Di Noia, J.M., and Neuberger, M.S. (2007). Annu. Rev. Biochem. *76*, 1–22.

Keim, C., Kazadi, D., Rothschild, G., and Basu, U. (2013). Genes Dev. *27*, 1–17.

Meng, F.-L., Du, Z., Federation, A., Hu, J., Wang, Q., Kieffer-Kwon, K.-R., Meyers, R.M., Amor, C., Wasserman, C.R., Neuberg, D., et al. (2014). Cell *159*, this issue, 1538–1548.

Nussenzweig, A., and Nussenzweig, M.C. (2010). Cell *141*, 27–38.

Pefanis, E., Wang, J., Rothschild, G., Lim, J., Chao, J., Rabadan, R., Economides, A.N., and Basu, U. (2014). Nature *514*, 389–393.

Qian, J., Wang, Q., Dose, M., Pruett, N., Kieffer-Kwon, K.-R., Resch, W., Liang, G., Tang, Z., Mathé, E., Benner, C., et al. (2014). Cell *159*, this issue, 1524–1537.

Storb, U. (2014). Adv. Immunol. *122*, 253–277.

Whyte, W.A., Orlando, D.A., Hnisz, D., Abraham, B.J., Lin, C.Y., Kagey, M.H., Rahl, P.B., Lee, T.I., and Young, R.A. (2013). Cell *153*, 307–319.

Acetate Fuels the Cancer Engine

Costas A. Lyssiotis[1,*] and Lewis C. Cantley[1,*]
[1]Meyer Cancer Center, Department of Medicine, Weill Cornell Medical College, New York City, NY 10065, USA
*Correspondence: col2007@med.cornell.edu (C.A.L.), lcantley@med.cornell.edu (L.C.C.)
http://dx.doi.org/10.1016/j.cell.2014.12.009

Cancer cells have distinctive nutrient demands to fuel growth and proliferation, including the disproportionate use of glucose, glutamine, and fatty acids. Comerford et al. and Mashimo et al. now demonstrate that several types of cancer are avid consumers of acetate, which facilitates macromolecular biosynthesis and histone modification.

Metabolic pathways in cancer cells are programmed to facilitate survival and proliferation in the nonnative microenvironment of a tumor. This involves changes in both the way extracellular nutrients are captured and how they are metabolized. Historically, research efforts have focused on the wiring of glucose metabolism, owing to the seminal observations of Warburg and to the dominant role glucose plays in many basic biosynthetic processes (Vander Heiden et al., 2009). The importance of other fuel sources, including glutamine, lipids, and protein, have received more recent attention upon realization that pathways governing their metabolism are often driven by oncogenes. In this issue of *Cell*, new studies from the McKnight and Tu (Comerford et al., 2014) and Maher and Bachoo labs (Mashimo et al., 2014) illustrate that a variety of cancers are also capable of capturing and metabolizing exogenous acetate and that this represents a metabolic adaptation that some tumors use to facilitate growth.

Acetate, when ligated to coenzyme A (acetyl-CoA), is among the most central and dynamic metabolites in intermediary metabolism (Figure 1). It can be generated by the oxidation of glucose, glutamine, or fatty acids; it is used to biosynthesize nucleotides, amino acids, and both principle components of the cell membrane in mammals (i.e., fatty acids and cholesterol); and it contributes to enzyme and gene regulation by reversibly adding to nonhistone protein and histone tails, respectively (Figure 1) (Kaelin and McKnight, 2013). Indeed, numerous studies have illustrated the fundamental roles that acetyl-CoA regulation plays in cell growth and proliferative processes (Wellen and Thompson, 2012). However, under oxygen limiting conditions, as are often seen in the microenvironment of a tumor, the ability of a cell to make acetyl-CoA is severely hampered. Intrigued by this conundrum, and based on the mechanisms by which yeast generate acetyl-CoA, Comerford et al. (2014) explored the functional relevance of the mammalian homologs of the yeast enzymes that generate acetyl-CoA. Mammals express three isoforms of short-chain acyl-CoA synthetases (ACSS) that convert acetate and coenzyme-A into acetyl-CoA by consuming ATP. Two of these are localized in mitochondria (ACSS1 and ACSS3), and one can access both the nuclear and cytoplasmic space, ACSS2 (Watkins et al., 2007). Comerford et al. (2014) find that knockdown of ACSS2, but not the mitochondrial isoforms, dramatically impairs the incorporation of exogenously supplied acetate into lipids and histone protein. These results illustrate that proliferating mammalian cells, including cancer cells, can consume and contribute acetate carbon to the cellular pool of acetyl-CoA.

