Meeting Report

Highlights of the National Cancer Institute Workshop on Mitochondrial Function and Cancer

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Introduction

This workshop was stimulated by the desire of the National Cancer Institute to examine various aspects of mitochondrial function as they relate to tumorigenesis, apoptosis, and cancer therapy. Through endosymbiosis, a bacterial ancestor took its position in the eukaryotic cytoplasm and serves as the cellular powerhouse. It has become increasingly clear, however, that not only do mitochondria produce ATP through the coupling of electron transport with proton pumping, they are also at the crossroads of many other metabolic activities, including heme biosynthesis, single carbon metabolism, and fatty acid metabolism. In addition to serving as central stations for many metabolic functions, mitochondria integrate stress signals to trigger programmed cell death or apoptosis. Aging and tumorigenesis are both associated with mitochondrial DNA mutations, although how these mutations impact mitochondrial function and whether they are a cause or a consequence of aging remains to be established. Although it is known that tumor hypoxia elicits an adaptive transcriptional response, how mitochondrial function changes in tumorigenesis and whether mitochondrial defects contribute to the Warburg effect (a universal high acidity in tumor tissues compared with the surrounding normal tissue; described in 1928 by Otto Warburg) remain controversial. The topics covered by this workshop have been selected to shed some light on these intriguing, yet not fully understood areas of mitochondrial function.

Mitochondrial DNA Mutations and Cancer

The workshop was opened by Kornelia Polyak (Dana-Farber Cancer Institute) who gave a presentation of her seminal work on somatic mutations in the mitochondrial genome of colorectal cancer cells. Polyak showed that mutations in mitochondrial DNA occur somatically and are present in the majority of human tumors. The cancer cells are “homoplasmic” for the mutation, meaning that all copies of the mitochondrial DNA contain the mutation. The mechanism by which the mitochondria become homoplasmic is not known, but may involve a replicative advantage on the part of the mitochondrial genome, on the mitochondria or on the cell. Polyak generated cells that differed solely in their mitochondrial DNA and demonstrated that mitochondrial DNA, in combination with nuclear factors, may influence the ability of cells to undergo p53-mediated apoptosis in response to stress, suggesting the mitochondrial genome may contribute causally to cancer. However, proof of this important concept remains elusive.

The high copy number and homoplasmy of mitochondria make them useful markers for detecting cancer from fine needle aspirates or paraffin sections (David Sidransky, Johns Hopkins School of Medicine). Squamous cell carcinoma of the head and neck is a devastating disease that often recurs after surgical resection. Sidransky showed that somatic mitochondrial mutations in head and neck cancers occur before dysplasia and can be used to detect early recurrences. In one patient, the same mitochondrial mutation was found in recurrences that arose over many years, indicating that mitochondria may be markers of clonal expansion. Furthermore, because of the homoplasmic nature and increased copy number of the mitochondrial genome, mutations in mitochondrial DNA were more readily detectable in dilute clinical samples than were mutations in single copy nuclear genes such as p53.

The tumor-associated mitochondrial DNA mutations are most likely initiated as polymerase errors or as a consequence of DNA damage by endogenous or exogenous agents. The ability of mitochondria to deal with DNA damage is limited, because the organelle lacks a full complement of the enzymes required for mismatch repair, nucleotide excision repair and recombinational repair (Daniel Bogenhagen, Stony Brook University). The incidence of mitochondrial mutations may be influenced by mitochondrial DNA binding proteins that either protect the DNA from damage or block the genome from DNA repair enzymes. Mitochondrial DNA must be highly packaged to fit into the organelle, but it is not packaged into nucleosomes. To begin to understand how mitochondrial DNA is packaged, Bogenhagen identified proteins that bind to mitochondrial DNA. One of these proteins, TFAM, acts as a transcriptional activator at low ratios of protein to DNA but actually inhibits transcription at high ratios. This same protein inhibits base excision repair at high ratios of protein to DNA, suggesting that the mitochondrial proteome may influence the incidence of mitochondrial DNA mutations.

