

## Mitochondrial function and cancer

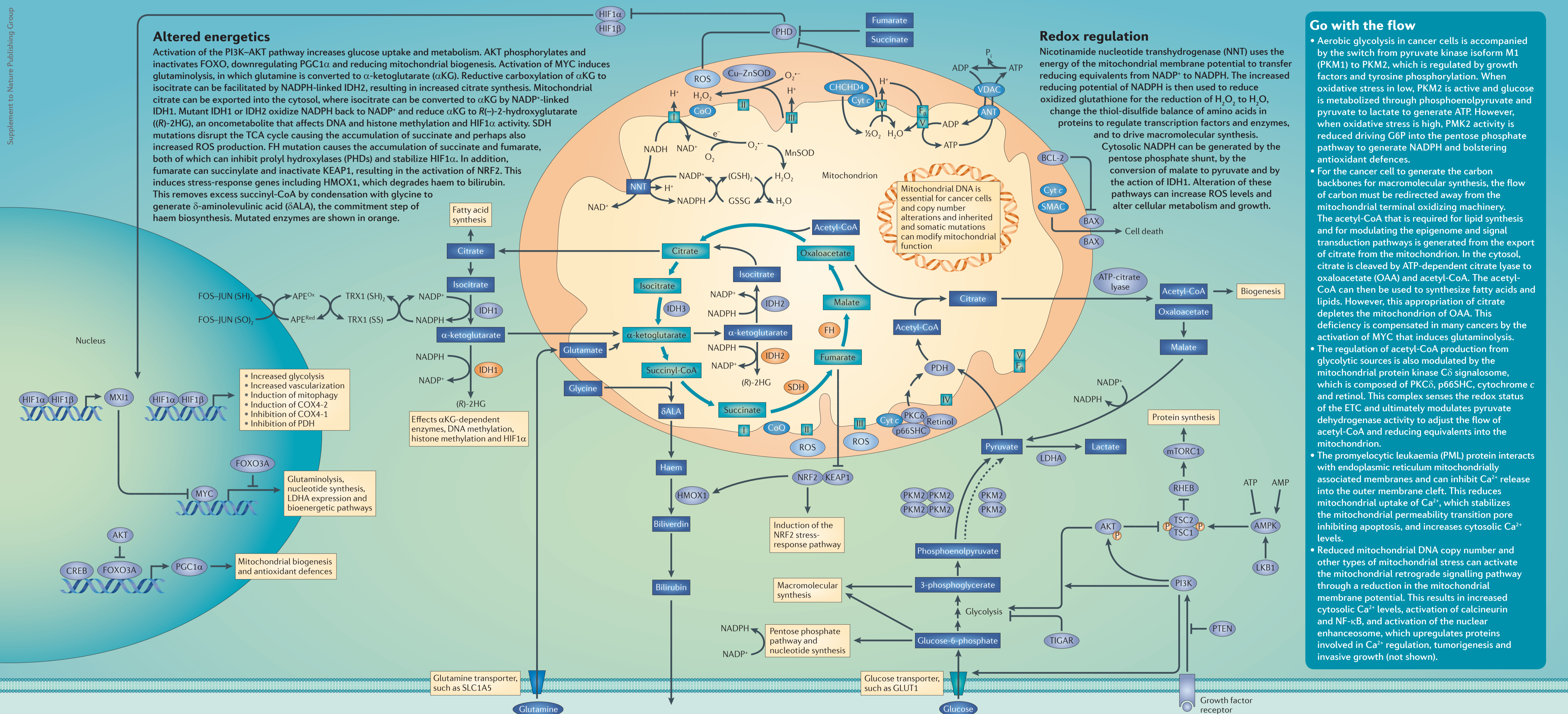
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In addition to compartmentalizing the metabolic pathways and physiological states of the cell, mitochondria generate much of the cellular energy, regulate the cellular oxidation–reduction (redox) state, produce most of the cellular reactive oxygen species (ROS), buffer cellular  $\text{Ca}^{2+}$  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  $\text{NADP}^+$  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 PGC1 $\alpha$  and reducing mitochondrial biogenesis. Activation of MYC induces glutaminolysis, in which glutamine is converted to  $\alpha$ -ketoglutarate ( $\alpha$ KG). Reductive carboxylation of  $\alpha$ KG 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  $\alpha$ KG by NADP<sup>+</sup>-linked IDH1. Mutant IDH1 or IDH2 oxidize NADPH back to NADP<sup>+</sup> and reduce  $\alpha$ KG to R(–)-2-hydroxyglutarate ((R)-2HG), an oncometabolite that affects DNA and histone methylation and HIF1 $\alpha$  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 HIF1 $\alpha$ . 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  $\delta$ -aminolevulinic acid ( $\delta$ ALA), the commitment step of haem biosynthesis. Mutated enzymes are shown in orange.



## 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 is low, PKM2 is active and glucose is metabolized through phosphoenolpyruvate and pyruvate to lactate to generate ATP. However, when oxidative stress is high, PKM2 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 C $\delta$  signalosome, which is composed of PKC $\delta$ , 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  $\text{Ca}^{2+}$  release into the outer membrane cleft. This reduces mitochondrial uptake of  $\text{Ca}^{2+}$ , which stabilizes the mitochondrial permeability transition pore inhibiting apoptosis, and increases cytosolic  $\text{Ca}^{2+}$  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  $\text{Ca}^{2+}$  levels, activation of calcineurin and NF- $\kappa$ B, and activation of the nuclear enhancosome, which upregulates proteins involved in  $\text{Ca}^{2+}$  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, cytochrome 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; HIF1 $\alpha$ , hypoxia-inducible factor 1 $\alpha$ ; HMOX1, haemoxygenase 1; IDH, isocitrate dehydrogenase; KEAP1, kelch-like ECH-associated protein 1; LDHA, lactate dehydrogenase A; LKB1, liver kinase B1; MnSOD, manganese superoxide dismutase; NNT, nicotinamide nucleotide

transhydrogenase; NRF2, nuclear factor erythroid related factor 2; PDH, pyruvate dehydrogenase; PGC1 $\alpha$ , peroxisome proliferator-activated receptor- $\gamma$  coactivator 1 $\alpha$ ; ROS, reactive oxygen species; SLC1A5, 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, tuberlin; VDAC, voltage-dependent anion channel.

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