ACTA ABP BIOCHIMICA POLONICA

Vol. 61, No 4/2014
671–678
on-line at: www.actabp.pl

Review

Role of mitochondria in carcinogenesis

Paulina Tokarz and Janusz Blasiak✉

Department of Molecular Genetics, Faculty of Biology and Environmental Protection, University of Lodz, Łódź, Poland

Mitochondria play the central role in supplying cells with ATP and are also the major source of reactive oxygen species (ROS) — molecules of both regulatory and destructive nature. Dysfunction of mitochondrial metabolism and/or morphology have been frequently reported in human cancers. This dysfunction can be associated with mitochondrial DNA (mtDNA) damage, which may be changed into mutations in mtDNA coding sequences, or the displacement-loop region, changes in the mtDNA copy number or mtDNA microsatellite instability. All these features are frequently associated with human cancers. Mutations in mtDNA can disturb the functioning of the ROS-producing organelle and further affect the entire cell which may contribute to genomic instability typical for cancer cells. Although the association between some mtDNA mutations and cancer is well established, the causative relationship between these two features is largely unknown. A hint suggesting the driving role of mtDNA mutations in carcinogenesis comes from the observation of tumor promotion after mtDNA depletion. Mitochondria with damaged DNA may alter signaling of the mitochondrial apoptosis pathway promoting cancer cell survival and conferring resistance to anticancer drugs. This resistance may be underlined by mtDNA copy number depletion. Therefore, mitochondria are considered a promising target in anticancer therapy and several mitochondria-targeting drugs are in preclinical and clinical trials. Some other aspects of mitochondrial structure and functions, including morphology and redox potential, can also be associated with cancer transformation and constitute new anticancer targets. Recently, several studies have disclosed new mechanisms underlying the association between mitochondria and cancer, including the protection of mtDNA by telomerase, suggesting new approaches in mitochondria-oriented anti-cancer therapy.

Key words: cancer, mitochondria, mtDNA, ROS, anti-cancer therapy

Received: 22 June, 2014; revised: 17 September, 2014; accepted: 03 November, 2014; available on-line: 11 December, 2014

MITOCHONDRIA AND CANCER

Cancer cells are resistant to pro-apoptotic signals, including those coming from mitochondria, so these organelles may play an import role in carcinogenesis. Cancer cells, due to their enormously high energy demand, are characterized by a high ATP/ADP ratio, maintained mainly by oxidation of glucose, a multi-step process with a key stage in mitochondria (Joce *et al*., 2010). Morphological differences between cancer and normal cells involve also mitochondria, which are usually present less numerous in cancer cells than in their normal counterparts, but display distinguishing morphological features (Arismendi-Morillo, 2009; Yu, 2011). Mutations in mitochondrial DNA (mtDNA), contributing to genomic instability, are observed in a variety of cancers (Larman *et al*., 2012). Genomic instability can be induced by an excessive production of reactive oxygen species (ROS) resulting from mitochondria dysfunction (Vives-Bauza *et al*., 2006). Mitochondrial redox potential has been implicated in cancer transformation, particularly in metastasis, through proton gradient generation and maintenance, which is then used to drive ATP synthesis (Li, 2012). Recent studies revealed new molecular mechanisms underlying the involvement of mtDNA damage and mitochondrial dysfunction in cancer transformation.

MITOCHONDRIAL MUTAGENESIS

Mitochondria are semi-autonomous organelles capable of replication of their mtDNA. The high mutation rate of mtDNA, at least ten times higher than in nuclear DNA, is attributed to a lack of protective histones, lower efficiency of DNA repair, and continuous exposure to mutagenic oxygen radicals generated by oxidative phosphorylation (Wallace, 1992; 2012; 2014). Most of the 16 569 bp of human mtDNA are coding sequences, indicating a potentially high impact of a change in the mtDNA sequence on the functioning of mitochondria and the whole cell (Fig. 1).

A diseased or aging tissue comprises a mosaic of cells containing mutated and non-mutated mtDNA (Taylor *et al*., 2003; Fayet *et al*., 2002; Linnane *et al*., 1989; Bender *et al*., 2006; de Grey, 1997). A cell is homoplasmic if all copies of its mtDNA have the same nucleotide sequence. The homoplasmy of cells with mutated mtDNA indicates that the cellular ubiquity of mutated mtDNA is not a consequence of accidental oxidative damage to mtDNA, but rather is due to a preferential accumulation of mutated mtDNA within a cell. The mechanism of acquired homoplasmy has been largely unknown and

✉e-mail: jblasiak@biol.uni.lodz.pl

Abbreviations: 2DG, 2-deoxy-D-glucose; 2-ME, 2-methoxyestradiol; 8-oxoG, 8-oxo-7,8-dihydroguanine; ALT, alternative lengthening of telomeres; BER, base excision repair; CML, chronic myeloid leukemia; D-loop, displacement loop; DSB, DNA double-strand break; ETC, electron transport chain; HIF-1, Hypoxia-Inducible Factor-1; IM, imatinib; ΔΨm, mitochondrial membrane potential; MDR1, Multidrug Resistance Protein 1; MMR, mismatch repair; mtDNA, mitochondrial DNA; MTATP6, mitochondrial ATP synthase subunit 6; mtMSI, mitochondrial microsatellite instability; ND, NADPH dehydrogenase; nDNA, nuclear DNA; OXPHOS, oxidative phosphorylation; PI3K, phosphoinositide 3-kinase; rho0 cells, cells depleted of mitochondrial DNA; ROS, reactive oxygen species; TERT, telomerase reverse transcriptase; VEGF, vascular endothelial growth factor

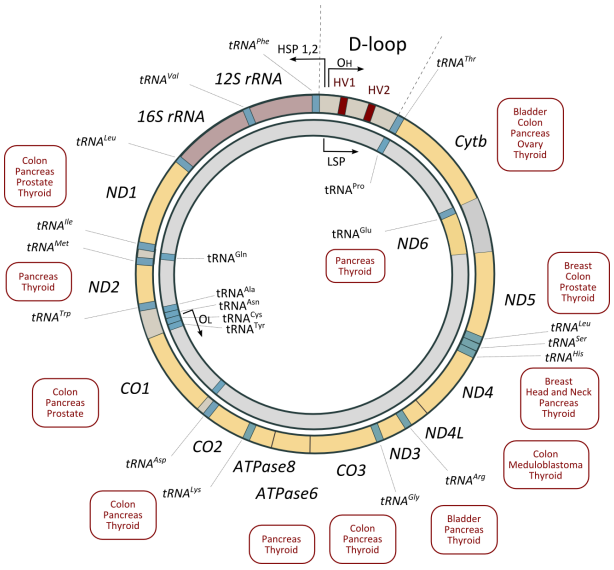

Figure 1. Structure of human mitochondrial genome with mutations in mtDNA the genes associated with human cancers. Mutations in polypeptide encoding genes are displayed in the boxes next to the gene names. 12,16 rRNA — mitochondrially encoded 12S and 16S ribosomal RNA; *ATPase6,8* — mitochondrially encoded ATP synthase 6,8; *CO1-3* — mitochondrially encoded cytochrome *c* oxidase 1-3; *Cytb* — mitochondrially encoded cytochrome *b* gene; D-loop — displacement loop; HSP 1,2 — heavy strand promoter 1 and 2; HV 1,2 — hypervariable regions 1,2; LSP — light strand promoter; *ND1-6* — mitochondrially encoded NADH dehydrogenase 1-6; O_H — origin of replication of heavy strand; O_L — origin of replication of light strand.

it was suggested that it can result from a lower exposure of mutated mtDNA to oxidative damage due to a reduced ROS production as a result of mutation(s) facilitating the escape of mitochondria from degradation and allowing their continuous proliferation (de Grey, 1997). Another hypothesis explaining the clonal expansion of mutated mtDNA is based on the assumption of random genetic drift in a pool of replicating mtDNA molecules (Elson *et al.*, 2001).

