-ketoglutarate when they are exposed to hypoxia (Metallo et al., 2012), in the presence of mitochondrial defects (Mullen et al., 2012), or upon glycolysis inhibition (Yang et al., 2014). Tumor cells can also use acetate to produce cytosolic acetyl-CoA, via the reaction catalyzed by the acyl-CoA synthetase short-chain family, member 2 (ACSS2) (Mashimo et al., 2014), especially in hypoxic conditions (Kamphorst et al., 2014; Schug et al., 2015).

Emerging evidence suggests that reversible lysine acetylation might be a dynamic protein post-translational modification that regulates metabolism through multiple mechanisms (Choudhary et al., 2014). Indeed, changes in protein acetylation have been well documented to confer adaptation to starvation and calorie restriction (Hebert et al., 2013; Hirschey et al., 2010; Someya et al., 2010). Recently, we have shown that under acidosis, the NAD^+-dependent activation of the deacetylase SIRT1 accounted for changes in the expression of transporter and enzymes involved in the metabolism of glutamine, HIF-2α deacetylation acting as the major event leading to this metabolic reprogramming in tumor cells (Corbet et al., 2014). Acidosis, like hypoxia, is nowadays considered as a hallmark of most human tumors (Brahimi-Horn et al., 2011; Gatenby and Gillies, 2008; Hashim et al., 2011). Tumor metabolic peculiarities, such as the exacerbated glycolytic metabolism and CO_2 hydratation, directly account for the acidification of the tumor microenvironment. Acidosis in turn contributes to the genetic instability of tumor cells (Morita et al., 1992) and profoundly alters their transcriptomic profile (Chen et al., 2008), leading to phenotypes that are particularly suited for survival and growth in an acidic environment.

We and others have documented that acidosis leads to a net reduction in the use of glucose by tumor cells (Corbet et al., 2014; Lamonte et al., 2013), thereby suppressing glucose oxidation as a source of acetyl-CoA. In the present study, we provide evidence that instead of glucose, fatty acids (FA), and glutamine to a lesser extent, contribute to acetyl-CoA generation under chronic acidosis. In particular, we identified how FA oxidation (FAO) and FA synthesis (FAS) could co-exist in acidosis-adapted cancer cells through mechanisms orchestrated by concomitant non-enzymatic hyperacetylation of mitochondrial proteins and histone deacetylation, the former limiting complex I activity and the latter repressing the expression of acetyl-CoA carboxylase ACC2. This study further provides evidence that the therapeutic targeting of key players of the fatty acid metabolism driven by the acidic tumor microenvironment may have detrimental effects on tumor growth.