Abstract

Mitochondria are found in nearly all eukaryotic cells, serving as energy producers and key regulators of metabolic pathways, such as the tricarboxylic acid (TCA) cycle and oxidative phosphorylation (OXPHOS). Their role goes beyond energy metabolism, as they are important for cell signalling, redox homeostasis, and apoptosis, i.e. processes vital for cellular growth, adaptation, and survival. Central to mitochondrial function is complex II (CII), also referred to as succinate dehydrogenase (SDH), which uniquely connects the TCA cycle with the electron transport chain (ETC) by facilitating electron transfer while regulating succinate and fumarate, metabolites with important signalling effects. Alterations in CII, both in its structure, function and assembly, have been increasingly implicated in various cancers.

Renal cell carcinoma (RCC) and pheochromocytoma/paraganglioma (PPGL) are two types of cancer where mitochondrial dysfunction, particularly involving CII, has emerged as a distinctive hallmark. RCC, notably in its clear cell subtype (ccRCC), exhibits unique metabolic reprogramming that contributes to its aggressive phenotype and resistance to conventional treatments. PPGLs, while less common, present distinct metabolic challenges in the clinical setting due to frequent genetic mutations impacting mitochondrial function. These types of cancer share similarities in their dependence on mitochondrial metabolism, but they also show unique mitochondrial alterations that may inform subtype-specific therapies.

In this study, we explore the role of CII in the metabolic changes of RCC subtypes. Using patient tumour samples, this work reveals that ccRCC tumours display significantly reduced mitochondrial DNA (mtDNA), protein content, and CII activity, all of which support a shift to glycolysis, a hallmark adaptation in ccRCC that fuels its proliferation under hypoxic conditions. In contrast, papillary (pRCC) and chromophobe (chRCC) RCC subtypes retain mitochondrial features similar to healthy kidney tissue. This subtype-specific mitochondrial profile emphasizes the potential of CII as both a biomarker and a therapeutic target in RCC, as its impaired function is linked to the aggressive behaviour of ccRCC.

Moreover, our further investigation complements these findings by providing deeper insights into the details of CII assembly. Using a PPGL cell line, this research has identified the critical roles of SDHAF2 and SDHAF4 assembly factors in SDHA subunit maturation. In knockout models, loss of SDHAF4 leads to abnormal CII assembly, reduced succinate dehydrogenase activity, and excessive succinate accumulation. This mechanistic insight into CII assembly is crucial for understanding how defects in assembly factor function could drive mitochondrial and metabolic abnormalities in tumours with CII dysfunction.

Together, these studies enhance our understanding of the diverse roles of CII in cancer metabolism and assembly, revealing CII as a key metabolic regulator. By linking structural and functional aberrations in CII to specific cancer subtypes, this research will support the development and deeper understanding of mitochondrial-targeted therapies, such as the mitochondria-specific agent MitoTam. As mitochondrial dysfunction and metabolic reprogramming remain central points in cancer biology, the findings of these studies contribute valuable insights into therapeutic strategies for targeting mitochondrial integrity and metabolism in renal and adrenal cancers.