Title

PGC1α drives a metabolic block on prostate cancer progression

Journal

Nature Cell Biology, 18(6)

ISSN

1465-7392

Authors

Wallace, Martina

Metallo, Christian M

Publication Date

2016-06-01

DOI

10.1038/ncb3365

Peer reviewed

higher-resolution reporter lines combined with single-cell expression analysis would be one possibility[13–15]. Such studies would offer a baseline for cell behaviour within the IFE that will be instrumental in our understanding of specific genetic phenotypes that affect only subsets of cells within the epidermis. However, the limitations of different techniques would have to be taken into account, with a plurality of experimental approaches likely to provide clearer answers. To that end, the observations of Tumbar and colleagues provide additional insights into the complexities of IFE maintenance and stem cell heterogeneity.

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

1. Sada, A. *et al. Nat. Cell Biol.* **18,** 619–631 (2016).
2. Schepeler, T., Page, M. E. & Jensen, K. B. *Development* **141,** 2559–2567 (2014).
3. Gomez, C. *et al. Stem Cell Rep.* **1,** 19–27 (2013).
4. Mackenzie, I. C. *Nature* **226,** 653–655 (1970).
5. Doupe, D. P., Klein, A. M., Simons, B. D. & Jones, P. H. *Dev. Cell* **18,** 317–323 (2010).
6. Clayton, E. *et al. Nature* **446,** 185–189 (2007).
7. Mascre, G. *et al. Nature* **489,** 257–262 (2012).
8. Lim, X. *et al. Science* **342,** 1226–1230 (2013).
9. Tumbar, T. *et al. Science* **303,** 359–363 (2004).
10. Page, M. E., Lombard, P., Ng, F., Gottgens, B. & Jensen, K. B. *Cell Stem Cell* **13,** 471–482 (2013).
11. Rompolas, P., Mesa, K. R. & Greco, V. *Nature* **502,** 513–518 (2013).
12. Alcolea, M. P. & Jones, P. H. *Nat. Rev. Cancer* **13,** 161–171 (2013).
13. Satija, R., Farrell, J. A., Gennert, D., Schier, A. F. & Regev, A. *Nat. Biotechnol.* **33,** 495–502 (2015).
14. Sun, J. *et al. Nature* **514,** 322–327 (2014).
15. Roy, E., Neufeld, Z., Livet, J. & Khosrotehrani, K. *Stem Cells* **32,** 3046–3054 (2014).

PGC1α drives a metabolic block on prostate cancer progression

Martina Wallace and Christian M. Metallo

Metabolic rewiring is essential for cancer cell survival. PGC1α, a transcriptional co-activator that is downregulated in prostate cancer, is now shown to control prostate cancer metabolism by activating an oxidative metabolic program that prevents tumour growth and metastatic dissemination.

Metabolism is a balancing act, where breakdown of extracellular nutrients must be coordinated to meet the bioenergetic and biosynthetic needs of cells in the context of their state, function and microenvironment. A distinctive feature of malignant transformation is metabolic reprogramming that facilitates anabolism for cell growth and survival through the provision of ATP, biosynthetic intermediates and reducing equivalents. Transcriptional profiling of human tumours can provide insights into key regulators of such reprogramming events, but functional analyses of metabolism and tumorigenesis are critical to establish the importance of specific pathways. In this issue of *Nature Cell Biology*, Torrano *et al.*[1] use human tumour transcriptional data, cell culture and *in vivo* mouse experiments to demonstrate that the transcriptional co-regulator PGC1α (peroxisome proliferator-activated receptor gamma co-activator 1 alpha) promotes oxidative metabolism and a general catabolic state to suppress prostate cancer growth and metastasis. This work takes a significant step forward in understanding the key drivers of prostate cancer, and sheds new light on the changes in complex transcriptional regulatory networks that are required to metabolically rewire cancer cells to promote growth, invasion and metastasis.

To identify transcriptional co-regulators important in prostate cancer progression, Torrano *et al.*[1] performed a bioinformatic analysis of gene expression across five independent data sets from prostate cancer specimens, normal tissue and metastases. Expression of *PGC1A* (also known as *PPARGC1A*) was consistently lower in tumour tissue, and further decreased within metastatic lesions relative to primary tumours. The authors subsequently explored the impact of *Pgc1a* deletion in the mouse prostate epithelium in combination with loss of *Pten* (a tumour suppressor upstream of PI(3)K that is commonly lost in this cancer type) on tumour progression. Compared to *Pten* deletion alone, combined deletion of *Pgc1a* and *Pten* led to increased tumorigenesis and bone metastasis, suggesting the decreased *PGC1A* expression observed in human tumours confers advantageous characteristics for prostate cancer metastasis. Notably, *Pgc1a* knockout alone did not promote tumour formation, indicating that loss of this transcription factor is not an initiating event. Consistent with these findings, ectopic expression of PGC1α in prostate cancer cell xenotransplants resulted in decreased metastases to the lung and bone.