Alterations in the mitochondrial genome, including mutations in the coding sequences, mutations in the mtDNA displacement-loop (D-loop) region, changes in the mtDNA copy number and mtDNA microsatellite instability, frequently occur in various types of cancers. D-loop, a non-coding region containing both replication and transcription regulatory elements, contains two hypervariable regions, HV1 and HV2, which are hot spots for mutations in malignant tumors (Taanman, 1999; Miller *et al.*, 1996; Fliss *et al.*, 2000). D-loop and particularly its poly(C)-T-poly(C) structural motifs, are also prone to mitochondrial microsatellite instability (mtMSI) associated with several human cancers and characterized by the variable length of short tandem repeats (Wang *et al.*, 2006). The cause of mtMSI is still elusive but it may be associated with the induction of oxidative stress and DNA damage, as has been shown in *Helicobacter pylori*-infected gastric mucosa cells (Bagchi *et al.*, 2002). Because MSI of nuclear DNA (nDNA) is a hallmark of mismatch repair (MMR) deficiency, it may be speculated that MMR defects could also evoke mtMSI (Boland & Goel, 2010). Indeed, mitochondria can execute MMR, but the efficiency and utility of this DNA repair pathway in the protection against mtMSI has not been demonstrated yet (de Souza-Pinto *et al.*, 2009). Besides somatic mutations, changes in mtDNA copy number have frequently been reported in various types of cancers including solid tumors and hematologic malignancies (Lee & Wei, 2009; Lu *et al.*, 2004).

The causes of the mtDNA content change in malignancies is not completely understood, although some concepts explaining the reduction in mtDNA copy number have emerged, including a hypothesis that this reduction may be attributed to less efficient mtDNA replication due to mutations in the D-loop or in the DNA polymerase gamma gene. On the other hand, quantitative change of mtDNA is suggested to be a consequence of the inherent feedback mechanism compensating for metabolic defects in mitochondria carrying mutated mtDNA and impaired respiratory system (Yu, 2011; Lee *et al.*, 2004; Singh *et al.*, 2009; Lee & Wei, 2005). Regardless of the cause of mtDNA alterations, this effect disturbs cell growth, apoptosis-related processes, anti-cancer drug sensitivity, hormone dependence of tumor cells as well as their invasive and metastatic potentials (Yu, 2011). The depletion of mtDNA copy number affects the epigenetic pattern of the nuclear genome, resulting in aberrant methylation of promoter CpG islands (Smiraglia *et al.*, 2008; Xie *et al.*, 2007). On the basis of published data we speculate that the loss of mtDNA may induce epigenetic changes in nDNA leading to alterations in gene expression directed at energy conservation in view of the comprised functioning of mitochondria. However, apart from the expected DNA methylation-associated gene expression changes to maintain efficient cell energy turnover, it is still unknown whether mtDNA depletion may be involved in carcinogenesis by disturbing the epigenetic profile of nDNA, especially since the DNA methylation changes can be reversed by mtDNA restoration. In this context, it is worth highlighting that cells depleted of mtDNA, rho0 cells, display a disturbed oxidative status (Delsite *et al.*, 2003). The oxidative processes resulting in lipid peroxidation and oxidative damage to the nuclear genome are augmented in rho0 cells indicating the importance of the mitochondrial genome for maintaining the nuclear genome stability.

Malignant transformation has been linked with an increase in the mitochondrial membrane potential ($\Delta\Psi m$) (Heerdt *et al.*, 2005). The increased $\Delta\Psi m$ found in the relatively minor subpopulation of primary or metastatic tumor cells has been related to their better survival and increased expansion. (Houston *et al.*, 2011). This fraction of tumor cells is less sensitive to anticancer agents and constitutively secrete vascular endothelial growth factor, VEGF, independently of hypoxia, indicating the capability of these cells to adjust rapidly to alterations in the microenvironment. Additionally, the enhanced invasive potential is only evident in metastatic tumor cells with an increased intrinsic $\Delta\Psi m$, implying a direct causal relationship between these two features. It is not known, however, which of them is primary.

Mitochondrial dysfunction has been associated with an increased cancer incidence and with aging, an important risk factor for cancer development. Aging correlates with the reduction in the number of mitochondria and changes in their morphology in both mouse and human cultured cells, an accumulation of mutations in mtDNA in human heart and brain, and a decline in the mitochondrial capacity for oxidative phosphorylation in human skeletal muscle (Taylor *et al.*, 2003; Herbener, 1976; Wilson & Franks, 1975; Lipetz & Cristofalo, 1972; Hattori *et al.*, 1991; Corral-Debrinski *et al.*, 1992; Cortopassi & Arnheim, 1990; Michikawa *et al.*, 1999; Boffoli *et al.*, 1994; Short *et al.*, 2005). A causative effect of mitochondrial mutagenesis on age-related pathologies is indi-

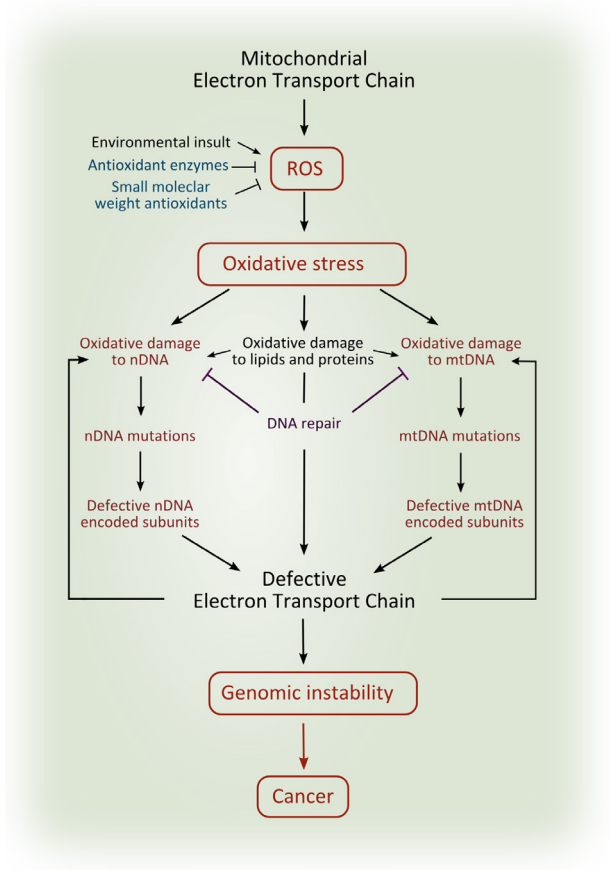

Figure 2. Scheme presenting the mitochondrial vicious cycle including reactive oxygen species (ROS) production and its involvement in carcinogenesis.
Environmental insult, antioxidant enzymes and small molecular weight antioxidants can modulate the level of ROS generated during electron chain transport. The ROS level exceeding mitochondria antioxidant capacity leads to oxidative stress resulting in damage to biomolecules. Oxidative damages induce mutations in both nuclear and mitochondrial DNA (nDNA and mtDNA, respectively), which can contribute to dysfunction of electron chain transport and impaired DNA repair resulting in a vicious cycle of mitochondrial ROS production.