In a parallel study, Mashimo et al. (2014) similarly find that exogenous acetate is captured and metabolized, here by human cancer cells grown in the brain of mice. The authors examined acetate metabolism in this context based on an earlier observation that a significant proportion of carbon in the acetyl-CoA pool could not be accounted for by tracing glucose and glutamine metabolism (Marin-Valencia et al., 2012). By tracing acetate carbon, Mashimo et al. (2014) reveal that TCA cycle intermediates consist of as much as 50% acetate-derived carbon by mass. In contrast, non-tumor-bearing brain incorporates on the order of 10% acetate-derived carbon into TCA cycle intermediates. These

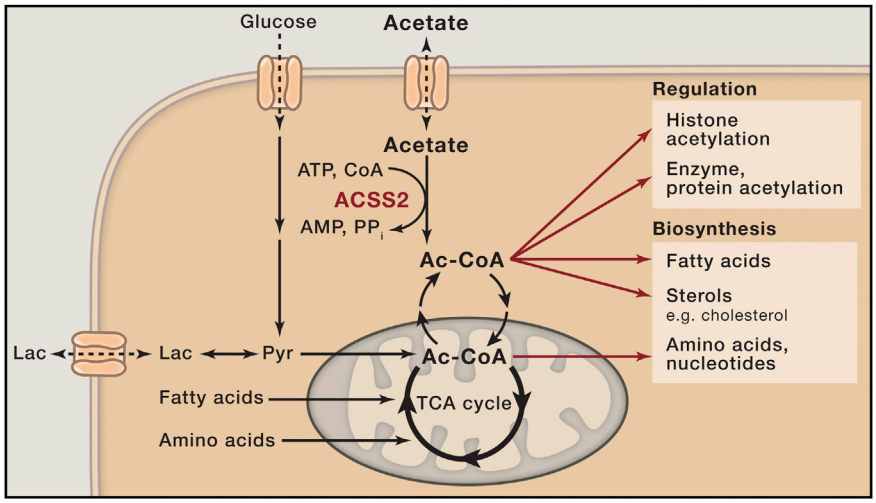

Figure 1. Acetyl-CoA Is a Central Node in Carbon Metabolism

Acetyl-CoA plays numerous roles in both regulatory and biosynthetic processes. It can be added in a posttranslational fashion to histone proteins to regulate gene expression or to other proteins and enzymes to dictate function or activity. Acetyl-CoA also serves as a principal building block for the generation of fatty acids, sterols, amino acids, and nucleotides. Acetyl-CoA is primarily generated in the mitochondria through catabolism of glucose, lipid, and amino acids. Mitochondrial acetyl-CoA is released into the cytoplasm by citrate export and breakdown. The cytoplasmic acetyl-CoA pool can also be filled by endogenous and exogenous acetate through reaction with coenzyme A by ACSS2.

observations are striking for several reasons, foremost because it illustrates that cancer cells are a sink for acetate and that acetate readily competes with glucose for generating TCA cycle intermediates, even though glucose is much more abundant. In these experiments, in vivo acetate levels are artificially raised to ~0.6 mM, and systemic glucose is maintained at ~5 mM. These results also provide validation of earlier, provocative work from the Bachoo and Maher labs (Marin-Valencia et al., 2012) that glutamine carbon is not actively oxidized in the TCA cycle in cells within the brain microenvironment (both brain cancer and metastases from other organ disease). Together, this argues that glucose and acetate metabolites are the dominant TCA cycle fuels in these cancers.

