Commentary

PGC1α curtails prostate cancer metastasis via metabolic rewiring

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Prostate cancer is the second most commonly diagnosed malignancy in men; and in spite of recent therapeutic advances, it remains the fifth leading cause of male cancer deaths worldwide (1,2). Aside from prostatectomy and radiation, used with curative intent for the treatment of localized prostate cancer, approved life-prolonging treatment options for metastasized prostate cancer are limited to androgen receptor signaling inhibitors, microtubule targeting taxane chemotherapeutics, the bone targeted radioisotope Ra223, and active immunotherapy with sipuleucel-T (2). Hence, to improve prostate cancer care it is essential to identify novel treatment targets (3). Comprehensive genetic analyses have revealed a number of actionable molecular aberrations, including alterations of the PI3K-AKT and WNT signaling pathways, and DNA repair defects (4-6).

Although alterations of metabolic pathways have been recognized as essential aspects of cancer progression and metastasis, there is a need to better understand the molecular mechanisms behind how the metabolic landscape of cancer cells changes in coordinated manner to support tumor growth (7). In a detailed and elegant study Torrano *et al.* examined the peroxisome proliferator-activated receptor gamma co-activator 1 alpha (PGC1α, also PPARGC1A) transcriptional network and its role in suppressing prostate cancer metastasis (8). Initially, a bioinformatics analysis was completed to identify regulators of prostate cancer metabolism responsible for disease progression. Amongst three metabolic co-regulators identified in most or all data sets studied, covering different stages of prostate cancer (i.e., PGC1α, PGC1β, HDAC1), the expression of PGC1α was the only one found to be associated with the Gleason scoring system and disease-free survival. The expression pattern of PGC1α was characteristic of a tumor suppressor.

Next, PGC1α was chosen for further analyses. While PGC1α deletion did not promote prostate cancer initiation, it was shown to be responsible for impairing prostate cancer growth and metastasis. PGC1α has been identified as a promoter of inflammation, angiogenesis and the production of reactive oxygen species; neither of these processes, however, contributed to the PGC1α-mediated anti-prostate cancer effects described by Torrano *et al.* In gene expression profiling and metabolomics analyses, PGC1α was found to significantly alter gene expression and metabolite levels with respect to mitochondrial catabolic programs and oxidative processes such as fatty-acid β-oxidation. Altogether, the findings suggest that in prostate cancer PGC1α may serve as a metabolic regulator balancing a catabolic, tumor suppressive state (high PGC1α expression) versus an anabolic, tumor promoting state (low PGC1α expression) (*Figure 1*).

Finally, Torrano *et al*. used promoter and gene set enrichment analyses to identify estrogen-related receptor alpha (ERRα or ESRRA) as a major transcription factor mediating the tumor suppressive activities of PGC1α. Furthermore, using two independent patient gene expression data sets they demonstrated that the PGC1α/ERRα transcriptional program is positively associated with time to prostate cancer recurrence.

ERRα and two additional ERR isoforms (i.e., ERRβ and ERRγ) belong to a subfamily of constitutively active, orphan nuclear receptors that share high homology with estrogen

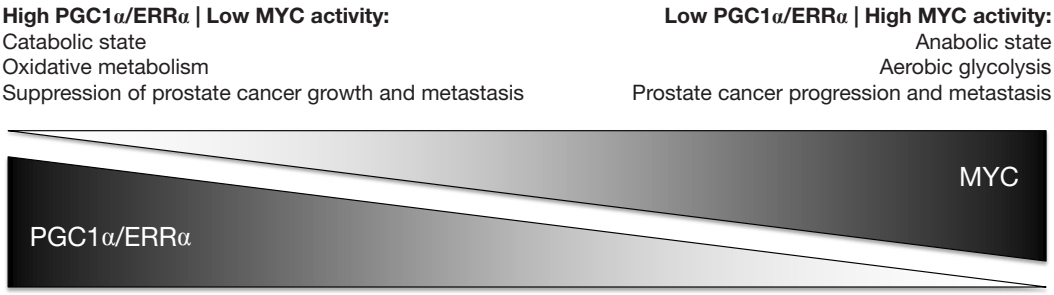

Figure 1 PGC1α/ERRα and MYC expression are inversely related to each other and control prostate cancer progression by metabolic rewiring.

receptors, have been implicated in metabolic regulation, are involved in prostate and breast cancer biology, and often exert opposing biological effects (9). A number of natural phytoestrogens have ERR-activating properties and could serve as lead compounds for the development of potent and specific ERRα agonists with potential anti-prostate cancer properties (9). Yet, are the findings by Torrano *et al*. compelling enough to consider PGC1α/ERRα activation as a novel treatment strategy for prostate cancer? Fittingly, the authors are cautious with the interpretation of their results.

