Mitochondrial function and cancer

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In addition to compartmentalizing the metabolic pathways and physiological states of the cell, mitochondria generate much of the cellular energy, regulate the cellular oxidation-reduction (redox) state, produce most of the cellular reactive oxygen species (ROS), buffer cellular Ca²⁺ and initiate cellular apoptosis. Mitochondria were first proposed to be relevant to cancer by Otto Warburg who reported that cancer cells exhibited "aerobic glycolysis." Although this was originally interpreted as indicating that the function of the mitochondria was defective, we now understand that cancer cells are in an altered metabolic state with increased glycolytic metabolism and the continued use of oxygen. Mutations that occur in nuclear-DNA-encoded mitochondrial proteins and mitochondrial-DNA-encoded proteins can re-orient cellular metabolism towards glycolysis, glutaminolysis, intense macro molecular biogenesis and the oxidation-reduction of NAD⁺ to NADPH. Both somatic and germline mitochondrial DNA mutations have been associated with many types of cancers, and recent data indicate that cancer cells may tolerate mitochondrial DNA mutations for two purposes: they alter cancer cell metabolism and/or proliferation and they enable adaption to a changing environment.

Altered energetics

Activation of the PI3K–AKT pathway increases glucose uptake and metabolism. AKT phosphorylates and inactivates FOXO3A, which induces stress-response genes including HMOX1, which degrades haem to bilirubin.

Induction of mitophagy

Inhibition of PDH

Glutaminolysis

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• Increased glucose uptake and metabolism

• Reduced mitochondrial DNA copy number and transient increases in mitochondrial terminal oxidase 3 (MT-III)

• Reduction of ROS levels and increased cell viability

• Acetyl-CoA

• Deregulation of HIF1α

• Proteins that are involved in the Warburg effect include HK2, hexokinase 2; HK1, hexokinase 1; PDK1, pyruvate dehydrogenase kinase 1; PKM1, pyruvate kinase M1 isozyme; PKM2, pyruvate kinase M2 isozyme; and PKM3, pyruvate kinase M3 isozyme. These enzymes are involved in the Warburg effect and are regulated by HK2, which stimulates HK2 activity and reduces the activity of HK1 and PKM1, which is regulated by HK2.

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