Review

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Special Focus – Metabolism

Mitochondrial oxidative phosphorylation TRAP(1)ped in tumor cells

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Many tumors undergo a dramatic metabolic shift known as the Warburg effect in which glucose utilization is favored and oxidative phosphorylation is downregulated, even when oxygen availability is plentiful. However, the mechanistic basis for this switch has remained unclear. Recently several independent groups identified tumor necrosis factor receptor-associated protein 1 (TRAP1), a mitochondrial molecular chaperone of the heat shock protein 90 (Hsp90) family, as a key modulator of mitochondrial respiration. Although all reports agree that this activity of TRAP1 has important implications for neoplastic progression, data from the different groups only partially overlap, suggesting that TRAP1 may have complex and possibly contextual effects on tumorigenesis. In this review we analyze these recent findings and attempt to reconcile these observations.

Mitochondrial bioenergetics in tumor cells

Neoplasms profoundly reorganize their core metabolism to sustain growth in a dynamic environment where oxygen and nutrients are often limiting [1,2]. Glycolysis is elevated in many cancers and is uncoupled from oxygen availability (the Warburg effect) [3–6], favoring cancer cell growth under hypoxic conditions found in the interior of the tumor mass [3]. The enhanced use of glucose confers further advantages to neoplasms, providing essential intermediates for cell growth and proliferation by funneling metabolites into the pentose phosphate pathway (PPP) [7–9] and causes lactate efflux into the tumor microenvironment, which decreases extracellular pH and enhances the activity of several proinvasive factors [10,11]. Moreover, PPP induction contributes to the reinforcement of antioxidant defenses through the synthesis of NADPH, a key component of reactive oxygen species (ROS) scavenging systems [12], thus helping tumors face fluctuations in their redox equilibrium, which could be lethal [13].

Concomitant with upregulation of glycolysis, most tumor cells undergo a decrease in mitochondrial respiration, which could be secondary to upregulated glycolysis or brought about by tumor suppressor inactivation or oncogene activation [14–17]. Oxidative phosphorylation (OXPHOS) can be directly curtailed in tumor cells by increased glycolysis (the Crabtree effect) [18,19], via activation of the phosphoinositide 3-kinase (PI3K)/Akt pathway, activation of the transcription factors c-Myc [20] and hypoxia-inducible factor 1 (HIF1) [21,22], or inactivation of p53 [23]. In cancer cells, the interplay between deregulated signal transduction and changes in mitochondrial metabolism is complex and multifaceted. For example, c-Myc is a master anabolic inducer that triggers mitochondrial biogenesis, increases synthesis of acetyl-coenzyme A (CoA) (which contributes to histone acetylation and lipid biosynthesis), and stimulates catabolism of glutamine, which is a primary source of energy, nitrogen, and carbon to support the biosynthetic processes of neoplastic cells [20,24].

A comprehensive dissection of mitochondrial changes in tumor cells is beyond the scope of this review and several excellent papers can be found on this topic (e.g.,[9,10,25–30]. Here we propose the possibility that modulation of normal mitochondrial function can itself be a general activator of tumorigenesis. Recent observations suggest a key role for mitochondria in the tumorigenic process, mainly through genetic alterations in their bioenergetic machinery. Inactivating mutations of the tricarboxylic acid cycle (TCA) genes encoding succinate dehydrogenase (SDH) and fumarate hydratase (FH) are oncogenic [17,27] and contribute to neoplastic transformation by promoting accumulation of succinate and fumarate, respectively, which have been termed oncometabolites for their preneoplastic effects [31]. Loss of function mutations of SDH and FH occur in a panel of tumors including paraganglioma, pheochromocytoma, some forms of renal cell carcinoma (RCC), uterine fibroids, and skin leiomyomata, making SDH and FH unique examples of mitochondrial tumor suppressor genes. Both succinate and fumarate can lead to the stabilization of HIF1 [32,33], even under normal oxygen tension (pseudohypoxia). HIF1 stabilization contributes to neoplasia by promoting

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angiogenesis, epithelial–mesenchymal transition, and metabolic changes [34,35]. In addition, fumarate can bind reactive thiols of proteins in a process called protein succination, which was recently found to modulate the activity of enzymes involved in the redox regulation of tumor cells [17]. Recently it was discovered that gain-of-function mutations of mitochondrial isocitrate dehydrogenase (IDH) 1 and 2 cause accumulation of another oncometabolite, 2-hydroxyglutarate (2HG) in glioma, chondrosarcoma, cholangiocarcinoma, and acute myeloid leukemia. 2HG affects the activity of dioxygenases, mainly histone and DNA demethylases, causing profound epigenetic changes in cancer cells [36]. Furthermore, inactivating mutations in genes encoding respiratory complex subunits are associated with oncocytomas [37] and thyroid and prostate cancers [38,39].

Taken together, these observations indicate that genetically defined mutations in enzymes involved in mitochondrial energy metabolism disrupt OXPHOS and stimulate various processes associated with neoplastic transformation. However, these mutations are restricted to specific tumor types. Recently several papers have reported that the widely expressed mitochondrial chaperone TRAP1, which has been previously implicated as an antitumor molecular target, is an important modulator of the metabolic machinery of tumor cells, suggesting a more general role of TRAP1-mediated mitochondrial bioenergetic changes in tumorigenesis. A fuller understanding of the complex actions and regulation of TRAP1 in regulating mitochondrial metabolism could provide important information on the molecular mechanisms that mediate the metabolic adaptations of tumor cells.

