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Mitochondrial ROS Control of Cancer

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Abstract

Mitochondria serve a primary role in energy maintenance but also function to govern levels of mitochondria-derived reactive oxygen species (mROS). ROS have long been established to play a critical role in tumorigenesis and are now considered to be integral to the regulation of diverse signaling networks that drive proliferation, tumor cell survival and malignant progression. mROS can damage DNA, activate oncogenes, block the function of tumor suppressors and drive migratory signaling. The mitochondrion's oxidant scavenging systems including SOD2, Grx2, GPrx, Trx and TrxR are key of the cellular redox tone. These mitochondrial antioxidant systems serve to tightly control the levels of the primary ROS signaling species, H_2O_2. The coordinated control of mROS levels is also coupled to the activity of the primary H_2O_2 consuming enzymes of the mitochondria which are reliant on the epitranscriptomic control of selenocysteine incorporation. This review highlights the interplay between these many oncogenic signaling networks, mROS and the H_2O_2 emitting and consuming capacity of the mitochondria.

Keywords

reactive oxygen species; tRNA; antioxidants; tumorigenesis; signal transduction

Introduction

Mitochondria have emerged as integral participants in the regulation of cellular signaling, in part, through the generation and consumption of reactive oxygen species (ROS) under both physiologic and pathologic conditions. ROS are produced in many cellular compartments including phagosomes, peroxisomes, endoplasmic reticulum, cellular membranes, and mitochondria [1–3]. Mitochondrial ROS (mROS), metabolic byproducts of normally and functionally active mitochondria as a result of electron leak during oxidative phosphorylation and reduction of molecular O_2[4], have gained the attention of the cancer research community as their critical role in tumorigenesis continues to be unraveled.

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mROS encompass a number of primary reactive species including superoxide anion ($O_2^{\bullet-}$), hydroxyl radical ($^{\bullet}OH$), hydrogen peroxide (H_2O_2), and singlet oxygen ($^1O_2$) [5–9]. Incomplete electron transfer through electron transport chain (ETC) complexes I and II results in $O_2^{\bullet-}$ production in the mitochondrial matrix, while electron leak at complex III generates $O_2^{\bullet-}$ in both matrix and intermembrane space. Intermembrane space $O_2^{\bullet-}$ can more readily travel to the cytosol and has been shown to modify DNA [10–13]. The contribution of the different ETC complexes in the production of mROS varies when comparing healthy to pathological states as reviewed by Zorov et at (2014) [9]. It is thought that under most pathologic conditions that complex I is the primary site of $O_2^{\bullet-}$ production while complex III generates $O_2^{\bullet-}$ as a result of hypoxic signaling and hypoxia inducible factor (HIF) activation in both pathological and physiological instances [14]. Mitochondrial-localized NADPH-oxidase 4 (Nox4) also produces mROS predominantly in the form H_2O_2[15,16]. Nox4 is implicated in the pathophysiology of numerous disease processes and its inhibition can induce mesothelioma cell apoptosis[9,17]; however the signaling events that drive the latter process are yet undefined. In addition, monoaminoxidase (MAO), an important flavoprotein resident of the outer mitochondrial membrane, is another H_2O_2 generator during ischemia/reperfusion injury in the brain and heart [18–20]. As noted, there are multiples sources of mROS with the capacity to modulate cellular physiology in both beneficial and deleterious ways.

As both ROS production and scavenging are necessary to maintain cellular health, different antioxidant systems such as SOD2, Grx2, GPrx, Trx and TrxR, play coordinate roles in preserving redox balance. Disruption or overpowering of the antioxidant systems can lead to oxidative stress that induces damage to biomolecules that participate in numerous disease processes including cancer [21–25].

Historically, tumors were associated with high levels of ROS that induce tumorigenesis through DNA damage. In addition tumors are associated with a switch in the metabolic activity of the mitochondria called the Warburg effect (aerobic glycolysis with lactate production)[26,27]. While those associations remain true, new discoveries have increased the interest of the scientific community in unraveling the role of the mitochondria in cancer pathophysiology, as mROS production, redox regulation, and apoptotic signaling are all linked to cancer etiology [28]. The exploration of mitochondria's beneficial and deleterious effects in cancer's pathophysiology through mROS regulation is an active research area. This review provides a summary of the mitochondria's role in the ROS regulation of cancer.

mROS in physiological cellular regulation

In physiological conditions mROS participate in the regulation of a diverse array of signaling networks. H_2O_2-mediated cysteine oxidation is the primary mode by which mROS participate in regulating proliferative and survival signals [29–32]. Cellular proliferation can also be regulated by H_2O_2 through different mechanisms such as: phosphatase with sequence homology to tensin (PTEN) inactivation [33,34], activation of cyclin dependent kinase 1 (Cdk1) [35] (Lim 2015), inhibition of the protein tyrosine phosphatase (PTP1b) and mitogen-activated protein kinase (MAPK) phosphatases [36,37], propagation of growth factor cascades by activation of Lyn and Syk kinases [38], and positive regulation of the transcription

factor activator protein 1 (AP-1) through c-Jun binding at the collagen production regulator CCN1 promoter site [39].

