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Short Communication

Horizontal mitochondrial transfer and dihydroorotate dehydrogenase function in recovery of tumorigenic capacity in mtDNA deficient cancer cells

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Abstract

Recently, we showed that cancer cells devoid of mitochondrial DNA (mtDNA) refered to as ⍰0 cells recover their tumour formation ability in syngeneic mice only after the acquisition of the host mtDNA.1 Thus, ⍰0 cancer cells are unable to form tumour unless mitochondria with mtDNA are acquired from normal cells in the tumour microenvironment to reconstitute their respiratory function.2 Therefore, mtDNA and mitochondrial respiration is needed for tumorigenesis.

We explored the functional consequences of horizontal transfer of mitochondria, and found that pyrimidine biosynthesis, which is dependent on respiration-linked dihydroorotate dehydrogenase (DHODH), is essential for overcoming cell-cycle arrest and hence for promotion of tumour formation3. DHODH is present and primed in mtDNA-devoid cells, and it is fully re-activated by complex III/IV respiration and coenzyme Q (CoQ) redox-cycling recovered as a consequence of mitochondrial transfer. Moreover, respiration recovery, which is necessary for tumour cell proliferation allowing for tumour formation and progression, is associated with efficient de novo pyrimidine synthesis. We propose that re-activation of DHODH, a rate-limiting enzyme in the de novo pyrimidine synthesis, is the key event for triggering tumour growth following horizontal transfer of mitochondria into mtDNA-compromised cancer cells and that it is intimately linked to mitochondrial respiration.

We therefore propose that DHODH is the critical link between de novo pyrimidine synthesis and respiration. We conclude that the CIII/CIV-CoQ-DHODH axis is the major promoter of tumour formation, making DHODH a potential broad-spectrum target for cancer therapy.

Biography:

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