Role of Mitochondria in Apoptosis

Douglas R. Green (La Jolla Institute for Allergy and Immunology) reported that among the earliest targets of the executioner caspases are the permeabilized mitochondria themselves. In the absence of caspase activation, cytochrome c can sustain electron transport and ATP generation in the permeabilized mitochondria. Once caspases are activated, electron transport is disrupted. Examination of caspase-3 substrates within the mitochondria permitted the identification of a key substrate, p75, a component of the large complex I of the electron transport chain, which is cleaved at a single site by caspase 3. Green showed that p75 cleavage by caspases disrupts mitochondrial integrity and leads to loss of electron transport, loss of ∆Ψm, generation of reactive oxygen species, and a rapid decline in ATP levels in the cell, thus preventing a recovery of ∆Ψm. However, p75 cleavage has no effect on cytochrome c release. p75 cleavage also accelerates phosphatidylserine externalization and loss of plasma membrane integrity without affecting other aspects of caspase-dependent apoptosis such as DNA fragmentation. Therefore, the rapid action of activated...
caspases on mitochondria with a permeabilized outer membrane is a major step in the dismantling of the cell during apoptosis and accounts for several of the events associated with caspase-dependent cell death.

Guido Kroemer (Institut Gustave Roussy) presented new insights into the function of apoptosis-inhibiting factor (AIF) in apoptosis. AIF is a flavoprotein with NADH oxidase activity normally contained in the mitochondrial intermembranous space. On apoptosis induction, AIF translocates from mitochondria to the nucleus and participates in apoptotic chromatinolysis that is independent of its NADH oxidase activity. During early nuclear condensation, AIF is associated with chromatin and binds to histones and DNA. AIF causes purified nuclei to undergo chromatin condensation, large-scale DNA degradation into ~50-kbp fragments and DNA loss. Kroemer reported that an extensive search for AIF-binding proteins that enhance or inhibit its apoptotic function revealed Hsp70 and cyclophilin A (CypA) as main binding partners. Hsp70 inhibits AIF by retaining it in the cytoplasm, whereas CypA works with AIF to promote apoptosis. Cooperation between recombiant AIF and CypA proteins is required for the \textit{in vitro} degradation of plasmid DNA and for inducing DNA loss in purified nuclei. AIF-dependent DNA fragmentation is less pronounced in CypA knockout cells, as compared with controls. Thus, biochemical and genetic evidence indicates that AIF and CypA collaborate in chromatinolysis. Although the molecular interactions of AIF and Hsp 70 or CypA provide insight into how AIF participates in apoptosis, the normal mitochondrial function of AIF remains undefined. Intriguingly, AIF knockout causes glucose dependence and increased lactate production because it leads to a defect in complex I assembly and compromises the respiratory chain. Thus, like cytochrome c, AIF is a protein with two functions: a vital bioenergetic function within mitochondria and a lethal function outside of mitochondria. The critical functions of these two proapoptotic proteins may explain why they are not mutated in cancer cells.

Sally Kornbluth (Duke University) presented her characterization of Reaper, a central regulator of apoptosis in \textit{Drosophila melanogaster}. In flies, apoptosis is regulated mainly through the inhibition of the inhibitor of apoptosis proteins (IAPs). Reaper inhibits the IAPs by stimulating their auto-ubiquitination and subsequent degradation. Kornbluth's laboratory found that Reaper could induce apoptosis in heterologous systems, \textit{i.e.}, in \textit{Xenopus} extracts, by promoting auto-ubiquitination of IAPs, suggesting that this pathway may be important for apoptosis in vertebrates. The central GH3 domain of Reaper is required for mitochondrial localization and for IAP degradation. Because the GH3 domain of Reaper had been implicated only to play a role in apoptosis in flies, Kornbluth searched for mammalian proteins with homology to the GH3 domain and found a similar domain in nonstructural bunyaviral proteins. Bunyaviruses cause encephalitis in people, and their nonstructural proteins kill cells in the brains of transgenic mice. Thus, the GH3 domain, which appears to localize proteins to the mitochondria, may be critical for some human pathologies.