In addition to cellular proliferation, angiogenesis is induced by the upregulation of vascular endothelial growth factor (VEGF), by mROS transcriptionally and through mROS-induced HIF stabilization [40–42]. mROS-induced HIF stabilization allows for its binding to hypoxia response element (HRE) to express hypoxic adaptation genes [43,44] in an adaptive response to low oxygen levels.

Therefore, while high levels of ROS have traditionally been considered harmful, evidence shows that the mitochondria's role in regulation of ROS production and homeostasis is crucial for maintaining normal cellular function.

mROS in cancer progression

Oxidative stress, or the abnormal accumulation of ROS has long been associated with several disease processes including cancer [45–49]. In fact the characteristic unrestricted growth pattern of tumor cells in response to ROS accumulation has been the focus of interest in several recent studies [50,51]. It has also been established that while ROS may have a mitogenic effect in tumors[50,51], at higher levels they can induce damage in cancer cells and induce apoptosis or necroptosis if not counteracted by antioxidant systems [27,52–55] (Figure 1). This shows that in terms of cellular growth and proliferation, just as healthy cells, cancer cells need to achieve a delicate redox balance to ensure survival.

As cancer cells utilize the mitogenic effects of ROS to induce cellular proliferation, several mechanisms exist to ensure an adequate ROS supply. Deactivation of tumor suppressor genes [56–58], oncogene expression [59] and mutations in mitochondrial DNA (mDNA) [60] are some mechanisms that are ROS-regulated and that can in turn regulate tumorigenic ROS production to ensure such supply.

Tumor suppressor genes that regulate cell proliferation, differentiation, apoptosis, and other vital cellular activities respond to oxidative stress by regulating both antioxidant and pro-oxidant responses as reviewed by Vurusaner 2012. In particular, mROS-mediated regulation of the tumor suppressors p53, p21, p16, FoxO, retinoblastoma (RB) and breast cancer susceptibility genes 1 and 2 (BRCA1 and BRCA2) [56] has been shown. p53 for example can both promote and limit ROS production to induce apoptosis or restrict DNA damage, respectively [6162]. The FoxO family of transcription factors controls antioxidant levels and both regulates and is regulated by ROS and mROS through acetylation, phosphorylation, and ubiquitination [63]. FoxOs can promote apoptosis in response to chemotherapy and can also induce cell quiescence [63]. In breast cancer cells the inhibitory phosphorylation of FoxO is induced by ROS-dependent protein tyrosine phosphatase PTPN12 oxidation, promoting tumorigenesis [64]. Also, Sirtuin 3 (SirT3), a mitochondrial localized tumor suppressor, [65] has been shown to decrease tumorigenesis in part by inhibiting mROS production and HIF-1α activation in fibroblast and colon carcinoma cell lines [66].

Oncogene expression may also affect mROS generation and tumor proliferation. The Ras and Myc oncogenes for instance, promote oxidant production in mitochondria and other

organelles and can modulate tumorigenic and migratory signaling [57,67–69]. Oncogene-driven ROS production induces mDNA mutations and mitochondrial dysfunction further enhancing ROS levels and apoptosis [70,71]. In a murine model of lung cancer, complex III [57], and complex I [72] were shown to be the major source or ROS required for Kras mediated anchorage-independent cell growth [73].

Mitochondrial DNA instability is another mechanism that contributes to tumorigenesis in a canonical Wnt/β-catenin independent pathway that involves increased mROS production and oxidative mDNA damage as shown in a mouse model for intestinal cancer, [74]. Further both mitochondria-generated $O_2^{\bullet-}$ and H_2O_2 have been shown to induce mutations in the gene of mitochondrial complex I's nicotinamide adenine dinucleotide dehydrogenase subunit 6 (ND6) in HepG2 cells[75]. This is consistent with the findings by Ishikawa et al. (2008) [72] where mutations in the gene encoding ND6a increased the metastatic potential of mouse tumor cell lines which was reversed by pretreatment with ROS scavengers. Moreover, inhibition of complex I in osteosarcoma cell lines results in increased mROS production and AKT activation which promotes cell survival [76].