cated by premature aging of mice expressing a defective mitochondrial DNA replicative enzyme — polymerase gamma. These mice develop the mtDNA mutator phenotype, showing an association between the increase in mtDNA somatic mutations and premature aging (Trifunovic *et al.*, 2004; Kujoth *et al.*, 2005). It has been suggested that mutations in mtDNA accumulate during the life span and this relationship has been shown in the brain, heart, and skeletal muscle of aging humans (Fayet *et al.*, 2002; Hattori *et al.*, 1991; Short *et al.*, 2005; Melov *et al.*, 1999). As an explanation of the age-related accumulation of mtDNA mutations, the vicious cycle hypotheses on the production of ROS in mitochondria has been proposed to support the mitochondrial theory of aging (Ozawa, 1995). According to this concept, ROS produced in mitochondria damage mtDNA, including genes encoding components of the electron transport chain (ETC). This can result in the impairment of electron transfer, leading to ROS overproduction (Lenaz, 1998). Thus, continuous repeating of this cycle may cause the accumulation of mutations in both mtDNA and nDNA (Fig. 2). Although the accumulation of irreversible oxidative damage is observed during aging it has been suggested that ROS may not be a triggering factor for aging (Lapointe & Hekimi, 2010). Regardless of the origin, damage to the genome may pose a threat to the homeostatic feedback mechanisms of normal cells and can result in their genomic instability. ROS generate a variety of DNA lesions, including oxidized DNA bases, abasic sites and DNA strand breaks (Krokan *et al.*, 1997). The most abundant and well-characterized DNA lesion generated by ROS is highly mutagenic 8-oxo-7,8-dihydroguanine (8-oxoG), which may result in a G:C to T:A transversion (Grollman & Moriya, 1993). Given that any DNA damage, if not repaired, may lead to a mutation and possibly pathogenic phenotype, the failure of DNA repair systems is crucial in the sequential accumulation of mutations and eventually the malignant transformation. With age, the efficacy of DNA repair diminishes, suggesting that it may contribute to the age-associated accumulation of DNA damage and thus to age-associated disorders (Meyer *et al.* 2007). Base excision repair (BER) is the predominant pathway repairing a broad range of oxidative DNA damage, including 8-oxoG. The lethality of embryos with key BER genes silenced, except from genes encoding the functionally replaceable DNA glycosylases, demonstrates the importance of this DNA repair pathway (Tebbs *et al.*, 1999). Defects in BER glycosylases and mild defects in other BER genes are associated with increased cancer susceptibility (Maynard *et al.*, 2009). DNA double-strand breaks (DSBs) arising from reactive oxygen stress are the most deleterious DNA lesions. DSBs are mainly repaired by non-homologous end joining or homologous recombination and the failure to repair or misrepairing of DSBs due to defects in these pathways can result in chromosomal rearrangements, cause genome instability and promote carcinogenesis.

CHANGES IN OXIDATIVE PHOSPHORYLATION IN PRECANCEROUS LESIONS AND CANCER CELLS

A shift from mitochondrial oxidative phosphorylation (OXPHOS) towards aerobic glycolysis as the main source of energy production, observed in various cancer cells, was originally thought to appear due to a permanent dysfunction of OXPHOS induced by cancer transformation. However, recent results suggest that OXPHOS is fully functional in most cancers, indicating that the switch to glycolysis provides cancer cells with a metabolic advantage (Koppenol *et al.*, 2011; Griguer *et al.*, 2005; Fantin *et al.*, 2006; Hsu & Sabatini, 2008; Lim *et al.*, 2011; Scott *et al.*, 2011). Indeed, due to this switch cells benefit from the availability of glucose, a high rate of ATP production and the production of lactate needed for biomolecules synthesis (Pfeiffer *et al.*, 2001; DeBerardinis *et al.*, 2008). Additionally, the glycolytic metabolism of cancer cells can contribute to hypoxia resistance, essential for tumor survival, through the induction of hypoxia-inducible factor (HIF)-1 expression (Maher *et al.*, 2007). A recent report has shown that an augmentation in OXPHOS efficiency is associated with an impediment of cancer progression by a decline in proliferation and invasiveness (Wang & Moraes, 2011). The increase in OXPHOS, observed in that research, was stimulated by the induction of mitochondrial biogenesis considered as the increase in mitochondrial proteins and enzyme activity showing the importance of mitochondria in cancer progression. Dichloroacetate (DCA), a chemical silencing glycolysis in favor of glucose oxidation is currently tested in a phase I clinical trial in patients with advanced solid tumors. Similarly, SB-204990, an inhibitor of ATP citrate lyase (ACL) coupling glucose metabolism with lipid syn-

thesis, has been reported to suppress tumor cell proliferation and growth *in vitro* and *in vivo* (Hatzivassiliou *et al.*, 2005).

Defective OXPHOS may be driven by mutations in genes encoding its components. Mutations in nuclear genes encoding subunits of succinate dehydrogenase or proteins involved in assembling OXPHOS complex II are associated with hereditary cancers (Ricketts *et al.*, 2012; Cao *et al.*, 2010). Also alterations in the mitochondria-encoded OXPHOS genes are associated with invasive properties in human cancer cell lines. One of the most convenient ways for exploring the contribution of mitochondrial mutagenesis in carcinogenesis is the use of cybrids – rho0 cells repopulated with the mtDNA of interest. Transmitochondrial cybrids with the 13997G>A mutation in the gene encoding NADH dehydrogenase subunit 6 (ND6) of mtDNA, derived from highly metastatic tumor cells, produced a higher amount of ROS which stimulated the transcription of HIF-1α and other metastasis-related genes, in comparison with low metastatic P29 cells (Koshikawa *et al.*, 2009). A missense mutation in the ND6 gene can result in a decrease of the activity of the respiratory complex I (Ishikawa *et al.*, 2008). The pretreatment of highly metastatic tumor cells with ROS scavengers reduces their metastatic potential in mice. Experiments involving inoculation of C57BL/6 mice with cybrids having high or low metastatic potential support an important role of mtDNA mutation in tumor progression. Cybrids with mtDNA derived from highly metastatic cells have a high metastatic potential, whereas cybrids with the P29 mtDNA have lost their metastatic potential, as assessed by counting the number of nodules formed in lungs. A cybrid cell line with prostate cancer PC3 cells with a point mutation in ATP synthase subunit 6 gene (MTATP6) manifests the growth advantage over cybrids of prostate cells with the non-mutated mtDNA in nude mice (Petros *et al.*, 2005; Shidara *et al.*, 2005). The mutant cybrids generate significantly more ROS and develop tumors seven times larger than the wild-type cybrids, which hardly generate tumors in mice (Petros *et al.*, 2005). The restoration of MTATP6 reduces tumor growth, whereas the expression of a mutant MTATP6 in wild-type cybrids decreases respiration and increases tumor growth (Shidara *et al.*, 2005). Interestingly, apoptosis occurrs less frequently in the mutant versus wild-type cybrids in cultures and tumors, thus demonstrating that pathogenic mtDNA mutations can promote tumors by apoptosis prevention. All these data suggest that alterations in mtDNA are not only associated with carcinogenesis but may also play a role in tumor progression (Singh *et al.*, 2005; Kulawiec *et al.*, 2006).

