A Mitochondrial Expatriate: Nuclear Pyruvate Dehydrogenase

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The pyruvate dehydrogenase complex (PDC) catalyzes the conversion of pyruvate into acetyl-CoA, a critical step in metabolism. Sutendra et al. now demonstrate that PDC can translocate from the mitochondria to the nucleus to provide acetyl-CoA necessary for histone acetylation, suggesting a new pathway for mitochondrial-nuclear communication.

The pyruvate dehydrogenase complex (PDC) plays a central role in cellular metabolism by catalyzing the irreversible conversion of pyruvate into acetyl-CoA. The activity of PDC is therefore tightly controlled via reversible inactivating phosphorylation due to the activity of specific kinases (PDK1-4) and phosphatases (PDP1-2). The localization of PDC has been thought to be strictly mitochondrial. In this issue, Sutendra et al. (2014) reveal that PDC also resides in the cell nucleus, where it generates acetyl-CoA, a substrate for histone acetylation (Figure 1).

Histone posttranslational modifications (PTMs), including acetylation, methylation, and O-GlcNAcylation, form a histone code that regulates nucleosome dynamics and serves as a platform for epigenetic readers. Though a diverse set of protein families mediates the processing of the histone code, recent studies highlight an additional level of control of histone modification via the cosubstrates of PTM reactions, such as acetyl-CoA for acetylation, S-adenosylmethionine for methylation, and N-acetylglucosamine for GlcNAcylation. Levels and routing of these metabolites have been demonstrated to play a significant role in driving histone PTM dynamics (Kaelin and McKnight, 2013).

Acetyl-CoA is a central metabolite that interconnects multiple metabolic pathways (Figure 1). Although a major fate of acetyl-CoA is its oxidation in the citric acid cycle, it is also used for many other cellular processes. Acetyl-CoA is the obligatory acetyl donor for lysine acetylation reactions in mammalian cells, linking metabolic activity with epigenetics. ATP-citrate lyase (ACL) and acetyl-CoA synthetase (ACS) are acetyl-CoA-generating enzymes localized in the cytosol and the nucleus, providing acetyl units for nuclear histone acetylation (Figure 1). Importantly, ACL is critical for differentiation of 3T3-L1 preadipocytes into mature adipocytes via histone acetylation (Wellen et al., 2009), and ACS-dependent histone acetylation is necessary for cell-cycle progression in yeast (Cai et al., 2011). These findings demonstrate that delivery of nuclear acetyl-CoA contributes to the control of cellular proliferation and differentiation.

Sutendra et al. now provide further support of metabolic control of histone acetylation via the generation of acetyl-CoA from pyruvate in the nucleus by PDC. Nuclear PDC levels, as well as the level of acetylation of histone 3 (Ac-H3), increase upon stimulation of cells with serum or epidermal growth factor (EGF) that triggers cell-cycle progression, whereas inhibition of EGF signaling lowers the nuclear PDC level. Furthermore, knockdown of one PDC subunit decreases not only the nuclear levels of the entire complex, but also the levels of Ac-H3 and cell-cycle progression markers. These findings imply that acetyl-CoA, as an important substrate source for histone acetylation, can be generated inside of the nucleus from pyruvate and that its nuclear synthesis is controlled by a growth-factor-mediated regulation of nuclear PDC.

An intriguing aspect of this study is the localization of PDC inside of the nucleus and its apparent translocation from the mitochondria. Upon serum stimulation, mitochondrial and nuclear PDC levels change in the opposite direction. Experiments using cycloheximide further confirm that the increase in nuclear PDC does not depend on protein translation. Interestingly, PDK is not present in the nucleus, and consequently, nuclear PDC is not subject to phosphorylation regulation. The nuclear translocation of PDC is a unique pathway by which mitochondria can communicate with the nucleus. Other well-studied signals arising from mitochondria are mostly peptides generated by the mitochondrial unfolded protein response (Haynes et al., 2010), redox state, and small molecule intermediates such as α-ketoglutarate, succinate, fumarate, AMP, and ROS (Gut and Verdin, 2013).

Although this work reveals that PDC can localize to the nucleus, new questions arise. Importantly, a mechanism that can explain the specific export of the PDC across the mitochondrial membrane remains unknown. Although mitochondria can export peptides into the cytosol and mitochondrial-encoded respiratory chain