Elisa Bossy-Wetzel (The Burnham Institute) discussed the cross-talk between nitric oxide, zinc, and mitochondrial injury in neuronal cell death. Nitric oxide (NO) and Zn$^{2+}$ are implicated in the etiology of a number of acute and chronic neurodegenerative disorders in which cell death is enhanced rather than repressed, as in cancer. Bossy-Wetzel showed that nitric oxide/peroxynitrite (NO/ONOO$^-$) triggers the release of Zn$^{2+}$ from internal stores such as metallothionein, the major endogenous Zn$^{2+}$ chelator, in primary neurons cocultured with glial cells. Similarly, pathophysiologic stimuli like N-methyl-D-aspartate (NMDA) receptor activation induces Zn$^{2+}$ release via endogenous NO production that leads to neuronal cell death. Free Zn$^{2+}$, similar to Ca$^{2+}$, induces the mitochondrial permeability transition, inhibits mitochondrial respiration, increases free radicals, decreases mitochondrial membrane potential and releases cytochrome c. In addition, a caspase-independent K$^+$ efflux with concomitant cell shrinkage occurs in the NO death pathway. Using whole cell patch clamp recording, Bossy-Wetzel's laboratory observed increased outward voltage-gated K$^+$ channel activity signaled by p38 mitogen-activated protein kinase after NO exposure. Zn$^{2+}$ chelation, scavenging of reactive oxygen species (ROS), BclXL overexpression, dominant-negative p38, and K$^+$ channel inhibitors all can partially block NO-induced K$^+$ efflux and neuronal apoptosis. These findings identify a novel connection between NO and Zn$^{2+}$ signaling pathways that may contribute to the pathogenesis of neurodegeneration. Theoretically these pathways could play important roles in tumor suppression.

Ute M. Moll (Stony Brook University) provided evidence that the tumor suppressor p53 has a direct apoptogenic role at the mitochondria. Whereas p53 can induce apoptosis by target gene regulation, evidence for a p53 transcription-independent action had, until recently, received little attention, and a mechanism for the latter was completely unknown. Moll's laboratory found that a fraction of induced p53 rapidly translocates to mitochondria after apoptotic stimuli. Targeting p53 directly to mitochondria of p53-null cells is sufficient to launch apoptosis directly from the mitochondrial platform, without the help of transactivation. Moll's laboratory also showed that the p53 protein can directly induce permeabilization of the outer mitochondrial membrane by forming inhibitory complexes with the protective BclXL and Bcl-2 proteins, and by inducing oligomerization and activation of Bak, which in turn results in the release of cytochrome c and other apoptotic activators. Thus, p53, by moving rapidly to the mitochondria, effectively "jump starts" and amplifies its slower-starting transcription-dependent effect in apoptosis. This direct mitochondrial p53 program participates in the physiologic p53 response after DNA damage in normal mice. In radiosensitive organs, mitochondrial p53 translocation triggers rapid caspase 3 activation and cell death. Conversely, transactivation-deficient tumor-derived missense mutants concomitantly lose or compromise their ability to interact with BclXL and to promote cytochrome c release and, thus, may represent "double hits," eliminating the transcriptional as well as the direct mitochondrial function of p53. Together, this suggests that the mitochondrial pathway also participates in tumor suppression.

John C. Reed (The Burnham Institute) described proteins that interact with and modulate the activity of Bcl-2-family proteins on the outer mitochondrial membrane through novel BH3-independent mechanisms. These proteins include TR3 (Nur77), an orphan member of the retinoid/steroid family of transcription factors, which binds with BclXL and to promote cytochrome c release and, thus, may represent "double hits," eliminating the transcriptional as well as the direct mitochondrial function of p53. Together, this suggests that the mitochondrial pathway also participates in tumor suppression.

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proteins called “Converters” (with TR3 as prototype), because they convert Bcl-2 from a protector to a BH3-only killer. These data might explain the paradoxical observation that higher Bcl-2 levels were associated with better patient survival in some studies of breast cancer and non-small-cell lung cancer. They also indicate that switching Bcl-2 to a proapoptotic function is a possible therapeutic strategy.

Role of Mitochondria in Cancer Cell Bioenergetics and Growth Signaling

Craig Thompson (University of Pennsylvania) addressed receptor-mediated signaling for cell proliferation and survival in the context of bioenergetics. He reported that both of the serine threonine kinases Pim2 and Akt could protect interleukin (IL)-3–dependent cells against apoptosis induced by IL-3 withdrawal, although not as effectively as ectopic expression of BclXL. These kinases did not stimulate the proliferation rate of the cells. Rather, Pim2 or Akt expression resulted in increased glucose uptake and excess lactate production through aerobic glycolysis, without affecting the rate of oxidative phosphorylation. Expression of activated Akt in other cells also resulted in increased glucose uptake and lactate production, suggesting that Akt plays an important role in the Warburg effect or aerobic glycolysis. Thus, Akt appears to promote cell survival under conditions of nutrient deprivation. These and other data suggest that receptor-mediated signaling involves at least two programs, one for the induction of cell proliferation and the other for cell survival through increased glucose flux through glycolysis. Constitutive activation of both programs may be critical for tumorigenesis.

