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> “forced expression of PGC1α protected cells against PLX4720”

In the April issue of *Nature Reviews Cancer* we highlighted a paper on peroxisome proliferator-activated receptor-γ coactivator 1α (PGC1α; encoded by *PPARGC1A*) and increased oxidative metabolism in a subset of melanoma cells. Now, Rizwan Haq and colleagues have extended these findings by linking the expression of PGC1α to that of oncogenic BRAF.

The authors used published gene expression profiles of melanomas with mutant BRAF that had been treated with vemurafenib, an inhibitor of BRAF-V600E, to look for genes that had altered expression levels after treatment. The expression of genes involved in the citric acid (also known as Krebs) cycle and oxidative phosphorylation and ATP generation was increased, and these findings were supported by quantitative PCR analyses in three melanoma cell lines. Moreover, treatment of these cell lines with PLX4720 (the preclinical analogue of vemurafenib) showed that loss of BRAF activity induced an increase in the numbers of mitochondria and their activity, and decreased lactate production (indicative of increased oxidative phosphorylation), but these effects were not evident in a BRAF wild-type cell line. Further experiments showed that BRAF-V600E suppressed the expression of *PPARGC1A*, a regulator of mitochondrial metabolism, and treatment of BRAF-mutant melanoma cell lines with PLX4720 increased the expression of PGC1α. The effect of BRAF-V600E on PGC1α seems to occur as a result of increased MEK–ERK signalling, as an inhibitor of MEK, PD0325901, also increased *PPARGC1A* mRNA levels. Interestingly, the link between oncogenic BRAF and PGC1α was not evident in colon cancer cell lines with mutant BRAF, nor was it apparent in microarray data from breast, lung and colon cancers treated with PD0325901, indicating a lineage-specific effect. Consistent with this, the authors found that the expression of PGC1α correlated with that of microphthalmia-associated transcription factor (MITF), the expression of which is limited to the melanocytic lineage. *In silico* analyses and chromatin immunoprecipitation and luciferase reporter assays showed that MITF binds to the *PPARGC1A* promoter and that increased expression of PCG1α is absent in cells in which BRAF-V600E is inhibited by PLX4720 and in which MITF expression is knocked down.

MITF is amplified in 30% of melanomas, and melanomas that had high expression levels of genes involved in oxidative phosphorylation also had increased expression levels of MITF. Moreover, MITF expression correlated with PGC1α-regulated gene expression. A comparison of immortalized human melanocytic isogenic cell lines that expressed BRAF-V600E and that only differed in their expression of MITF showed that MITF protects against reduced ATP generation when BRAF-V600E is inhibited. Moreover, the isogenic cells expressing MITF were more sensitive to a mitochondrial uncoupling agent.

Using eight patient-derived melanoma cell lines the authors also found that PGC1α was induced after treatment with vemurafenib and ATP levels responded accordingly; however, the magnitude of these responses varied considerably between the cell lines. High levels of PGC1α are associated with a poor prognosis, and the authors found that forced expression of PGC1α protected cells against PLX4720, and that sensitivity to PLX4720 increased when this drug was combined with a mitochondrial uncoupler.

These findings indicate that the increased expression of MITF and PGC1α represents an adaptive metabolic response that limits sensitivity to BRAF inhibitors.

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ORIGINAL RESEARCH PAPER Haq, R. *et al.* Oncogenic BRAF regulates oxidative metabolism via PGC1α and MITF. *Cancer Cell* **23**, 302–315 (2013)
FURTHER READING Vazquez, F. *et al.* PGC1α expression defines a subset of human melanoma tumors with increased mitochondrial capacity and resistance to oxidative stress. *Cancer Cell* **23**, 287–301 (2013) | McCarthy, N. Horses for courses. *Nature Rev. Cancer* **13**, 222 (2013)