

Mitochondrial DNA mutations in ageing and cancer - What's the connection?

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Alterations in mitochondrial metabolism are major hallmarks of both ageing cells and cancer. Age is the biggest risk factor for the development of a significant number of cancer types and this therefore raises the question of whether there is a link between age-related mitochondrial dysfunction and the advantageous changes in mitochondrial metabolism prevalent in cancer cells. A common underlying feature of both ageing and cancer cells is the presence of somatic mutations of the mitochondrial genome (mtDNA). MtDNA mutations are particularly enriched in colorectal cancers (Gorelick et al. (2021) *Nat Metab* 3: 558-570), and we have previously shown that individual normal human colonic crypt stem cells also accumulate somatic mtDNA point mutations with age (Greaves et al. (2010) *Exp Gerontol* 45: 573-579). This shows that somatic mtDNA mutations and altered metabolic pathways are present in colonic crypts prior to malignant transformation, suggesting that mtDNA mutations may either increase the risk of malignant transformation, promote tumour progression, or are selectively propagated during tumour development. To investigate this we generated a mouse model in which we induced tumours specifically in intestinal stem cells with and without mtDNA mutation-induced mitochondrial dysfunction. We found that the mice with mitochondrial dysfunction had similar numbers of tumours to controls but they were growing significantly faster resulting in a shortened lifespan (Smith et al. (2020) *Nature Cancer* 1: 976-989). Multi-omics analysis revealed the underlying mechanism to be an upregulation of the de novo serine synthesis pathway and mitochondrial one-carbon metabolism in response to mitochondrial dysfunction. These anabolic pathways are important regulators of cellular biomass production and, excitingly, may represent metabolic vulnerabilities for therapeutic exploitation in human colorectal cancer.

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