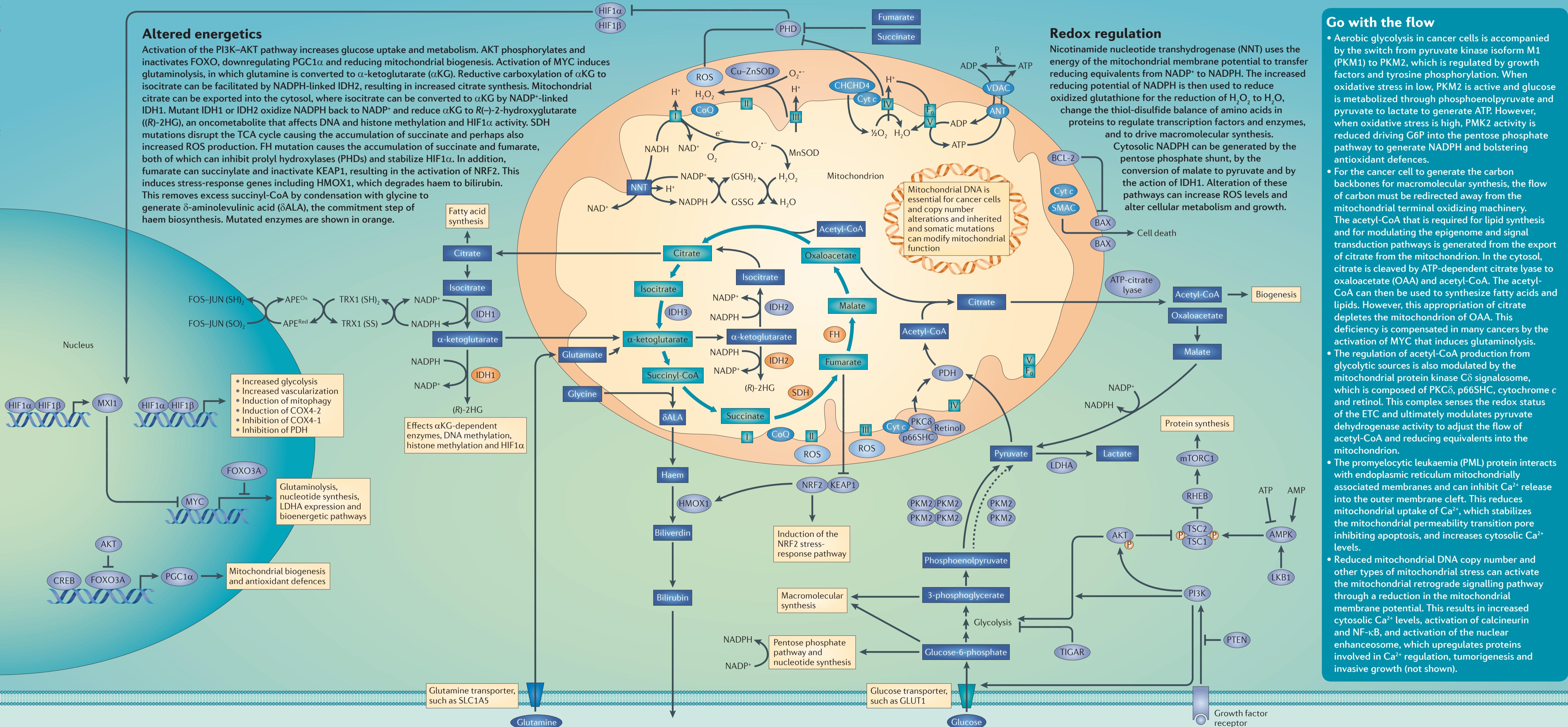


In addition to compartmentalizing the metabolic pathways and physiological states of the cell, mitochondria generate much of the cellular energy, regulate the cellular oxidation-reduction (redox) state, produce most of the cellular reactive oxygen species (ROS), buffer cellular Ca^{2+} and initiate cellular 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.



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Abbreviations

- ANT; adenine nucleotide transporter; CHCHD4, coiled-coil-helix-coiled-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 α , hypoxia-inducible factor 1 α ; HMOX1, haemoxigenase 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 α , peroxisome proliferator-activated receptor- γ coactivator 1 α ; 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, tuberin; VDAC, voltage-dependent anion channel.

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