Other ROS-mediated pathways in cancer include the activation of kinases, inhibition of phosphatases, and regulation of phosphoproteins and proteinases [77–81]. Some other pathways are shared between healthy and cancer cells in term of cellular proliferation. As an example, the mechanisms by which mROS induce angiogenesis during hypoxia via mROS-induced HIF-1α stabilization, are also utilized by cancer cells to induce tumor growth and proliferation with deleterious effects to the host [66,82,83]. HIF-1α has been associated with invasiveness of several types of cancer [25,84–87]. In addition, matrix metalloproteinases (MMPs), a group of endopeptidases that hydrolyze extracellular matrix (ECM) components, have long been known to participate in tumor progression [88–90]. As both MMPs and HIF-1α may play critical roles in metastatic disease progression, and mROS play critical roles in the regulation of both MMPs [91,92] and HIF-1α [93], it is very likely that their contribution to tumorigenesis may be controlled by redox-dependent programming under mitochondrial control.

Mitochondrial antioxidant systems

It is known that a precise regulation of ROS formation and scavenging is crucial for maintaining cellular and organismal homeostasis. For this purpose several enzymatic and non-enzymatic processes occur in order to coordinate the conversion of molecules from highly reactive into less reactive ones [9,24]. Examples of these processes are the oxidant-scavenging activity that occurs through the superoxide dismutases (SOD), peroxidase, and catalase enzymatic systems at distinct cellular locations [94]. For instance, reactive $O_2^{\bullet-}$ is converted into H_2O_2, by superoxide dismutase (SOD)1 in the cytosol, by SOD2 in the mitochondrial matrix, and by SOD3 in the extracellular space [24,95]. Reduction of H_2O_2 into H_2O restricts reactive $^{\bullet}OH$ formation through fenton chemistry and is regulated by both the catalase and the peroxidase systems such as the thioredoxin/ thioredoxin reductase/ peroxiredoxin (Trx/TrxR/Prx) and the glutathione/glutathione peroxidase (GSH/GPx) systems [94] (Figure 2). These redox systems seem to be independently regulated, and allow for the selective signaling regulation of the redox state [96]. Moreover, the

compartmentalization of some of these systems also denotes a localized effect of their regulating functions; for instance, the Trx2/TrxR2/Prx3 system in the mitochondria is an independent system from the Trx1/TrxR1/Prx system in the cytoplasm and the nucleus. The GSH system on the other hand is not exclusive of the mitochondria as it interacts with the cytosolic GSH system to enact its effects[97].

The detoxification from ROS in the cytoplasm, or mROS in the mitochondria, is the main purpose of these antioxidant systems. When H_2O_2 is not cleared by these systems, it can produce protein thiol oxidation, which alters cellular signaling pathways for cellular division, differentiation and apoptosis [50]. The protein thiol oxidation can be reversed by Trx and Grx, both of which depend on TrxR and GSH for reduction [98]. In turn, both TrxR and GSH's reduction depends on NADPH oxidation to maintain a cellular redox balance. The thiol-reducing activity of GSH and Trx is then crucial for the other antioxidant elements to function properly. In addition to its role in the regulation of the cellular redox state, both Trx1 and Trx2 can activate an apoptotic response via forming a complex with apoptosis signal-regulating kinase 1 (ASK-1) in response to oxidative stress [99].

It is no surprise then, that while the mitochondrial production of ROS promotes tumor cell proliferation and metastasis, efficient ROS scavenging often inhibits cell proliferation in distinct cancer cells types and has been used to assign a tumor suppressor function to a number of ROS mitigation newtworks[28]. Thus, a special interest continues to develop in the mitochondria's antioxidant systems and their role in cancer pathophysiology as described below.

SOD2 / MnSOD2

Manganese superoxide dismutase (SOD2) is a mitochondrial antioxidant enzyme that catalyzes the conversion of $O_2^{\bullet-}$ to H_2O_2 [100,101]. SOD2 contributes to the regulation of cell proliferation, transformation, migration, invasion and angiogenesis primarily through the redox-dependent modulation of the transcription factors NF-KB, HIF-1, AP-1 and p53 [100,102–104]. SOD2 deficiency has been shown to have both pro- and antitumorigenic activity [102,105–107]. High SOD2 expression can inhibit cell proliferation directly [108] or sensitize cells to the cytotoxicity of the anti-cancer drugs [109]. In contrast, the SOD2-dependent production of H_2O_2 enhances the malignant properties of tongue squamous cell carcinoma cells by increasing Snail, MMP1, and pERK1/2 protein levels and repressing E-cadherin [110]. SOD2 can also promote epithelial to mesenchymal transition (EMT) [111]in breast cancer cells, which promotes tumor migration. Increased expression of SOD2 in tumor cells can also contribute to anoikis resistance [112], a type of apoptosis induced by disruption of cell-extracellular matrix contact [113], prolonging tumor cell's survival. As reviewed by Hempel et al (2011), a bimodal role for SOD2 during tumorigenesis is now considered. While SOD2 may have tumor suppressor activity during the initial stages of tumor progression, at later stages SOD2 levels appear to positively contribute to metastatic disease progression [108].

