WHY DO CANCER CELLS WITH DAMAGED MITOCHONDRIAL DNA STEAL MITOCHONDRIA FROM THE STROMA?

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Cancer cells without mitochondrial DNA (mtDNA) do not form tumors unless they reconstitute oxidative phosphorylation (OXPHOS) by mitochondria acquired from host stroma. To understand why functional respiration is crucial for tumorigenesis, we used time-resolved analysis of tumor formation by mtDNA-depleted cells and genetic manipulations of OXPHOS. We show that pyrimidine biosynthesis dependent on respiration-linked dihydroorotate dehydrogenase (DHODH) is required to overcome cell-cycle arrest, while mitochondrial ATP generation is dispensable for tumorigenesis. Latent DHODH in mtDNA-deficient cells is fully activated with restoration of complex III/IV activity and coenzyme Q redox-cycling after mitochondrial transfer, or by introduction of an alternative oxidase. Further, deletion of DHODH interferes with tumor formation in cells with fully functional OXPHOS, while disruption of mitochondrial ATP synthase has little effect. Our results show that DHODH-driven pyrimidine biosynthesis is an essential pathway linking respiration to tumorigenesis, pointing to inhibitors of DHODH as potential anti-cancer agents.