Peter Pedersen (Johns Hopkins University) recapitulated earlier findings indicating that glycolytic rates increase with the degree of neoplasia in the Morris hepatoma model. Pedersen’s group identified Type II hexokinase (HKII), the first enzyme in glycolysis responsible for the phosphorylation and retention of glucose in the cytosol, as a mitochondrial outer membrane-associated protein. HKII is expressed at very low levels in normal hepatocytes but at increased levels in hepatocarcinomas. Pedersen and his colleagues were also pivotal in the characterization of the mitochondrial ATP synthasome, and he provided a model suggesting that the mitochondrial association of HKII allows it to use newly synthesized ATP to phosphorylate glucose. The high efficiency of HKII suggested that this enzyme might be critical for meeting the bioenergetic demands of the cancer cells. The Pedersen laboratory sought small molecules that could inhibit both glycolysis and mitochondrial respiration and found that 3-bromopyruvate is effective not only in vitro but also in a rabbit model of liver transplantation. Their work showed that Akt inhibits the mitochondrial association of HKII, thus allowing it to use newly synthesized ATP to phosphorylate glucose. This high efficiency of HKII suggested that this enzyme might be critical for meeting the bioenergetic demands of the cancer cells. The Pedersen laboratory sought small molecules that could inhibit both glycolysis and mitochondrial respiration and found that 3-bromopyruvate is effective not only in vitro but also in a rabbit model of liver transplantation. Their work showed that Akt inhibits the mitochondrial association of HKII, thus allowing it to use newly synthesized ATP to phosphorylate glucose.

Nic Denko (Stanford University) and Navdeep Chandel (Northwestern University) addressed the mitochondrial response to hypoxia. This aspect of mitochondrial function is particularly important because of the pervasive hypoxic microenvironment in tumors. Mitochondria respond to reduced oxygen both by decreasing oxidative phosphorylation and by participating in the cell death decision. Denko reported that hypoxia-mediated induction of apoptosis is greatly accelerated by wild-type p53 and relies on the release of cytochrome c from the mitochondria. Hypoxia-mediated apoptosis, however, appears to be independent of the p53 transcriptional target, Bax. Hypoxia does alter gene expression to a large extent through the hypoxia-inducible factor (HIF1), but Denko and his colleagues have been unable to identify hypoxia-responsive genes that are responsible for the apoptogenic effects of hypoxia. They found HIF1-mediated induction of Bnip3 and Bnip3L to be mitochondrial associated but poorly apoptogenic. Through expression profiling, they have identified a whole host of mitochondrial proteins that are induced in hypoxia, and Denko plans to establish their specific effects on the inhibition of mitochondrial respiration and the stimulation of apoptosis.

Navdeep Chandel addressed the issue of how mitochondrial function might regulate the stability of HIF1. In the presence of atmospheric oxygen, the HIF1α subunit of HIF1 undergoes prolyl-hydroxylation, leading to its proteosomal degradation. Under hypoxic conditions, the protein is stabilized because of reduced prolyl-hydroxylation. Chandel noted that there might be signaling from the mitochondrion to prolyl hydrolases, because the biochemical response of prolyl hydrolases to reduced oxygen tension does not parallel the appearance of HIF1 protein. Furthermore, cells lacking mitochondrial DNA (rho zero) fail to stabilize HIF1 under hypoxic conditions, suggesting that mitochondrial activity is required. It is hypothesized that reactive oxygen species emanating from hypoxic mitochondria somehow signal the inactivation of prolyl hydrolases, which themselves depend on molecular oxygen for function. The ubiquinone (Q) cycle is suspected to be the source of mitochondrial ROS, which in turn inhibits the prolyl hydroxylases. Thus, HIF1α may be part of a regulatory circuit in which the mitochondria regulate the level of a nuclear transcription factor, which in turns regulates the expression of mitochondrial proteins that influence mitochondrial function.