The mutation frequency in mtDNA is related to energy metabolism, which has been shown by a 3-fold lower mtDNA random mutation frequency accompanying a shift in glucose metabolism from OXPHOS to glycolysis in colorectal cancer cells, when compared to adjacent normal colon (Ericson *et al.*, 2012). The reduced prevalence of these mutations in tumor cells relative to normal cells suggests that mitochondrial genome stability, unlike that of nDNA, increases during carcinogenesis. The difference in the mutation rate between tumor and normal cells result from a decline in C:G to T:A transitions, the most common oxidative stress-induced mutation, indicating that mtDNA mutagenesis is at least partially a consequence of OXPHOS-generated oxidative stress (Ericson *et al.*, 2012; Wang *et al.*, 1998). Although the overall mtDNA mutation rate decreases in carcinogenesis, the level of mutations in the OXPHOS genes may increase, as shown for the NADH dehydrogenase (respiratory complex I) subunits, which is in accordance with the OXPHOS-glycolysis switch in cancer cells (De Paepe, 2012). A switch to aerobic glycolysis in tumor cells is also associated with changes in nDNA, including gain of function mutations in proto-oncogenes, loss or mutation of tumor suppressors, and the activation of phosphoinositide 3-kinase (PI3K) (Vander *et al.*, 2009). Further research has revealed that changes in mitochondrial metabolism are associated with oncogene-induced cancer transformation (Weinberg *et al.*, 2010). The Ras oncogene promotes production of mitochondrial ROS, which further stimulates cellular proliferation in human colon cancer HCT116 cell line (Weinberg *et al.*, 2010). This effect is abrogated in the presence of mitochondria-targeted antioxidants indicating that mitochondrial ROS may serve as signaling molecules regulating cell proliferation (Weinberg *et al.*, 2010). Additionally, the Kras-induced rho0 cells, which do not generate ROS due to the lack of mtDNA, do not grow in an anchorage-independent manner, typical for cancer cells. In contrast, cells with a disrupted ATP complex III generate ROS and grow in an anchorage dependent-manner. Finally, the loss of the TFAM protein, essential for mtDNA replication and transcription, diminishes tumorigenicity in an oncogenic Kras-induced mouse model of lung adenocarcinoma, demonstrating that mitochondrial metabolism is required for carcinogenesis *in vivo*.

MITOCHONDRIA-DEPENDENT RESISTANCE TO APOPTOSIS AND ITS ROLE IN ANTICANCER THERAPY

Because mitochondria can play a pivotal role in apoptosis, damage to mtDNA may promote tumors formation by the inhibition of apoptosis of pre-cancerous cells. This presents a perspective for a new mitochondria-oriented anticancer treatment. Indeed, rho0 cells derived from human osteosarcoma are less sensitive toward different apoptosis-inducers, including staurosporine, doxorubicin, daunomycin and quercetin, when compared to parental cells (Ferraresi *et al.*, 2008). Furthermore, rho0 cells exhibit over-expression of multidrug resistance 1 (*MDR1*) gene and its product P-glycoprotein (P-gp). Also, a partial depletion of mtDNA induces the resistance to staurosporine-mediated apoptosis in C2C12 myoblasts (Biswas *et al.*, 2005). This effect is transient as accessed by the restoration of mtDNA content to near-normal, approximately 90%, level implying a direct association between mitochondrial stress and the development of apoptotic resistance. The observed resistance to apoptosis is attributed to impaired Bid processing and altered compartmentalization of proapoptotic proteins, BAD, Bax and Bid on the mitochondrial inner membrane under stress conditions. In addition, the mtDNA-depleted cells fail to release proapoptotic proteins and display a decreased sensitivity and accumulation of chemotherapeutic drugs doxorubicin, vincristine, and paclitaxel, which correlate with the up-regulated expression of MDR1 at mRNA and protein levels (Yu, 2011; Biswas *et al.*, 2005). In addition to mtDNA content alteration, mtDNA mutations have also been shown to influence the resistance to apoptosis (Kulawiec *et al.*, 2009). The break of apoptotic-resistance is achieved by the suppression of the pro-survial members of Bcl-2 protein family, which control mitochondrial apoptosis, in hematological malignancies as well as different types of solid tumors in single or combined therapy. The molecules that target Bcl-2 members belong to BH3 mimetics,

small molecules structurally and functionally resembling BH3-only proteins. The BH3 mimetic ABT-737 demonstrates a potent antitumor activity against several mouse models of human cancers, including small cell lung cancer (SCLC) and acute leukemia (Hann *et al*., 2008; Konopleva *et al*., 2066; Mason *et al*., 2008; 2009). ABT-263 (Navitoclax) has passed through phase I/II trials for SCLC treatment and is under phase I/II trials clinical evaluation for chronic lymphocytic leukemia (CLL) and lymphoid malignancies as a single agent or in combination with various anticancer drugs (Gandhi *et al*., 2011; Rudin *et al*., 2012; National Institutes of Health, 2013). Obatoclax mesylate (GX15-070) has been demonstrated to have a modest single-agent activity in patients with advanced CLL undergoing intensive therapy (O'Brien *et al*., 2009). AT-101 has been tested against prostate cancer in a phase I clinical study as a single therapy (Liu *et al*., 2009). Overcoming the resistance of cancer cells to imatinib (IM), a tyrosine kinase inhibitor, is the leading challenge in chronic myeloid leukemia (CML) treatment. The disease is characterized by the expression of the fusion *BCR/ABL1* oncogene, whose product is a tyrosine kinase with constitutively enhanced activity. Mitochondrial alterations have been found in the leukemic cells from IM-resistant CML patients. These included the accumulation of tricarboxylic acid (TCA) cycle intermediates, an increased NADH level and low oxygen consumption, which were attributed to the dysfunction of ETC. Although a lower activity and expression of ETC proteins were noted in the IM-resistant cells, they exhibited a higher level of ROS in comparison to IM-sensitive cells. Since ROS overproduction was associated with the IM resistance, it was postulated that mitochondrial dysfunction may participate in genomic instability of cancer cells by inducing oxidative DNA damage (Koptyra *et al*., 2006). This hypothesis is coherent with the finding that oxidative stress induced mutations in the kinase domain of BCR/ABL1 contributing to the emergence of resistant cells (Slupianek *et al*., 2013). Furthermore, the generation of oxidative stress decreased the viability of IM-resistant leukemic cells in a syngenic mouse tumor model showing that this strategy can be exploited for CML treatment (Kluza *et al*., 2011; Zhang *et al*., 2008).

OTHER ASPECTS OF MITOCHONDRIAL CARCINOGENESIS

Recent findings indicate that, intriguingly, telomerase may protect mitochondria during carcinogenesis. Telomerase is a ribonucleoprotein responsible for maintaining the length of telomeres – structures protecting the ends of linear chromosomes from recognition as DSBs and activation of DNA damage response. The catalytic subunit of telomerase – telomerase reverse transcriptase (TERT) — is exported from the nucleus to mitochondria under oxidative stress in a dose- and time-dependent manner in human embryonic lung MRC5 fibroblasts (Ahmed *et al*., 2008). This process was reversible when cells were transferred back from hyperoxia to normoxia. The presence of TERT in mitochondria protected mtDNA against oxidative DNA damage under acute and chronic stress conditions. In TERT-overexpressing cells mitochondrial function was enhanced as confirmed by the increase in mitochondrial membrane potential and the reduction in mitochondrial superoxide production and cellular peroxide levels. TERT has been shown to localize to mitochondria of cancer HEK293 (human embryonic kidney) cell line and non-cancer cells (human umbilical vein endothelial cells, HUVEC) (Haendeler *et al*., 2009; Jacob & Haendeler, 2007). In the HEK cell line TERT bound to mtDNA in the region coding for NADH dehydrogenase subunits 1 and 2 (ND1 and ND2) and protected mtDNA against UVB-induced damage (Haendeler *et al*., 2009). The presence of TERT protected respiratory chain activity and the effect was most pronounced for complex I and correlated with the TERT binding to mtDNA and the reverse transcriptase activity of the enzyme, when compared to a TERT mutant lacking reverse transcriptase activity but preserving the ability to bind to mtDNA *in vivo*. The presence of wild type TERT reduced the generation of ROS in mitochondria and restricted the H2O2-induced apoptosis. Since the increase in the expression of TERT may play a role in carcinogenesis, the protective function of TERT toward mtDNA opens a possibility that mitochondria-localized TERT may participate in the stabilization of the mtDNA genome in cancer and could be exploited in new strategies for anticancer treatment.

