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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 Ca^{2+} 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 macromolecular biogenesis and the oxidoreduction of $NADP^+$ 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 FOXO, downregulating PGC1α and reducing mitochondrial biogenesis. Activation of MYC induces glutaminolysis, in which glutamine is converted to α-ketoglutarate (αKG). Reductive carboxylation of αKG to isocitrate can be facilitated by NADPH-linked IDH2, resulting in increased citrate synthesis. Mitochondrial citrate can be exported into the cytosol, where isocitrate can be converted to αKG by $NADP^+$-linked IDH1. Mutant IDH1 or IDH2 oxidize NADPH back to $NADP^+$ and reduce αKG to *R*(–)-2-hydroxyglutarate ((*R*)-2HG), an oncometabolite that affects DNA and histone methylation and HIF1α activity. SDH mutations disrupt the TCA cycle causing the accumulation of succinate and perhaps also increased ROS production. FH mutation causes the accumulation of succinate and fumarate, both of which can inhibit prolyl hydroxylases (PHDs) and stabilize HIF1α. In addition, fumarate can succinylate and inactivate KEAP1, resulting in the activation of NRF2. This induces stress-response genes including HMOX1, which degrades haem to bilirubin. This removes excess succinyl-CoA by condensation with glycine to generate δ-aminolevulinic acid (δALA), the commitment step of haem biosynthesis. Mutated enzymes are shown in orange.

Redox regulation

Nicotinamide nucleotide transhydrogenase (NNT) uses the energy of the mitochondrial membrane potential to transfer reducing equivalents from $NADP^+$ to NADPH. The increased reducing potential of NADPH is then used to reduce oxidized glutathione for the reduction of H_2O_2 to H_2O, change the thiol-disulfide balance of amino acids in proteins to regulate transcription factors and enzymes, and to drive macromolecular synthesis.

Cytosolic NADPH can be generated by the pentose phosphate shunt, by the conversion of malate to pyruvate and by the action of IDH1. Alteration of these pathways can increase ROS levels and alter cellular metabolism and growth.

Go with the flow

- Aerobic glycolysis in cancer cells is accompanied by the switch from pyruvate kinase isoform M1 (PKM1) to PKM2, which is regulated by growth factors and tyrosine phosphorylation. When oxidative stress in low, PKM2 is active and glucose is metabolized through phosphoenolpyruvate and pyruvate to lactate to generate ATP. However, when oxidative stress is high, PMK2 activity is reduced driving G6P into the pentose phosphate pathway to generate NADPH and bolstering antioxidant defences.
- For the cancer cell to generate the carbon backbones for macromolecular synthesis, the flow of carbon must be redirected away from the mitochondrial terminal oxidizing machinery. The acetyl-CoA that is required for lipid synthesis and for modulating the epigenome and signal transduction pathways is generated from the export of citrate from the mitochondrion. In the cytosol, citrate is cleaved by ATP-dependent citrate lyase to oxaloacetate (OAA) and acetyl-CoA. The acetyl-CoA can then be used to synthesize fatty acids and lipids. However, this appropriation of citrate depletes the mitochondrion of OAA. This deficiency is compensated in many cancers by the activation of MYC that induces glutaminolysis.
- The regulation of acetyl-CoA production from glycolytic sources is also modulated by the mitochondrial protein kinase Cδ signalosome, which is composed of PKCδ, p66SHC, cytochrome *c* and retinol. This complex senses the redox status of the ETC and ultimately modulates pyruvate dehydrogenase activity to adjust the flow of acetyl-CoA and reducing equivalents into the mitochondrion.
- The promyelocytic leukaemia (PML) protein interacts with endoplasmic reticulum mitochondrially associated membranes and can inhibit Ca^{2+} release into the outer membrane cleft. This reduces mitochondrial uptake of Ca^{2+}, which stabilizes the mitochondrial permeability transition pore inhibiting apoptosis, and increases cytosolic Ca^{2+} levels.
- Reduced mitochondrial DNA copy number and other types of mitochondrial stress can activate the mitochondrial retrograde signalling pathway through a reduction in the mitochondrial membrane potential. This results in increased cytosolic Ca^{2+} levels, activation of calcineurin and NF-κB, and activation of the nuclear enhanceosome, which upregulates proteins involved in Ca^{2+} regulation, tumorigenesis and invasive growth (not shown).

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Abbreviations
ANT; adenine nucleotide transporter; CHCHD4, coiled-coil-helix–coiled-coil-helix domain-containing protein 4; CoQ, coenzyme Q; COX, cyctochrome *c* oxidase; Cu–ZnSOD, copper–zinc superoxide dismutase; Cyt *c*, cytochrome *c*; ETC, electron transport chain; FH, Fumarate hydratase; G6P, glucose 6-phosphate; GLUT1, glucose transporter 1; GSH, reduced glutathione; HIF1α, hypoxia-inducible factor 1α; HMOX1, haemoxygenase 1; IDH, isocitrate dehydrogenase; KEAP1; kelch-like ECH-associated protein 1; LDHA, lactate dehyrogenase A; LKB1, liver kinase B1; MnSOD, manganese superoxide dismutase; NNT, nicotinamide nucleotide transhydrogenase; NRF2, nuclear factor erythroid related factor 2; PDH, pyruvate dehydrogenase; PGC1α, peroxisome proliferator-activated receptor-γ coactivator 1α; ROS, reactive oxygen species; SCL1A5, solute carrier family 1 (neutral amino acid transporter) member 5; SDH, succinate dehydrogenase TIGAR, TP53-induced glycolysis and apoptosis regulator; TRX, thioredoxin; TSC1, hamartin; TSC2, tuberin; VDAC, voltage-dependent anion channel.

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