# Ecological effects of mitochondrial dysfunction in pancreatic cancer

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Tumors can be described as evolving ecosystems, where cancer cells act as invasive species that increase their fitness compared to non-tumoral cells. In this framework, ecological fitness refers to the ability of tumor cells to survive, proliferate, evolve within the TME, and adapt to selective pressures. One of the most aggressive and early metastatic neoplasia is the pancreatic ductal adenocarcinoma (PDAC), the most common type of pancreatic cancer, known for its high mortality rate and poor prognosis. In the fitness of PDAC cells, mitochondrial metabolism plays a fundamental role. Indeed, dysfunctions in metabolic pathways lead to alterations in tumor progression and therapeutic resistance.

We investigated how mitochondrial dysfunction affects the ecological fitness of PDAC cells by silencing *NDUFS3*, a gene coding for an essential subunit of mitochondrial complex I, in YAPC and MIA PaCa-2 cell lines. Decreased levels of NDUFS3 affected mitochondrial function and led to reduced proliferation, migration, and invasion. These functional effects were associated with a less aggressive phenotype.

From an ecological-evolutionary perspective, our results reflect how mitochondrial dysfunctions introduce an energetic impairment that modifies cancer cell behavior. Interpreting these findings through the lens of ***Resource Allocation Theory***, less energy availability may obligate a redistribution of resources in the cell, reducing investment in invasion and survival. Therefore, according to ***Performance Theory***, these mitochondrial dysfunctions may be translated into lower ecological fitness, making tumor cells less competitive.

Overall, mitochondrial alterations emerge as a vulnerability of PDAC cells, suggesting that targeting mitochondrial metabolism could represent a strategy to decrease cancer cell fitness, limiting tumor progression and opening new therapeutic perspectives.

**Keywords: pancreatic cancer, ecological fitness, metabolic dysfunction.**