THERAPEUTIC POTENTIAL OF MITOCHONDRIA IN CANCER

Mitochondrial functions, including ATP production, maintaining intracellular Ca^{2+} homeostasis, ROS generation, and regulation of apoptosis, altered in cancer may constitute a therapeutic target. Combined with standard anticancer strategies, application of compounds directly affecting mitochondrial functions is a promising approach for eradication of chemotherapy-resistant cancer cells. Mitochondria-oriented drugs, unlike conventional ones, induce defects in mitochondria independently of the upstream signaling events. Given that cancer cells generally rely on ATP production *via* glycolysis, the suppression of this pathway could be most efficient in cells harboring mitochondrial alterations or hypoxic cells (Pelicano *et al*., 2006). In contrast, this strategy may produce an opposite effect in cancer cells with functional mitochondria as mitochondrial ATP synthesis would compensate for the inhibited glycolysis. Hence, combined strategies involving blocking of mitochondrial activity along with the suppression of glycolysis could be required for the induction of cancer cell death. In support of this concept, shifting the balance from the anaerobic toward aerobic ATP biosynthesis sensitized several previously resistant cancer cell lines to an inhibitor of mitochondrial ATP synthase (Salomon *et al*., 2000). A similar effect was observed when 2-deoxyglucose was applied instead of oxamate to inhibit glycolysis. Concomitantly with an altered ETC, cancer cells exhibited an increased ROS production. As a consequence, cancer cells are more prone to the ROS-induced apoptosis in comparison to normal, especially non-dividing, cells. Indeed, mitochondrial electron transport chain blockers and mitochondrially targeted anti-cancer drugs with prooxidant properties (mitocans) have been demonstrated to eradicate cancer cells specifically. A drug combination strategy exploiting increased mitochondrial ROS generation and the inhibition of ROS elimination was effective against cultured leukemia cells and primary leukemia cells isolated from patients (Pelicano *et al*., 2003). The combination of 2-methoxyestradiol (2-ME) — an inhibitor of superoxide dismutase — with either rotenone, an inhibitor of complex I, or with arsenic trioxide, As_2O_3, a ROS-generating agent, promoted synergistically apoptosis. The ability of As_2O_3, used in clinical anticancer treatment, to interfere with mitochondrial respiration and to

increase ROS generation implies that the anticancer activity of other currently applied ROS-generating agents, such as doxorubicin, bleomycin, and cisplatin, could be improved in combination with 2-ME and similarly acting compounds. In addition, treatment of human colon cancer cell lines HT29 and HCT116 with 2-deoxy-D-glucose (2DG), an inhibitor of glucose metabolism, combined with the ETC blocker rotenone enhanced cancer cell death (Fath *et al*., 2009). In contrast, 2-methoxy-antimycin A, which does not affect ETC, does not promote the 2DG-induced cytotoxicity in cancer cells. Furthermore, rotenone does not increase the toxicity of 2DG in normal human fibroblasts and the combination of 2DG with rotenone restricts tumor growth in HT29 tumor-bearing mice when compared to control or either drug singly.

Other anticancer strategies are focused on the neutralization of anti-apoptotic Bcl-2 family proteins. This can be achieved by synthetic compounds corresponding to the BH3 domain, BH3 mimetics, that antagonize the anti-apoptotic function of Bcl-2 family members. Despite their promising action achieved *in vitro*, these next generation therapeutics need to be further investigated *in vivo* to be fully exploited clinically, either as a single or in combined therapy.

The oxidative-stress mediated localization of TERT to mitochondria rises the possibility of telomerase-oriented anticancer treatment. Cancer cells exhibit robust telomerase activity and the extinction of telomerase immediately gives rise to an adaptive mechanism — the emergence of the alternative lengthening of telomeres (ALT) (Hu *et al*., 2012). The viability of ALT-positive cancer cells is dependent on the expression of PGC-1b, a master regulator of mitochondrial biogenesis and function indicating that preserving some mitochondrial function is vital in cancer cells. Therefore, ALT-positive cancer, constituting approximately 15% of human cancers, could be sensitive to compounds disturbing mitochondrial maintenance.

CONCLUSION AND PERSPECTIVES

Mitochondria are essential organelles involved in several important cellular processes, whose disturbance may bring serious consequences for the functioning of an organism. The involvement and important role of mitochondria in cancer transformation is underlined by several mechanisms, including the mutagenesis of mtDNA. Each aspect of the association between mitochondria and cancer can be exploited for its usefulness in anticancer therapy. Because these aspects are apparent as differences between normal and cancer cells, the greater the difference, the higher their potential in therapy. Mitochondria-dependent drug resistance can be modulated by some modifications of the intrinsic apoptotic pathway, which can also be involved in the proliferation of cancer cells and their metastatic potential. Overproduction of ROS in mitochondria and the involvement of these species in cancer transformation should be further exploited in prospective anticancer therapy, because ROS may be associated with many aspects of carcinogenesis. Manipulation of the mitochondrial potential with agents influencing the electrochemical gradient across the mitochondrial membrane can be both a goal for combating cancer cells and serve to improve the delivery of mitochondria-targeting drugs. Some long-term perspectives in exploiting mitochondria in cancer therapy involve manipulation of mitochondria in cancer and mtDNA-targeted gene therapy.

Acknowledgement

This study was supported by the grant number 2011/03/B/NZ2/01396 from National Science Center, Poland.

REFERENCES

Ahmed S, Passos JF, Birket MJ, Beckmann T, Brings S, Peters H, Birch-Machin MA, von Zglinicki T, Saretzki G (2008) Telomerase does not counteract telomere shortening but protects mitochondrial function under oxidative stress. *J Cell Sci* **121**: 1046–1053.

Arismendi-Morillo G (2009) Electron microscopy morphology of the mitochondrial network in human cancer. *Int J Biochem Cell Biol* **41**: 2062–2068.

Bagchi D, McGinn TR, Ye X, Bagchi M, Krohn RL, Chatterjee A, Stohs SJ (2002) Helicobacter pylori-induced oxidative stress and DNA damage in a primary culture of human gastric mucosal cells. *Dig Dis Sci* **47**: 1405–1412.

Bender A, Krishnan KJ, Morris CM, Taylor GA, Reeve AK, Perry RH, Jaros E, Hersheson JS, Betts J, Klopstock T, Taylor RW, Turnbull DM (2006) High levels of mitochondrial DNA deletions in substantia nigra neurons in aging and Parkinson disease. *Nat Genet* **38**: 515–517.

Biswas G, Anandatheerthavarada HK, Avadhani NG (2005) Mechanism of mitochondrial stress-induced resistance to apoptosis in mitochondrial DNA-depleted C2C12 myocytes. *Cell Death Differ* **12**: 266–278.

De Paepe B (2012) Mitochondrial markers for cancer: relevance to diagnosis, therapy, and prognosis and general understanding of malignant disease mechanisms. International Scholarly Research Network 2012: article ID 217162.

Boffoli D, Scacco SC, Vergari R, Solarino G, Santacroce G, Papa S (1994) Decline with age of the respiratory chain activity in human skeletal muscle. *Biochim Biophys Acta* **1226**: 73–82.

Boland CR, Goel A (2010) Microsatellite instability in colorectal cancer. *Gastroenterology* **138**: 2073–2087.

