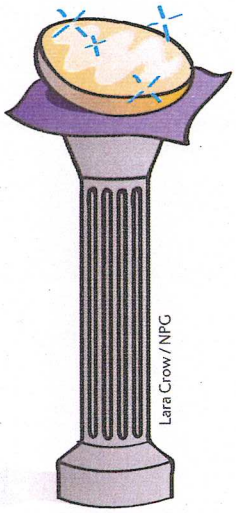
METABOLISM

The mitochondria thief

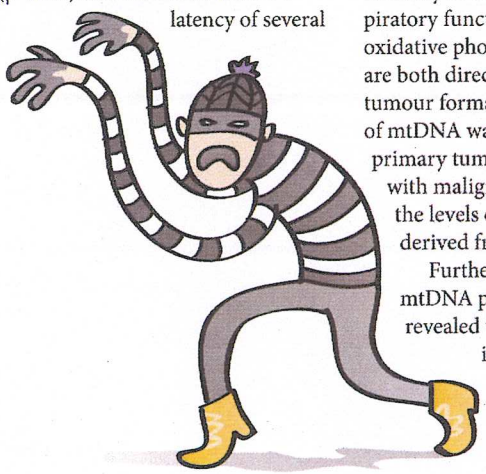
> ρ° cells acquire mitochondria from the host to restore their metabolic capacities to a 'threshold' level that enables them to form tumours



Lara Crow / NPG

Cancer is characterized by altered energy metabolism, which is triggered by genetic alterations not only in nuclear DNA but also in mitochondrial DNA (mtDNA). However, how mutations in mtDNA contribute to tumour initiation, progression and metastasis is unclear. Tan *et al.* have described that tumour cells without mtDNA show delayed tumour growth, which is then fuelled by the acquisition of mtDNA from host cells.

To analyse the contribution of mtDNA to tumorigenesis, the authors developed two stable mouse cancer cell lines (B16 melanoma and 4T1 breast carcinoma) that lacked mtDNA and investigated whether these cells could form tumours in syngeneic mice. mtDNA-null cells (ρ° cells) formed tumours with a latency of several weeks compared to parental controls that contained mtDNA. However, once the delayed tumours emerged, they progressed almost as rapidly as tumours derived from parental cells. The authors then established cell cultures from ρ° cell-derived tumours at different stages of tumour progression: primary tumours, circulating tumour cells and lung metastases. When these different cell cultures were subsequently injected into syngeneic mice, they formed tumours with different latencies; tumours originating from lung metastasis cultures grew faster than those originating from circulating tumour cells, which in turn grew faster than those from primary tumours. Furthermore, these tumours also showed gradual recovery of mitochondrial respiratory function and restoration of oxidative phosphorylation, which are both directly linked to efficient tumour formation. The abundance of mtDNA was highly elevated in primary tumours but decreased with malignant progression to the levels observed in tumours derived from parental cells.



Further experiments and mtDNA polymorphism studies revealed that mtDNA contained in these tumours was not amplified from residual mtDNA from the original cancer cell line but was instead acquired from the host cells in the tumour microenvironment.

How can mtDNA be transferred from the host cells to the tumour cells? To address this question, the authors investigated the phenotypic and morphological properties of the mitochondria in tumour-derived cultures and found that they were different in morphology, structure and content of cristae membranes, as well as in many metabolic and biochemical properties, compared with the mitochondria in ρ° cells. In fact, mitochondria in cell cultures derived from lung metastases resembled those in parental cells. These observations — together with the fact that there is no known mechanism for intercellular transfer of mtDNA across mitochondrial membranes and the plasma membrane — led the authors to hypothesize that transfer of whole mitochondria between the microenvironment and the tumour cells is the most likely explanation. Therefore, ρ° cells acquire mitochondria from the host to restore their metabolic capacities to a 'threshold' level that enables them to form tumours.

These results show that mitochondrial respiration is required for tumour progression and highlight the ability of tumours to overcome unfavourable circumstances, further confirming their high level of plasticity.

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ORIGINAL RESEARCH PAPER Tan, A. S. *et al.* Mitochondrial genome acquisition restores respiratory function and tumorigenic potential of cancer cells without mitochondrial DNA. *Cell Metab.* **21**, 81–94 (2015)