Toren Finkel (National Heart, Lung and Blood Institute) addressed the role of ROS in intracellular signaling. Earlier work by Finkel and coworkers uncovered a role for ROS in signaling downstream of the platelet-derived growth factor (PDGF) receptor in that a burst of ROS (H2O2), discernible minutes after exposure of cells to PDGF, was accompanied by increased protein tyrosine phosphorylation. The increase in phosphorylation was shown to be due in part to the oxygen radical-mediated modification of sulfhydryl moieties on tyrosine phosphatases. These results suggested that ROS production within cells was tightly regulated, a concept that most likely extends to mitochondrial ROS production. Evidence supporting this notion comes from several observations. First, Ras-induced senescence of primary fibroblasts is associated with increased mitochondrial ROS production as determined by fluorescent confocal imaging studies. Second, low ambient oxygen tension, as well as the radical scavenger N-acetylcysteine, is able to rescue cells from Ras-induced senescence, suggesting that respiration-related ROS is required. Furthermore, fibroblasts from the p66 shc knockout mouse, which displays a 30% longer life span than wild-type mice, showed diminished ROS production. P66 shc localizes to mitochondria, and its absence results in altered mitochondrial oxygen consumption. These observations suggest that ROS from the mitochondrion are involved in signaling, in particular with regard to cellular senescence.
Mitochondrial Proteomics and Assembly

The final session in the workshop was led by Paul Herrmann (FDA-NCI Clinical Proteomics Program), who presented an analysis of mitochondrial cytochrome c oxidase subunit levels in carcinoma cells with laser capture microdissection. A consistent finding across 30 patients was an increased ratio of nuclear-encoded subunits of cytochrome oxidase (COX IV, Vb, Vlc) to mitochondrial DNA-encoded proteins (COX I, II) in prostatic carcinoma cells compared with normal prostatic epithelium from the same individual. Two different quantitative methods, probed by Western blots with multiple antibodies and reverse-phase protein arrays, gave similar results. Interestingly, the nuclear-to-mitochondrial subunit ratio increased with stage of malignancy, with changes detectable even in benign hyperplastic epithelium from prostate cancer. Because a structure/functional correlation could not be made with fixed primary tissue, prostate and bladder cancer cell lines derived from normal and cancerous tissue were analyzed and compared. The tumor-derived cell lines displayed increased ratios of nuclear-to-mitochondrial-encoded cytochrome oxidase subunits compared with cell lines derived from normal cells. Metabolic analysis of the same cell lines with glucose 14C-labeled at the C1 and C6 positions revealed a greater use of the hexose monophosphate shunt pathway, relative to the Krebs cycle, in the cancer-derived cell lines.

William Dowhan (University of Texas-Houston Medical School) summarized a series of elegant studies into the essential role of cardiolipin (CL) and phosphatidylglycerol (PG) in mitochondrial activities. Saccharomyces cerevisiae strains deficient in the cardiolipin synthase enzyme, CRD1, grow slowly on nonfermentable substrates and have partially assembled electron transport chain complexes III and IV. Increased levels of PG are found in CRD1-deficient strains, which may partially compensate for the absence of CL. Yeast mutants deficient in phosphatidylglycerolphosphate synthase (PGS1), a proximal enzyme required for synthesis of both CL and PG, show complete loss of growth on nonfermentable substrates or at elevated temperatures (>37°C). PGS1-deficient yeast have severely reduced-absent levels of mitochondrial encoded proteins as well as a subset of nuclear-encoded mitochondrial proteins. Dowhan’s group identified a block in translation affecting both mitochondrial and cytoplasmic mRNAs coding for mitochondrial proteins, as a striking example of mitochondria-to-nuclear signaling. Translational repression in PGS1-deficient strains maps to the 5′ untranslated regions of both mitochondrial and cytoplasmic mRNAs. CL levels decline with age, are low in patients with Barth’s syndrome and associated cardiomyopathy, and are dramatically reduced under conditions of oxidative stress such as perfusion after ischemia. In these conditions, compensating levels of PG are not found. Dowhan summarized results demonstrating that acute loss of CL in cardiomyocytes highly correlates with the release of cytochrome c to the cytoplasm and to the onset of apoptosis, independent of generation of ROS or alterations in ceramide levels. There is little information available on mitochondrial CL/PG content in cancer cells versus normal cells.