Cao Z, Song JH, Kang YW, Yoon JH, Nam SW, Lee JY, Park WS (2010) Analysis of succinate dehydrogenase subunit B gene alterations in gastric cancers. *Pathol Int* **60**: 559–565.

Corral-Debrinski M, Horton T, Lott MT, Shoffner JM, Beal MF, Wallace DC (1992) Mitochondrial DNA deletions in human brain: regional variability and increase with advanced age. *Nat Genet* **2**: 324–329.

Cortopassi GA, Arnheim N (1990) Detection of a specific mitochondrial DNA deletion in tissues of older humans. *Nucleic Acids Res* **18**: 6927–6933.

de Grey AD (1997) A proposed refinement of the mitochondrial free radical theory of aging. *Bioessays* **19**: 161–166.

de Souza-Pinto NC, Mason PA, Hashiguchi K, Weissman L, Tian J, Guay D, Lebel M, Stevnsner TV, Rasmussen LJ, Bohr VA (2009) Novel DNA mismatch-repair activity involving YB-1 in human mitochondria. *DNA Repair (Amst)* **8**: 704–719.

DeBerardinis RJ, Lum JJ, Hatzivassiliou G, Thompson CB (2008) The biology of cancer: Metabolic reprogramming fuels cell growth and proliferation. *Cell Metab* **7**: 11–20.

Delsite RL, Rasmussen LJ, Rasmussen AK, Kalen A, Goswami PC, Singh KK (2003) Mitochondrial impairment is accompanied by impaired oxidative DNA repair in the nucleus. *Mutagenesis* **18**: 497–503.

Elson JL, Samuels DC, Turnbull DM, Chinnery PF (2001) Random intracellular drift explains the clonal expansion of mitochondrial DNA mutations with age. *Am J Hum Genet* **68**: 802–806.

Ericson NG, Kulawiec M, Vermulst M, Sheahan K, O'Sullivan J, Salk JJ, Bielas JH (2012) Decreased mitochondrial DNA mutagenesis in human colorectal cancer. *PLoS Genet* **8**: e1002689.

Fantin VR, St-Pierre J, Leder P (2006) Attenuation of LDH-A expression uncovers a link between glycolysis, mitochondrial physiology, and tumor maintenance. *Cancer Cell* **9**: 425–434.

Fath MA, Diers AR, Aykin-Burns N, Simons AL, Hua L, Spitz DR (2009) Mitochondrial electron transport chain blockers enhance 2-deoxy-D-glucose induced oxidative stress and cell killing in human colon carcinoma cells. *Cancer Biol Ther* **8**: 1228–1236.

Fayet G, Jansson M, Sternberg D, Moslemi AR, Blondy P, Lombes A, Fardeau M, Oldfors A (2002) Ageing muscle: clonal expansions of mitochondrial DNA point mutations and deletions cause focal impairment of mitochondrial function. *Neuromuscul Disord* **12**: 484–493.

Ferraresi R, Troiano L, Pinti M, Roat E, Lugli E, Quaglino D, Taverna D, Bellizzi D, Passarino G, Cossarizza A (2008) Resistance of mtDNA-depleted cells to apoptosis. *Cytometry A* **73**: 528–537.

Fliss MM, Usadel H, Caballero OL, Wu L, Buta MR, Ele. SM, Jen J, Sidransky D (2000) Facile detection of mitochondrial DNA mutations in tumors and bodily fluids. *Science* **287**: 2017–2019.

Gandhi L, Camidge DR, Ribeiro de Oliveira M, Bonomi P, Gandara D, Khaira D, Hann CL, McKeegan EM, Litvinovich E, Hemken

PM, Dive C, Enschede SH, Nolan C, Chiu YL, Busman T, Xiong H, Krivoshik AP, Humerickhouse R, Shapiro GI, Rudin CM (2011) Phase I study of Navitoclax (ABT-263), a novel Bcl-2 family inhibitor, in patients with small-cell lung cancer and other solid tumors. *J Clin Oncol* **29**: 909–916.

Griguer CE, Oliva CR, Gillespie GY (2005) Glucose metabolism heterogeneity in human and mouse malignant glioma cell lines. *J Neurooncol* **74**: 123–133.

Grollman AP, Moriya M (1993) Mutagenesis by 8-oxoguanine: an enemy within. *Trends Genet* **9**: 246–249.

Haendeler J, Dröse S, Büchner N, Jakob S, Altschmied J, Goy C, Spyridopoulos I, Zeiher AM, Brandt U, Dimmeler S (2009) Mitochondrial telomerase reverse transcriptase binds to and protects mitochondrial DNA and function from damage. *Arterioscler Thromb Vasc Biol* **29**: 929–935.

Hann CL, Daniel VC, Sugar EA, Dobromilskaya I, Murphy SC, Cope L, Lin X, Hierman JS, Wilburn DL, Watkins DN, Rudin CM (2008) Therapeutic efficacy of ABT-737, a selective inhibitor of BCL-2, in small cell lung cancer. *Cancer Res* **68**: 2321–2328.

Hattori K, Tanaka M, Sugiyama S, Obayashi T, Ito T, Satake T, Hanaki Y, Asai J, Nagano M, Ozawa T (1991) Age-dependent increase in deleted mitochondrial DNA in the human heart: possible contributory factor to presbycardia. *Am Heart J* **121**: 1735–1742.

Hatzivassiliou G, Zhao F, Bauer DE, Andreadis C, Shaw AN, Dhanak D, Hingorani SR, Tuveson DA, Thompson CB (2005) ATP citrate lyase inhibition can suppress tumor cell growth. *Cancer Cell* **8**: 311–321.

Heerdt BG, Houston MA, Augenlicht LH (2005) The intrinsic mitochondrial membrane potential of colonic carcinoma cells is linked to the probability of tumor progression. *Cancer Res* **65**: 9861–9867.

Herbener GH (1976) A morphometric study of age-dependent changes in mitochondrial population of mouse liver and heart. *J Gerontol* **31**: 8–12.

Houston MA, Augenlicht LH, Heerdt BG (2011) Stable differences in intrinsic mitochondrial membrane potential of tumor cell subpopulations reflect phenotypic heterogeneity. *Int J Cell Biol* **2011**: 978583.

Hsu PP, Sabatini DM (2008) Cancer cell metabolism: Warburg and beyond. *Cell* **134**: 703–707.

Hu J, Hwang SS, Liesa M, Gan B, Sahin E, Jaskelioff M, Ding Z, Ying H, Boutin AT, Zhang H, Johnson S, Ivanova E, Kost-Alimova M, Protopopov A, Wang YA, Shirihai OS, Chin L, DePinho RA (2012) Antitelomerase therapy provokes ALT and mitochondrial adaptive mechanisms in cancer. *Cell* **148**: 651–663.

Ishikawa K, Takenaga K, Akimoto M, Koshikawa N, Yamaguchi A, Imanishi H, Nakada K, Honma Y, Hayashi J (2008) ROS-generating mitochondrial DNA mutations can regulate tumor cell metastasis. *Science* **320**: 661–664.

Jakob S, Haendeler J (2007) Molecular mechanisms involved in endothelial cell aging: role of telomerase reverse transcriptase. *Z Gerontol Geriatr* **40**: 334–338.

Jose C, Bellance N, Rossignol R (2010) Choosing between glycolysis and oxidative phosphorylation: a tumor's dilemma? *Biochim Biophys Acta* **1807**: 552– 561.

Kluza J, Jendoubi M, Ballot C, Dammak A, Jonneaux A, Idziorek T, Joha S, Dauphin V, Malet-Martino M, Balayssac S, Maboudou P, Briand G, Formstecher P, Quesnel B, Marchetti P (2011) Exploiting mitochondrial dysfunction for effective elimination of imatinib-resistant leukemic cells. *PLoS One* **6**: e21924.

