Abstract

Mitochondria are essential organelles as they produce most ATP to support cellular activities, synthesize critical metabolic factors and are involved in lipid and phospholipid metabolism as well as calcium signalling. The oxidative phosphorylation (OXPHOS) system, present at the inner mitochondrial membrane, plays role in regulation of cellular metabolism and survival of cancer cells. Recent studies show importance of OXPHOS in growth of cancer cells via regulation of the *de novo* pyrimidine synthesis pathway. Dihydroorotate dehydrogenase (DHODH), a flavoprotein localized in the inner mitochondrial membrane, converts dihydroorotate (DHO) to orotate within the *de novo* pyrimidine synthesis pathway, generating electrons that are transferred, via redox-cycling of ubiquinone, to complex III (CIII) of respiratory chain. Since DHODH is functionally linked to CIII activity, impairment of respiration results in reduced activity of DHODH and pyrimidine synthesis. Therefore, mitochondrial damage or mutation in mitochondrial DNA (mtDNA) leads to decreased respiration, cancer cell proliferation and delay of tumour growth.

As a compensation for damaged mitochondria, horizontal transfer of functional mitochondria from donor somatic cells to the mitochondria-damaged tumour cells was demonstrated. This mitochondrial renewal leads to tumour progression dependent on respiration recovery. *In vivo* transfer of mitochondria from donor cells to mtDNA-damaged tumour cells has been described in mouse models of melanoma and mammary tumours. It can be mediated by different mechanisms including extracellular microvesicles, cytoplasmic fusion or gap junctions. Another mechanism, described *in vitro* on the model of 4T1 breast cancer cells and B16 melanoma cells, is to transfer mitochondria through highly sensitive *de novo* formed nanotube structures between cells, representing complex networks described as tunnelling nanotubes (TNT).

Using tumour cells with depleted mitochondria (rho0 cells) this work confirmed the essential role of mitochondrial transfer from donor cells in respiration recovery and tumour formation initiation. This work also clarifies the role of TNTs in the horizontal mitochondrial transfer as well as the properties of such way of transfer.