The importance of metabolic rewiring for malignant growth in general, and the role of the PGC1 co-activator and ERR transcription factor families for oncogenic metabolic reprogramming in particular, are widely recognized (7,10). However, the consequences of PGC1/ERR signaling are highly context-dependent. Torrano *et al*. describe prostate cancer suppressive PGC1α/ERRα activities. Conversely, the expression of PGC1α/ERRα has been associated with tumor promoting properties in prostate and other cancers by others. As an example, Fradet *et al*. showed that ERRα promotes prostate cancer progression in bone (11). Although the opposing conclusions of the Torrano and Fradet studies are not easily reconciled, one notes that the anti-metastatic consequences of inducing PGC1α expression in PC-3 prostate cancer cells in the study by Torrano *et al*. are more pronounced regarding visceral (i.e., lung) than bone metastases (8). Could it be that the role of PGC1α/ERRα signaling is not only tumor type dependent, but also dependent on the organ site of metastasis?

Although a PGC1α/ERRα activation strategy may be particularly promising in tumors with low PGC1α and/or ERRα activity, it is currently not known how frequently such a constellation would exist in prostate cancer. Copy number alterations or mutations of PGC1α and ERRα are rarely found in prostate adenocarcinomas, and therefore are unlikely genetic driver aberrations (*Table 1*) (4,5). Indeed, PGC1α deletion alone was not found to initiate prostate carcinogenesis in the study by Torrano *et al*. (8). On the other hand, the PGC1α transcriptional network is under the control of MYC, a master regulator of cancer cell metabolism (12). MYC and PGC1α expression are inversely related to each other (*Figure 1*) (13,14). Intriguingly, MYC is amplified in more than 50% of neuroendocrine prostate cancers (*Table 1*), which are characterized by aggressive clinical behavior, are rarely diagnosed de novo, but are increasingly recognized as a prostate cancer phenotype in patients with inherent or acquired resistance to androgen receptor signaling inhibitors (6). Furthermore, the PC-3 prostate cancer cell line, prominently used in the study by Torrano *et al*., harbors neuroendocrine features. Thus, MYC amplification may contribute to a PGC1α low state, potentially amenable to a PGC1α/ERRα activation strategy, and may serve as a predictive marker for such a treatment approach.

In summary, the findings by Torrano *et al*. identify the PGC1α/ERRα transcriptional network as one of only few well-defined molecular mechanisms of prostate cancer metastasis. Accounting for the opposing biological functions attributed to PGC1α and ERRα in different tumor models, the study by Torrano *et al*. serves as an invaluable starting point to obtain a more detailed picture of the complex interplay between tumor cell metabolism and prostate cancer metastasis. Only time will tell if PGC1α/ERRα modulation will become a strategy to treat prostate cancer. The latter may apply especially to neuroendocrine prostate cancers, an area of increasing therapeutic need, due to the widespread use of second-generation androgen receptor

Table 1 Genetic alterations of PPARGC1A, ESRRA and MYC in prostate cancer

Data set	TCGA†	SU2C†	NEPC†
Tumor stage	Primary prostate cancer	Advanced prostate cancer	Neuroendocrine prostate cancer
Number of patients	N=333	N=150	N=77
Amplifications (%)			
PPARGC1A	0.3	0	8
ESRRA	0.3	0	23
MYC	7.2	12.6	53
Deletions (%)			
PPARGC1A	0.9	1.3	0
ESRRA	0.3	0	0
MYC	0.6	0	0
Mutations (%)			
PPARGC1A	0	3.3	0
ESRRA	0	0.7	0
MYC	0	0.6	0

†, data retrieved from http://www.cbioportal.org (October 27/2016; *Sci Signal* 2013;6:pl1, *Cancer Discov* 2012;2:401-4): TCGA (*Cell* 2015;163:1011), SU2C (*Cell* 2015;161:1215), NEPC (*Nat Med* 2016;22:298).

signaling inhibitors.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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