PGC1α is a well-characterized regulator of mitochondrial biogenesis and oxidative metabolism, and can interact with a diverse range of transcription factors to control metabolic function[2]. Functional analyses of prostate cancer cells differentially expressing PGC1α indicated this factor alone could impact cell growth, tumour formation, lung and bone metastases, and metabolism. Specifically, respiration, glucose oxidation and fatty acid oxidation were increased at the expense of *de novo* lipogenesis in PGC1α-expressing cells, indicating that they underwent a 'switch' from anabolic pathway flux towards catabolism. Transcriptional data indicated a role for the nuclear receptor ERRα (oestrogen-related receptor alpha) in mediating these effects, which were dependent on the interaction between PGC1α and nuclear receptors. Furthermore, directly targeting *ERRα* (*ESRRA*) enhanced the incidence of metastases, suggesting that a PGC1α–ERRα regulatory axis is antagonistic to prostate cancer progression (Fig. 1). This PGC1α–ERRα gene

Martina Wallace and Christian M. Metallo are in the Department of Bioengineering, University of California, San Diego, La Jolla, California, USA. Christian M. Metallo is also at the Moores Cancer Center, University of California, San Diego, La Jolla, California, USA.
e-mail: cmetallo@ucsd.edu

expression signature could provide prognostic insights into prostate cancer patient recurrence and outcomes.

Through their analyses of tumorigenesis and metabolic function, Torrano *et al.*[1] provide evidence that PGC1α influences prostate cancer progression and metastasis by modulating the metabolic state of cells. However, the specific mechanisms through which suppression of PGC1α becomes advantageous for prostate cancer tumorigenesis remain unclear. Suppressing glucose and fatty acid oxidation could allow cells to better divert nutrients towards nucleotide, non-essential amino acid and lipid synthesis. However, mitochondria also play critical roles in the production of reducing equivalents and various biomass components, so their activity can be beneficial to tumour growth as well. More detailed metabolic characterizations of prostate cancer cells following *PGC1A* overexpression may provide additional insights into the mechanisms at play.

Metabolic pathways beyond glycolysis, respiration and lipogenesis may also influence the increased tumour growth observed following downregulation of PGC1α. Nutrients other than glucose and fatty acids, including valine, leucine and isoleucine, are catabolized in mitochondria for energy generation or biosynthesis. Indeed, the catabolism of these branched-chain amino acids (BCAAs) is often suppressed in highly proliferative cancer cells[3]. Suppression of this pathway may allow cells to maintain adequate stores of these essential amino acids for protein synthesis and/or activation of mTOR (mechanistic target of rapamycin)[4]. Thus, downregulation of this PGC1α-induced catabolic state could ensure that the availability of various biosynthetic intermediates or signalling molecules is not a limiting step for cancer growth. Notably, the BCAA degradation pathway was altered in *PGC1A*-expressing prostate cancer cells, but the role of this potential mechanism is yet to be investigated. These findings suggest that saving, rather than breaking down, essential nutrients could be important in the differing microenvironments that cancer cells encounter during metastasis.

Anchorage-independent growth and survival are also critical steps in the metastatic process. The maintenance of NADPH pools in both the mitochondria and cytosol are an important buffer against the oxidative stress induced by matrix detachment, and cancer cells reprogram various pathways to facilitate growth and survival under these conditions,

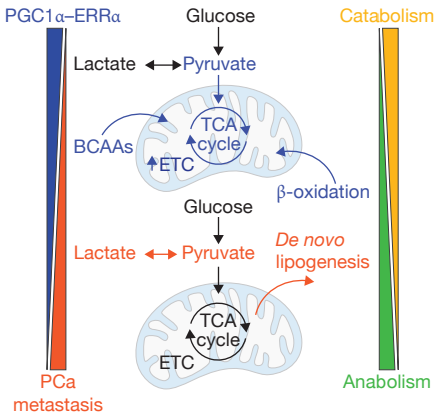

Figure 1 A PGC1α–ERRα gene expression signature induces a catabolic state in prostate cancer that decreases metastasis. Induction of PGC1α expression and its interaction with ERRα suppresses metastasis, and this expression profile is decreased in human prostate cancer (PCa). PGC1α promotes a catabolic state of enhanced glucose and fatty acid oxidation, decreased lipid biosynthesis, and increased expression of the BCAA catabolic pathway. PGC1α therefore controls the balance of anabolism and catabolism to influence prostate cancer growth and metastasis.