Konopleva M, Contractor R, Tsao T, Samudio I, Ruvolo PP, Kitada S, Deng X, Zhai D, Shi YX, Sneed T, Verhaegen M, Soengas M, Ruvolo VR, McQueen T, Schober WD, Watt JC, Jiffar T, Ling X, Marini FC, Harris D, Dietrich M, Estrov Z, McCubrey J, May WS, Reed JC, Andreeff M (2006) Mechanisms of apoptosis sensitivity and resistance to the BH3 mimetic ABT-737 in acute myeloid leukemia. *Cancer Cell* **10**: 375–388.

Koppenol WH, Bounds PL and Dang CV (2011) Otto Warburg's contributions to current concepts of cancer metabolism. *Nat Rev Cancer* **11**: 325–337.

Koptyra M, Falinski R, Nowicki MO, Stoklosa T, Majsterek I, Nieborowska-Skorska M, Blasiak J, Skorski T (2006) BCR/ABL kinase induces self-mutagenesis *via* reactive oxygen species to encode imatinib resistance. *Blood* **108**: 319–327.

Koshikawa N, Hayashi J, Nakagawara A, Takenaga K (2009) Reactive oxygen species-generating mitochondrial DNA mutation up-regulates hypoxia-inducible factor-1alpha gene transcription *via* phosphatidylinositol 3-kinase-Akt/protein kinase C/histone deacetylase pathway. *J Biol Chem* **284**: 33185–33194.

Krokan HE, Standal R, Slupphaug G (1997) DNA glycosylases in the base excision repair of DNA. *Biochem J* **325**: 1–16.

Kujoth GC, Hiona A, Pugh TD, Someya S, Panzer K, Wohlgemuth SE, Hofer T, Seo AY, Sullivan R, Jobling WA, Morrow JD, Van Remmen H, Sedivy JM, Yamasoba T, Tanokura M, Weindruch R, Leeuwenburgh C, Prolla TA (2005) Mitochondrial DNA mutations, oxidative stress, and apoptosis in mammalian aging. *Science* **309**: 481–484.

Kulawiec M, Arnouk H, Desouki MM, Kazim L, Still I, Singh KK (2006) Proteomic analysis of mitochondria-to-nucleus retrograde response in human cancer. *Cancer Biol Ther* **5**: 967–975.

Kulawiec M, Owens KM, Singh KK (2009) Cancer cell mitochondria confer apoptosis resistance and promote metastasis. *Cancer Biol Ther* **8**: 1378–1385.

Lapointe J, Hekimi S (2010) When a theory of aging ages badly. *Cell Mol Life Sci* **67**: 1–8.

Larman TC, DePalma SR, Hadjipanayis AG; Cancer Genome Atlas Research Network, Protopopov A, Zhang J, Gabriel SB, Chin L, Seidman CE, Kucherlapati R, Seidman JG (2012) Spectrum of somatic mitochondrial mutations in five cancers. *Proc Natl Acad Sci USA* **109**: 14087–14091.

Lee HC, Li SH, Lin JC, Wu CC, Yeh DC, Wei YH (2004) Somatic mutations in the D-loop and decrease in the copy number of mitochondrial DNA in human hepatocellular carcinoma. *Mutat Res* **547**: 71–78.

Lee HC, Wei YH (2005) Mitochondrial biogenesis and mitochondrial DNA maintenance of mammalian cells under oxidative stress. *Int J Biochem Cell Biol* **37**: 822–834.

Lee HC, Wei YH (2009) Mitochondrial DNA instability and metabolic shift in human cancers. *Int J Mol Sci* **10**: 674–701.

Li LZ (2012) Imaging mitochondrial redox potential and its possible link to tumor metastatic potential. *J Bioenerg Biomembr* **44**: 645–653.

Lim HY, Ho QS, Low J, Choolani M, Wong KP (2011) Respiratory competent mitochondria in human ovarian and peritoneal cancer. *Mitochondrion* **11**: 437–443.

Linnane AW, Marzuki S, Ozawa T, Tanaka M (1989) Mitochondrial DNA mutations as an important contributor to ageing and degenerative diseases. *Lancet* **1**: 642–645.

Lipetz J, Cristofalo VJ (1972) Ultrastructural changes accompanying the aging of human diploid cells in culture. *J Ultra Res* **39**: 43–56.

Liu G, Kelly WK, Wilding G, Leopold L, Brill K, Somer B (2009) An open-label, multicenter, phase I/II study of single-agent AT-101 in men with castrate-resistant prostate cancer. *Clin Cancer Res* **15**: 3172–3176.

Lu J, Sharma LK, Bai Y (2009) Implications of mitochondrial DNA mutations and mitochondrial dysfunction in tumorigenesis. *Cell Res* **19**: 802–815.

Maher JC, Wangpaichitr M, Savaraj N, Kurtoglu M, Lampidis TJ (2007) Hypoxia-inducible factor-1 confers resistance to the glycolytic inhibitor 2-deoxy-D-glucose. *Mol Cancer Ther* **6**: 732–741.

Mason KD, Khaw SL, Rayeroux KC, Chew E, Lee EF, Fairlie WD, Grigg AP, Seymour JF, Szer J, Huang DC, Roberts AW (2009) The BH3 mimetic compound, ABT-737, synergizes with a range of cytotoxic chemotherapy agents in chronic lymphocytic leukemia. *Leukemia* **23**: 2034–2041.

Mason KD, Vandenberg CJ, Scott CL, Wei AH, Cory S, Huang DC, Roberts AW (2008) In vivo efficacy of the Bcl-2 antagonist ABT-737 against aggressive Myc-driven lymphomas. *Proc Natl Acad Sci USA* **105**: 17961–17966.

Maynard S, Schurman SH, Harboe C, de Souza-Pinto NC, Bohr VA (2009) Base excision repair of oxidative DNA damage and association with cancer and aging. *Carcinogenesis* **30**: 2–10.

Melov S, Schneider JA, Coskun PE, Bennett DA, Wallace DC (1999) Mitochondrial DNA rearrangements in aging human brain and in situ PCR of mtDNA. *Neurobiol Aging* **20**: 565–571.

Meyer JN, Boyd WA, Azzam GA, Haugen AC, Freedman JH, Van Houten B (2007) Decline of nucleotide excision repair capacity in aging Caenorhabditis elegans. *Genome Biol* **8**: R70.

Michikawa Y, Mazzucchelli F, Bresolin N, Scarlato G, Attardi G (1999) Aging-dependent large accumulation of point mutations in the human mtDNA control region for replication. *Science* **286**: 774–779.

Miller KWP, Dawson JL, Hagelberg E (1996) A concordance of nucleotide substitutions in the first and second hypervariable segments of the human mtDNA control region. *Int J Legal Med* **109**: 107–113.

National Institutes of Health (2013) Available at http: //www.nih.gov/. Accessed 10 Jul 2013.

O'Brien SM, Claxton DF, Crump M, Faderl S, Kipps T, Keating MJ, Viallet J, Cheson BD (2009) Phase I study of obatoclax mesylate (GX15-070), a small molecule pan-Bcl-2 family antagonist, in patients with advanced chronic lymphocytic leukemia. *Blood* **113**: 299–305.

Ozawa T (1995) Mechanism of somatic mitochondrial DNA mutations associated with age and diseases. *Biochim Biophys Acta* **1271**: 177–189.