TRAP1: the mitochondrial Hsp90

TRAP1, also referred to as Hsp75, is a molecular chaperone of the Hsp90 family. The human *TRAP1* gene spans 60 kb and is located on chromosome 16p13. It comprises 18 exons, with 14 potential alternative transcripts and several nucleotide polymorphisms. At the protein level, it is predicted that differential splicing or amino acid changes can generate at least six major TRAP1 variants, but the biological meaning of this variability remains unclear. The main *trap1* transcript encodes a protein of 704 amino acids comprising an N-terminal mitochondrion-targeting sequence, an ATPase domain and a C-terminal chaperone domain similar to that of cytosolic Hsp90s, which suggests functional similarity between TRAP1 and Hsp90. Hsp90 is a chaperone endowed with essential functions in priming client proteins for various biological processes, including protein–protein or protein–ligand interactions, subcellular trafficking, and control of protein maturation and stability [40,41].

Given the large number of Hsp90 clients (possibly 10% of the whole proteome), this chaperone plays a crucial role throughout the lifetime of cells. Hsp90 functions as a homodimer in conjunction with several cochaperones. A large body of experiments has established a model for its functional cycle, whereby conformational changes of the two protomers are regulated through rounds of ATP binding, hydrolysis, and release, although it is not fully understood how ATP hydrolysis is coupled to client maturation [40,41]. Less information has been collected on the biochemical activity of TRAP1, but the recent determination of the TRAP1 crystal structure [42] has greatly improved our understanding of its conformational cycle. ATP binding places TRAP1 in a high-energy, closed configuration with a peculiar asymmetry between the two protomers. An N-terminal 'strap' not found in Hsp90 further stabilizes this closed state [42]. Dissociation of ATP and chaperone reopening is predicted to be slower than ATP hydrolysis [43], whose energy is used during client remodeling in a two-step process: hydrolysis of the first ATP causes a change in protomer symmetry followed by rearrangement of the client-binding site, which is in turn coupled to structural changes in the client conformation; finally, the ADP-bound chaperone releases the client and eventually ADP [42]. Currently, no TRAP1 cochaperones have been identified, and until recently little was known of its client proteins. However, the finding that TRAP1 is primarily restricted to mitochondria [44], specifically in the matrix and associated with the inner membrane [45], has fundamental implications for its biological activity.

TRAP1: promoter or suppressor of neoplasia?

Although TRAP1 and its biological functions remain poorly investigated, recent results are beginning to place this chaperone at the center of mitochondrial physiology. TRAP1 has been implicated in critical mitochondrial pathways such as regulation of mitochondrial dynamics [46], mitophagy [47,48], protection from oxidative damage [49–51], and cell death [52]. Moreover, recent evidence suggests that TRAP1, and in particular its antioxidant activity, is

Box 1. Pathophysiology of TRAP1 in non-cancer settings

TRAP1 transcripts are expressed at different levels in various tissues, including skeletal muscle, liver, heart, brain, kidney, pancreas, lung, and placenta [78]. More recent data, mainly obtained by immunohistochemistry, have identified the TRAP1 protein in the central nervous system, the gastrointestinal tract, the reproductive system, and many other tissues (see Table 1 and http://www.proteinatlas.org), but a detailed analysis of its expression pattern and levels in each tissue remains lacking.In addition to its role in cancer, TRAP1 may play a part in neurodegeneration. Evidence exists linking TRAP1 to Parkinson's disease (PD), a disorder where poor quality control of mitochondria and unbalanced redox cycling play key roles [79]. Mutations in the E3 ubiquitin ligase Parkin or in the Ser/Thr kinase PINK1 cause inherited forms of PD, and both proteins participate in the maintenance of a healthy mitochondrial pool [80]. TRAP1 is a phosphorylation target of PINK1 [51] and has been found to rescue mitochondrial dysfunction in parallel with, or upstream of, Parkin in neuronal models where PINK1 is silenced [47,48]. TRAP1 also protects cells from oxidative toxicity caused by respiratory complex I inhibition via an α-Synuclein protein variant known to induce a genetic form of PD [81]. In further accord with its role as an antioxidant molecule, overexpression of TRAP1 protects rats from free radical generation, impairment of mitochondrial function, and brain infarction following cerebral ischemia [82]. The rise in ROS levels elicited by ischemic damage induces the permeability transition pore (PTP) a mitochondrial channel whose opening irreversibly commits cells to death [83]. Indeed, TRAP1 prevents cell damage in hypoxic cardiomyocytes by inhibiting PTP opening [84]. Furthermore, recessive mutations in the *TRAP1* gene have been recently found in two families with congenital abnormalities of the kidney and urinary tract (CAKUT) and in three families where CAKUT is associated with congenital abnormalities in multiple organs [85], suggesting that *TRAP1* mutations may be involved in the enigmatic etiology of these disorders.