including the oxidative pentose phosphate pathway[5], folate-mediated one-carbon metabolism (FOCM)[6], and reductive carboxylation[7]. In contrast, non-transformed epithelial cells undergo cell death following detachment, which can be prevented by antioxidants[5]. As increased PGC1α expression could lead to elevated levels of reactive oxygen species (ROS) production through increased oxidative metabolism, Torrano *et al.*[1] also tested whether ROS levels contributed to the decreased metastasis observed in their prostate cancer models. Notably, they observed no difference in ROS production using reporters in cultured cells or lipid peroxidation *in vivo*. Further analysis of redox pathways in prostate cancer cells differentially expressing PGC1α in microenvironments that mimic aspects of metastasis, or actively metastasizing cells, would be needed to shed light on the mechanism of action.

The role of PGC1α in tumour formation, growth and metastasis has been previously explored in various cancer types. Increased PGC1α expression can induce oxidative stress to suppress intestinal epithelial tumours[8] and cell growth in Von Hippel–Lindau (VHL)-deficient renal cell carcinoma[9]. Subsets of melanoma and pancreatic tumour cells differentially express *PGC1A*, rendering them more susceptible to therapies that inhibit oxidative phosphorylation or induce ROS[10–12]. On the other hand, mitochondrial function promoted by PGC1α in breast cancer cell lines has been reported to positively influence *in vivo* growth[13] and metastasis[14], contrasting with the suppressive role reported in prostate cancer by Torrano *et al.* However, both the microenvironment and tissue of origin can influence the metabolic state of cancer cells and their response to specific genetic perturbations, which may play a part in the differing roles of PGC1α reported in these studies. Indeed, prostate epithelia have a unique metabolic phenotype in that they accumulate zinc and produce large amounts of citrate during normal function, but this characteristic is lost during transformation[15]. Other metabolic aspects of prostate epithelia that are not lost during tumorigenesis may impact prostate cancer phenotypes in response to PGC1α, and it will be interesting to investigate these in future work.

These open questions notwithstanding, the combined use of transcriptomics, genetically engineered mouse models, mouse xenograft experiments and functional metabolic analyses by Torrano *et al.*[1] provide strong evidence for a role of PGC1α in suppressing prostate cancer progression and metastasis. These results further our understanding of the complex mechanisms through which PGC1α contributes to metabolic reprogramming in cancer. A more detailed picture of the different metabolic pathways reprogrammed downstream of PGC1α and their relative importance to metastasizing cancer cells will help clarify the mechanisms through which the PGC1–ERRα signalling axis compromises prostate cancer metastasis, and may provide new prognostic indications for prostate cancer progression.

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

1. Torrano, V. *et al. Nat. Cell Biol.* **18,** 645–656 (2016).
2. Lin, J., Handschin, C. & Spiegelman, B. M. *Cell Metab.* **1,** 361–370 (2005).
3. Green, C. R. *et al. Nat. Chem. Biol.* **12,** 15–21 (2016).
4. Lynch, C. J., Fox, H. L., Vary, T. C., Jefferson, L. S. & Kimball, S. R. *J. Cell. Biochem.* **77,** 234–251 (2000).
5. Schafer, Z. T. *et al. Nature* **461,** 109–113 (2009).
6. Piskounova, E. *et al. Nature* **527,** 186–191 (2015).
7. Jiang, L. *et al. Nature* **532,** 255–258 (2016).
8. D'Errico, I. *et al. Proc. Natl Acad. Sci. USA* **108,** 6603–6608 (2011).
9. LaGory, E. L. *et al. Cell Rep.* **12,** 116–127 (2015).
10. Haq, R. *et al. Cancer Cell* **23,** 302–315 (2013).
11. Sancho, P. *et al. Cell Metab.* **22,** 590–605 (2015).
12. Vazquez, F. *et al. Cancer Cell* **23,** 287–301 (2013).
13. Audet-Walsh, E. *et al. Cell Rep.* **14,** 920–931 (2016).
14. LeBleu, V. S. *et al. Nat. Cell Biol.* **16,** 992–1003 (2014).
15. Singh, K. K., Desouki, M. M., Franklin, R. B. & Costello, L. C. *Mol. Cancer* **5,** 14 (2006).