Chi Dang (Johns Hopkins) reviewed transcriptional targets of c-Myc involved in metabolic control and specifically mitochondrial functions. The core c-Myc DNA-binding sequence is shared with HIF1, the oxygen-sensitive transcription factor that regulates cellular responses to hypoxia. Two novel transcriptional targets of c-Myc were discussed. PRC (PGC-1 related coactivator) is a nuclear coactivator of the NRF-1 transcription factor involved in mitochondrial biogenesis. PRC is ubiquitously expressed and, unlike PGC-1 (PPAR-γ coactivator-1), is not induced during brown fat thermogenesis, but responds to proliferative stimuli. Under the control of a tet-regulated promoter, Myc induces PRC and stimulates oxygen consumption in fibroblasts, and increases both mitochondrial DNA copy number and COX I expression. The second gene is PRDX3, a thioredoxin peroxidase imported to mitochondria. Antisense-mediated down-regulation of PRDX3 sensitizes cells to glucose starvation, resulting in increased ROS, lowered mitochondrial membrane potential, and aberrant mitochondrial morphologies. As c-Myc is also known to directly up-regulate glycolytic enzymes, including LDH-A, the metabolic consequences of Myc deregulation may depend on the availability of coactivators and corepressors, in addition to other mechanisms for fine-tuning transcriptional responses.

David Hockenbery (Fred Hutchinson Cancer Research Center) presented two experimental models that raise the possibility of defective mitochondrial assembly in cancer cells. In previously published work, his group identified noncanonical E box elements within NRF-1-responsive sites that function as binding sites for Myc:Max dimers. Cells with deregulated c-Myc produce high levels of NRF-1-regulated, nuclear-encoded mitochondrial proteins. Under conditions of serum deprivation, cells with active Myc acquire misspliced mitochondria and undergo apoptosis, both of which are suppressed by coexpression of a truncated, dominant-negative NRF-1 allele. Significantly, Myc-dependent apoptosis, but not proliferation, requires transactivation of NRF-1 target genes. The second model presented induction of terminal differentiation and apoptosis in a colon cancer cell line by herbimycin A, an hsp90 inhibitor. Colo-205 colon cancer cells are predominantly glycolytic but undergo a massive expansion of mitochondrial mass with herbimycin A treatment. Several nuclear and mitochondrial DNA-encoded mitochondrial proteins are up-regulated posttranslationally in herbimycin A-treated cells, suggesting there may be a high basal rate of hsp90-dependent mitochondrial protein turnover in de-differentiated cancer cells.

Summary

The workshop illuminated several ways in which mitochondria are involved in cancer. The mitochondrial genome has become a useful source of markers for early detection of cancers. In addition, mutations in the mitochondrial genome may contribute to the development of cancer. The development of methods to engineer cells with homoplasmic, targeted mutations in their mitochondria would be a major advance toward answering this question. The mitochondrial proteome is also altered in cancer cells. Some of these alterations affect both mitochondrial bioenergetics and apoptosis regulation through dual function proteins, suggesting that these two processes are linked. Examples of such dual function proteins are cytochrome c, AIF, and HKII.

We heard how extensively mitochondria communicate with other cellular compartments, influencing both transcription (through ROS and HIF1) and translation (through cardiolipin). In turn, the nuclear functions of Myc and HIF1 influence mitochondrial function. The mitochondria also exchange proteins with other organelles. For example, TR3 and p53 travel to the mitochondrial surface to stimulate apoptosis. In turn, AIF and cytochrome c are released from the mitochondria to exert their apoptogenic effects. It will be important to elucidate the regulatory mechanisms mediating transport of these proteins to various subcellular compartments and to decipher the specific function of each protein in each compartment.

Both tumor suppressors and oncproteins use and influence mitochondrial functions. The p53 tumor suppressor induces apoptosis, at least in part, by binding to the mitochondrial surface and activating Bax and Bak. ROS, thought to be generated from the mitochondria, plays a direct role in growth factor signaling. The Akt survival factor interacts with the bioenergetic protein HKII to prevent apoptosis. In addition, Akt can stimulate aerobic glycolysis without influencing
mitochondrial oxidative phosphorylation, providing cells a survival advantage in conditions of nutrient deprivation. HIF1, which promotes angiogenesis, regulates expression of a number of mitochondrial proteins that may be involved in the adaptive response to hypoxia. Moreover, the c-Myc proto-oncoprotein induces expression of several mitochondrial proteins, some of which are involved in energy metabolism.

The workshop participants enumerated a number of outstanding questions, including some very basic ones about mitochondrial biology. How are mitochondria replicated? How is their number controlled? How is homoplasmy obtained? Some more physiologic questions remain as well. How are energy metabolism and apoptosis linked? Is oxidative phosphorylation altered in cancer cells, or only glycolysis? What regulatory mechanisms control the switch to aerobic metabolism that is so characteristic of cancer cells? Can we target aerobic glycolysis to selectively kill tumor cells? Although we await the answers to these questions, the mitochondria are already providing us with diagnostic markers and treatment strategies for cancer.
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