The independent but convergent findings from these two teams, which illustrate that acetate is readily captured and metabolized by cancer cells, prompted an exploration of the functional relevance and necessity of ACSS2 and acetate metabolism in cancer. To this end, Comerford et al. (2014) generate and cross an *ACSS2* null mouse into two models of liver cancer. In both cases, the tumor burden is significantly blunted. Consistent with this finding, high ACSS2 protein expression is observed in a subset of human triple-negative breast cancer samples, and this elevation correlates with poor survival. Similar correlations between ACSS2 elevation and poor outcome are obtained by Mashimo et al. (2014) in low-grade brain tumors (astrocytomas and oligodendrogliomas).

In both manuscripts, the authors illustrate that not only is ACSS2 expressed in tumors but that it is functional. Comerford et al. (2014) utilize radioactive carbon-labeled acetate, [^{11}C]acetate, and PET imaging. They find that acetate avidity correlates well with ACSS2 expression in murine tumors. Tumors devoid of ACSS2 consume much less acetate, and tumors with high ACSS2 expression are acetate avid. Mashimo et al. (2014) utilize nonradioactive [^{13}C]acetate and NMR to monitor in vivo acetate metabolism in tumors. The advantage of this technique is that the metabolism of acetate can be traced into downstream products. Initially, using orthotopic models with patient-derived material, they illustrate that acetate contributes a significant fraction of carbon to TCA cycle intermediates. Moreover, they show, using the identical technique in human patients, that brain tumors growing in human beings metabolize acetate in a manner nearly identical to tumors grown orthotopically in the mouse brain.

Collectively, these results have several important therapeutic implications. First, they provide a clear demonstration that acetate is a metabolic fuel in vivo that is preferentially utilized by a subset of cancers. They also illustrate that this is mediated by ACSS2, whose expression correlates with tumor aggressiveness in the six different organ diseases analyzed. This suggests that acetate avidity and metabolism may be a general feature of many cancers. In contrast, normal cells appear unaffected by loss of ACSS2-mediated acetate metabolism, as *ACSS2* null mice do not exhibit any overt phenotypic defects. Taken together, it is reasonable to conclude that acetate metabolism may represent an addiction of certain cancer cells. Furthermore, the results presented in these studies illustrate the clinical applicability of two different acetate-measuring technologies—i.e., [^{11}C]acetate-PET and [^{13}C]acetate-NMR. Such strategies could be used to identify patients likely to respond to an antimetabolism therapy and could also be used as markers of therapeutic response.

These findings beg the question as to how ACSS2 inhibition would affect an established tumor. The only experiment presented in this regard revealed that ACSS2 knockdown by short hairpin RNA (shRNA) in brain cancer cells grown in 3D culture resulted in cell death and an overall reduction in neurospheres. The astute reader may recognize that, under such conditions (growth in culture), very little acetate is present. More to this point, the concentration of serum acetate under physiological circumstances is on the order of 0.2 mM (Tollinger et al., 1979), raising the question of how a relatively low abundance molecule could contribute meaningfully to biomass in a rapidly proliferating cell. To address this, Comerford et al. (2014) put forth a persuasive argument for tumor cell evolution, relating it to that of bacterial cells evolving in a population, where seemingly minor advantages can ultimately have profound impacts. We put forth an additional, but not mutually exclusive, point of view based on three pieces of experimental data from these studies. First, exogenous acetate, by way of

acetyl-CoA, is found on histone proteins. Second, ACSS2 is readily observed in the nucleus of tumor cells, as evidenced by histological staining. And third, as noted above, ACSS2 knockdown in human patient tumor cell lines, grown in media devoid of acetate, is growth inhibitory. These finding suggest that the major role of ACSS2 is to capture acetate released from deacetylated proteins and to reincorporate that into the acetyl-CoA pool for epigenetic regulation. As Comerford et al. (2014) point out, the half-life of histone acetylation is on the order of minutes, and a considerable fraction of acetate could be produced in vivo by the turnover of histone acetylation. ACSS2 in the nucleus provides a rapid way to reconvert this acetate to acetyl-CoA for use in reacetylating histones and thereby maintaining the epigenetic code. Although ACSS2 is not essential for this function in normal tissues, as evidenced by the viable *ACSS2* knockout mouse, it is possible that certain cancer cells require this function to maintain gene expression profiles optimized for rapid growth. Exogenous acetate, in this case, is treated equivalently to that generated by deacetylation. Regardless of the mechanism(s) by which cancer cells utilize acetate, the insights provided by these studies position acetate metabolism as a potentially exploitable vulnerability in cancer metabolism.