Pelicano H, Feng L, Zhou Y, Carew JS, Hileman EO, Plunkett W, Keating MJ, Huang P (2003) Inhibition of mitochondrial respiration: a novel strategy to enhance drug-induced apoptosis in human leukemia cells by a reactive oxygen species-mediated mechanism. *J Biol Chem* **278**: 37832–37839.

Pelicano H, Martin DS, Xu RH, Huang P (2006) Glycolysis inhibition for anticancer treatment. *Oncogene* **25**: 4633–4646.

Petros JA, Baumann AK, Ruiz-Pesini E et al (2005) MtDNA mutations increase tumorigenicity in prostate cancer. *Proc Natl Acad Sci USA* **102**: 719–724.

Pfeiffer T, Schuster S, Bonhoeffer S (2001) Cooperation and competition in the evolution of ATP-producing pathways. *Science* **292**: 504–507.

Ricketts CJ, Shuch B, Vocke CD, Metwalli AR, Bratslavsky G, Middelton L, Yang Y, Wei MH, Pautler SE, Peterson J, Stolle CA, Zbar B, Merino MJ, Schmidt LS, Pinto PA, Srinivasan R, Pacak K, Linehan WM (2012) Succinate dehydrogenase kidney cancer: an aggressive example of the Warburg effect in cancer. *J Urol* **188**: 2063–7113.

Rudin CM, Hann CL, Garon EB, Ribeiro de Oliveira M, Bonomi PD, Camidge DR, Chu Q, Giaccone G, Khaira D, Ramalingam SS, Ranson MR, Dive C, McKeegan EM, Chyla BJ, Dowell BL, Chakravartty A, Nolan CE, Rudersdorf N, Busman TA, Mabry MH, Krivoshik AP, Humerickhouse RA, Shapiro GI, Gandhi L (2012) Phase II study of single-agent navitoclax (ABT-263) and biomarker correlates in patients with relapsed small cell lung cancer. *Clin Cancer Res* **18**: 3163–3169.

Salomon AR, Voehringer DW, Herzenberg LA, Khosla C (2000) Understanding and exploiting the mechanistic basis for selectivity of polyketide inhibitors of F(0)F(1)-ATPase. *Proc Natl Acad Sci USA* **97**: 14766–14771.

Scott DA, Richardson AD, Filipp FV, Knutzen CA, Chiang GG, Ronai ZA, Osterman AL, Smith JW (2011) Comparative metabolic flux profiling of melanoma cell lines: beyond the Warburg effect. *J Biol Chem* **286**: 42626–42634.

Shidara Y, Yamagata K, Kanamori T et al (2005) Positive contribution of pathogenic mutations in the mitochondrial genome to the promotion of cancer by prevention from apoptosis. *Cancer Res* **65**: 1655–1663.

Short KR, Bigelow ML, Kahl J, Singh R, Coenen-Schimke J, Raghavakaimal S, Nair KS (2005) Decline in skeletal muscle mitochondrial function with aging in humans. *Proc Natl Acad Sci USA* **102**: 5618–5623.

Singh KK, Ayyasamy V, Owens KM, Koul MS, Vujcic M (2009) Mutations in mitochondrial DNA polymerase-gamma promote breast tumorigenesis. *J Hum Genet* **54**: 516–524.

Singh KK, Kulawiec M, Still I, Desouki MM, Geradts J, Matsui SI (2005) Inter-genomic cross talk between mitochondria and the nucleus plays an important role in tumorigenesis. *Gene* **354**: 140–146.

Slupianek A, Falinski R, Znojek P, Stoklosa T, Flis S, Doneddu V, Pytel D, Synowiec E, Blasiak J, Bellacosa A, Skorski T (2013) BCR-ABL1 kinase inhibits uracil DNA glycosylase UNG2 to enhance oxidative DNA damage and stimulate genomic instability. *Leukemia* **27**: 629-634.

Smiraglia DJ, Kulawiec M, Bistulfi GL, Gupta SG, Singh KK (2008) A novel role for mitochondria in regulating epigenetic modification in the nucleus. *Cancer Biol Ther* **7**: 1182–1190.

Taanman JW (1999) The mitochondrial genome: structure, transcription, translation and replication. *Biochim Biophys Acta* **1410**: 103–123.

Taylor RW, Barron MJ, Borthwick GM, Gospel A, Chinnery PF, Samuels DC, Taylor GA, Plusa SM, Needham SJ, Greaves LC, Kirkwood TB, Turnbull DM (2003) Mitochondrial DNA mutations in human colonic crypt stem cells. *J Clin Invest* **112**: 1351–1360.

Tebbs RS, Flannery ML, Meneses JJ, Hartmann A, Tucker JD, Thompson LH, Cleaver JE, Pedersen RA (1999) Requirement for the Xrcc1 DNA base excision repair gene during early mouse development. *Dev Biol* **208**: 513–529.

Trifunovic A, Wredenberg A, Falkenberg M, Spelbrink JN, Rovio AT, Bruder CE, Bohlooly-Y M, Gidlöf S, Oldfors A, Wibom R, Törnell J, Jacobs HT, Larsson NG (2004) Premature ageing in mice expressing defective mitochondrial DNA polymerase. *Nature* **429**: 417–423.

Vander Heiden MG, Cantley LC, Thompson CB (2009) Understanding the Warburg effect: The metabolic requirements of cell proliferation. *Science* **324**: 1029–1033.

Vives-Bauza C, Gonzalo R, Manfredi G, Garcia-Arumi E, Andreu AL (2006) Enhanced ROS production and antioxidant defenses in cybrids harbouring mutations in mtDNA. *Neurosci Lett* **391**: 136–141.

Wallace DC (1992) Diseases of the mitochondrial DNA. *Annu Rev Biochem* **61**: 1175–1212.

Wallace DC (1994) Mitochondrial DNA mutations in diseases of energy metabolism. *J Bioenerg Biomembr* **26**: 241–250.

Wallace DC (2012) Mitochondria and cancer. *Nat Rev Cancer* **12**: 685–698.

Wang D, Kreutzer DA, Essigmann JM (1998) Mutagenicity and repair of oxidative DNA damage: insights from studies using defined lesions. *Mutat Res* **400**: 99–115.

Wang X, Moraes CT (2011) Increases in mitochondrial biogenesis impair carcinogenesis at multiple levels. *Mol Oncol* **5**: 399–409.

Wang Y, Liu VW, Tsang PC et al (2006) Microsatellite instability in mitochondrial genome of common female cancers. *Int J Gynecol Cancer* **16** Suppl 1: 259–266.

Weinberg F, Hamanaka R, Wheaton WW, Weinberg S, Joseph J, Lopez M, Kalyanaraman B, Mutlu GM, Budinger GR, Chandel NS (2010) Mitochondrial metabolism and ROS generation are essential for Kras-mediated tumorigenicity. *Proc Natl Acad Sci USA* **107**: 8788–8793.

Wilson PD, Franks LM (1975) The effect of age on mitochondrial ultrastructure and enzymes. *Adv Exp Med Biol* **53**: 171–183.

Xie CH, Naito A, Mizumachi T, Evans TT, Douglas MG, Cooney CA, Fan CY, Higuchi M (2007) Mitochondrial regulation of cancer associated nuclear DNA methylation. *Biochem Biophys Res Commun* **364**: 656–661.

Yu M (2011) Generation, function and diagnostic value of mitochondrial DNA copy number alterations in human cancers. *Life Sci* **89**: 65–71.

Zhang H, Trachootham D, Lu W, Carew J, Giles FJ, Keating MJ, Arlinghaus RB, Huang P (2008) Effective killing of Gleevec-resistant CML cells with T315I mutation by a natural compound PEITC through redox-mediated mechanism. *Leukemia* **22**: 1191–1199.