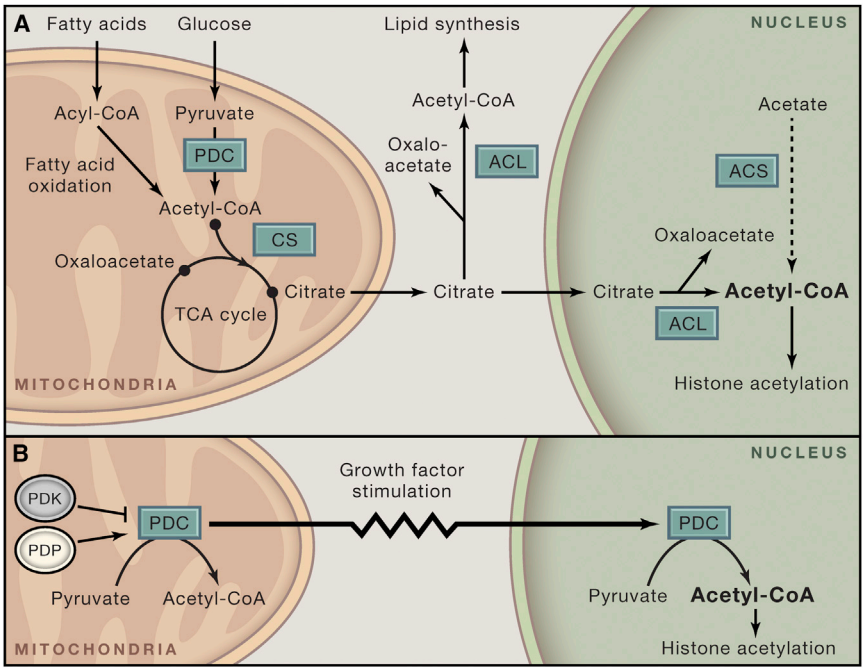

Figure 1. Sources of Nuclear Acetyl-CoA

(A) Acetyl-CoA is mainly produced in the mitochondrion as a result of glycolysis and fatty acid oxidation. Glycolysis and degradation of specific amino acids yield pyruvate, which can be oxidized to acetyl-CoA by the pyruvate dehydrogenase complex (PDC). The mitochondrial membrane is impermeable for acetyl-CoA. Therefore, acetyl-CoA is thought to exit the mitochondrion as citrate, the product of citrate synthase (CS). Nuclear (and cytosolic) citrate is converted to acetyl-CoA and oxaloacetate by ATP-citrate lyase (ACL). Another source of acetyl-CoA is acetyl-CoA synthetase (ACS), which uses acetate as a substrate. (B) The activity of PDC in mitochondria is regulated by specific kinases (PDK1-4) and phosphatases (PDP1-2). Sutendra et al. show that PDC can exit the mitochondrion and localize to the nucleus to produce acetyl-CoA that is necessary for histone acetylation.

subunits into the mitochondrial inner membrane (Bauerschmitt et al., 2010; Haynes et al., 2010), these processes are unlikely to be responsible for the exit of one of the largest multienzyme complexes that has been known. The identification of this mechanism will be instrumental for further studying the regulation and specificity of this mode of mitochondrial-nuclear communication.

The study also raises the intriguing question of whether other mitochondrial matrix proteins are able to exit the mitochondria. In this respect, it is worth mentioning that ketolysis and fatty acid oxidation are additional sources of mitochondrial acetyl-CoA, especially during fasting (Figure 1). Fatty acid oxidation has recently been shown to be an important source for mitochondrial acetylation (Pougovkina et al., 2014). In addition, the newly discovered histone lysine crotonylation modification is likely to use crotonyl-CoA as the substrate (Tan et al., 2011), which is solely generated by oxidation of fatty acids and specific amino acids. Indeed, the finding showing that the ketone body β-hydroxybutyrate can inhibit histone deacetylases and consequently alter specific histone acetylation marks (Gut and Verdin, 2013) further supports a role for signals arising from fatty acid oxidation to contribute to histone epigenetic regulation.

Lastly, one may wonder whether the acetyl-CoA generated by nuclear PDC can be used for other biochemical processes such as lipid synthesis. Because proliferating tumor cells critically rely on cytosolic acetyl-CoA for membrane generation (Lunt and Vander Heiden, 2011), it will be interesting to further explore this hypothesis.

In summary, the work by Sutendra et al. reveals a new pathway for mitochondrial-nuclear signaling and intriguingly demonstrates that protein complexes, like many scientists, can become expatriates. Whether this particular expatriate would ever return to its organelle of origin and, if so, what the functional significance for that process would be, remain open questions for future investigation.

REFERENCES

Bauerschmitt, H., Mick, D.U., Deckers, M., Vollmer, C., Funes, S., Kehrein, K., Ott, M., Rehling, P., and Herrmann, J.M. (2010). Mol. Biol. Cell *21*, 1937–1944.

Cai, L., Sutter, B.M., Li, B., and Tu, B.P. (2011). Mol. Cell *42*, 426–437.

Gut, P., and Verdin, E. (2013). Nature *502*, 489–498.

Haynes, C.M., Yang, Y., Blais, S.P., Neubert, T.A., and Ron, D. (2010). Mol. Cell *37*, 529–540.

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

Lunt, S.Y., and Vander Heiden, M.G. (2011). Annu. Rev. Cell Dev. Biol. *27*, 441–464.

Pougovkina, O., te Brinke, H., Ofman, R., van Cruchten, A.G., Kulik, W., Wanders, R.J., Houten, S.M., and de Boer, V.C. (2014). Hum. Mol. Genet.

Sutendra, G., Kinnaird, A., Dromparis, P., Paulin, R., Stenson, T.H., Haromy, A., Hashimoto, K., Zhang, N., Flaim, E., and Michelakis, E.D. (2014). Cell *158*, this issue, 84–97.

Tan, M., Luo, H., Lee, S., Jin, F., Yang, J.S., Montellier, E., Buchou, T., Cheng, Z., Rousseaux, S., Rajagopal, N., et al. (2011). Cell *146*, 1016–1028.

Wellen, K.E., Hatzivassiliou, G., Sachdeva, U.M., Bui, T.V., Cross, J.R., and Thompson, C.B. (2009). Science *324*, 1076–1080.