ACKNOWLEDGMENTS

C.A.L. is funded by a Pathway to Leadership grant from the Pancreatic Cancer Action Network and a Dale F. Frey Breakthrough award from the Damon Runyon Cancer Research Foundation. L.C.C. owns equity in, receives compensation from, and serves on the Board of Directors and Scientific Advisory Board of Agios Pharmaceuticals. Agios Pharmaceuticals is identifying metabolic pathways of cancer cells and is developing drugs to inhibit such enzymes in order to disrupt tumor cell growth and survival.

REFERENCES

Comerford, S.A., Huang, Z., Du, X., Wang, Y., Cai, L., Witkiewicz, A.K., Walters, H., Tantawy, M.N., Fu, A., Manning, H.C., et al. (2014). Cell *159*, this issue, 1591–1602.

Kaelin, W.G., Jr., and McKnight, S.L. (2013). Cell *153*, 56–69.

Marin-Valencia, I., Yang, C., Mashimo, T., Cho, S., Baek, H., Yang, X.L., Rajagopalan, K.N., Maddie, M., Vemireddy, V., Zhao, Z., et al. (2012). Cell Metab. *15*, 827–837.

Mashimo, T., Pichumani, K., Vemireddy, V., Hatanpaa, K.J., Singh, D.K., Sirasanagandla, S., Nannepaga, S., Piccirillo, S.G., Kovacs, Z., Foong, C., et al. (2014). Cell *159*, this issue, 1603–1614.

Tollinger, C.D., Vreman, H.J., and Weiner, M.W. (1979). Clin. Chem. *25*, 1787–1790.

Vander Heiden, M.G., Cantley, L.C., and Thompson, C.B. (2009). Science *324*, 1029–1033.

Watkins, P.A., Maiguel, D., Jia, Z., and Pevsner, J. (2007). J. Lipid Res. *48*, 2736–2750.

Wellen, K.E., and Thompson, C.B. (2012). Nat. Rev. Mol. Cell Biol. *13*, 270–276.

A New "Spin" on Recovery after Spinal Cord Injury

Andrea Tedeschi[1,*] and Frank Bradke[1,*]
[1]Laboratory for Axon Growth and Regeneration, German Center for Neurodegenerative Diseases (DZNE), Ludwig-Erhard-Allee 2, 53175 Bonn, Germany
*Correspondence: andrea.tedeschi@dzne.de (A.T.), frank.bradke@dzne.de (F.B.)
http://dx.doi.org/10.1016/j.cell.2014.12.014

Functional recovery can occur after incomplete spinal cord injury. Takeoka et al. now report that such recovery relies on muscle spindle feedback that is necessary for neuronal circuit remodeling, suggesting novel targets to restore motor functions following spinal cord injuries.

Following incomplete lesions of the spinal cord, substantial recovery of sensory motor functions is observed (Curt et al., 2008; Martinez et al., 2012). Previous work has shown that such a recovery correlates with the formation of intraspinal circuits that bypass the injury (Bareyre et al., 2004; Courtine et al., 2008). Although sensory afferents are known to play a key role in the recovery process (Helgren and Goldberger, 1993), the sensory modality that allows the injured nervous system to re-establish functional connections has remained elusive. In this issue, Takeoka et al. (2014) provide evidence for the role of muscle spindle feedback in promoting neuroplasticity and motor recovery following spinal cord injury (SCI).

Muscle spindles are sensory mechanoreceptors specialized for proprioception. They are located in skeletal muscles, and consist of several specialized intrafusal muscle fibers surrounded by a capsule of connective tissue (Figure 1A). Muscle spindles are innervated by specialized motor and sensory axons. Deformation of intrafusal muscle fibers generates action potentials by activating stretch-sensitive ion channels expressed along the sensory axons that are coiled around the central part of the spindle. These axons connect to spinal motorneurons and different classes of interneurons that control muscle activity necessary for accurate body movements.