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MELANOMA

Horses for courses

GETTY

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The ability of cancer cells to adapt to changes in their microenvironment is likely to be crucial for tumour progression, and metabolic changes are seen as being important facilitators of this process. Pere Puigserver and colleagues have looked at metabolic adaptations in melanoma cell lines and found that differences in the expression level of peroxisome proliferator-activated receptor-γ coactivator 1α (PGC1α; encoded by *PPARGC1A*) are associated with modifications in melanoma metabolism.

PGC1α expression is induced in response to increases in metabolic demand, but whether this regulator of mitochondrial function and reactive oxygen species (ROS) generation is also activated by oncogenic signals is unclear. To answer this question, the authors examined mRNA expression levels of *PPARGC1A* in publicly available gene expression databases. They found that melanoma samples and melanoma cell lines could be split into two groups: those with high levels of PGC1α expression and those with low or undetectable levels. Moreover, high expression of PGC1α was associated with poor survival in patients with melanoma. Gene set enrichment analyses showed that increased expression of PGC1α was associated with an increase in the expression of mitochondrial genes and genes involved in energy generation. Further analyses of the Riker melanoma data set and additional experiments indicated that PGC1α expression was associated with and caused by the expression of microphthalmia-associated transcription factor (MITF), which is a known melanoma oncogene.

So, what metabolic effect does PGC1α expression have on melanoma cells? The authors found that PGC1α-negative melanoma cell lines have a glycolytic phenotype and produce high levels of lactate, whereas cell lines expressing PGC1α have increased oxygen consumption and increased levels of mitochondrial oxidative metabolism. Short hairpin RNAs (shRNAs) targeting PGC1α resulted in the induction of apoptosis in PGC1α-positive cells, indicating that these cells are dependent on the metabolic effects of PGC1α for survival. Loss of PGC1α resulted in the reduced expression of genes involved in ROS detoxification and increased levels of ROS. Indeed, several agents that are known to induce cell death through the induction of ROS were able to kill PGC1α-negative, but not PGC1α-positive, cell lines unless the levels of PGC1α were reduced.

These findings indicate that PGC1α expression levels are associated with metabolic differences in melanoma cells that might be therapeutically exploitable.

Nicola McCarthy

ORIGINAL RESEARCH PAPER Vazquez, F. *et al.* PGC1α expression defines a subset of human melanoma tumors with increased mitochondrial capacity and resistance to oxidative stress. *Cancer Cell* 14 Feb 2013 (doi:10.1016/j.ccr.2012.11.020)

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