In a recent comprehensive meta-analysis a relation between SOD2 polymorphism and the development of non-Hodgkin lymphoma, lung cancer, and colorectal cancer was found [114]

supporting the potential of SOD2 as a cancer biomarker [115]. In addition, SOD2/catalase and SOD2/GPx1 ratios have been recently proposed as biomarkers for tumor progression and metastasis in several types of cancer [116]. Considering the different roles of SOD2 in cancer progression, metastasis and inhibition according to different cancer types and stages[108], careful assessment of SOD2 as a therapeutic target is indicated.

Grx2

Glutaredoxin-2 (Grx2) is another mitochondrial antioxidant system crucial for thiol/disulfide redox homeostasis [117]. Grx2 system has been shown to be associated with anti-apoptotic signaling by protecting Trx2/1 from oxidation in HeLa cells[118]. Grx2 is also associated with regulation of angiogenesis in embryonic cells [119] and may have a similar function in tumor cells. Grx2 silencing sensitizes HeLa cells to death by anti-cancer drugs [120]. Thus, the Grx2 system has an anti-apoptotic function via thiol redox modulation in several cancer cell models[28].

GPx-1 and GPx-4

Glutathione peroxidases (GPx) are another group of isoenzymes capable of metabolizing H_2O_2, using reduced glutathione (GSH) as a cofactor. From this group, GPx-1 and GPx-4 are found in mitochondria [28]. Both GPx-1 and GPx-4 are selenoproteins that use selenocysteine as a key active site amino acid [121]. GPx-1 overexpression suppresses intracellular ROS[122] which attenuates growth factor receptor activation mediated by oxidative stress [123], resulting in decreased cellular proliferation [122]. Moreover, the loss of heterozygosity of the Gpx1 gene located on chromosome 3p is a prevalent event during early carcinogenesis in many types of cancers including lung [124], head and neck [125], breast [126] and colon cancer [127]. In GPx4, a single nucleotide polymorphism within the 3'UTR has been linked to an increase risk of colorectal cancer [128]. While in normal cells GPx4 prevents necroptosis [129], in cancer cells overexpression of GPx4 decreases the growth of fibrosarcoma and pancreatic cancer cells while having no effect on melanoma cell growth [130]. Similar to other antioxidant systems, the mechanisms related to GPx and its effects on tumors, are not yet fully understood.

Trx2/TrxR2/Prx3

The mitochondrial thioredoxin/ thioredoxin reductase/peroxiredoxin (Trx2/TrxR2/Prx3) system, with detoxifying effects via inhibition of mROS[131], consists of a unique thioredoxin (Trx2) that is reduced via NADPH by its unique corresponding thioredoxin reductase (TrxR2), and by a corresponding peroxiredoxin (Prx3) that depends on Trx2 for its reduction after the resulting oxidation from its H_2O_2-scavenging functions[50,97]. The Trx/TrxR thioredoxin systems modulate thiol-dependent thiol-disulfide exchange reactions that control cell growth, proliferation, and other cellular functions [132].

The importance of this axis as a H_2O_2 scavenging system in the mitochondria, has been shown by increased sensitivity to ROS-inducing toxins [133], and by the presence of lethal phenotypes in mice lacking any of the Trx2/TrxR2/Prx3 components [134]. Besides having a

key role in mitochondrial redox homeostasis, Trx2 also exerts a redox-dependent regulation of transcription and signaling factors that inhibit apoptosis through NF-Kβ [97] and ASK-1 pathways [135]. In HeLa cells, Trx2 reduces TNFα-mediated mROS production and apoptosis, with inhibition of subsequent signaling pathways [97,135].

TrxRs are a group of selenoproteins that are important for maintaining cellular redox balance and eliminating ROS. TrxR2 is the mitochondrial isoform of the three known TrxRs found in mammals. TrxR2 catalyzes the NADPH-dependent reduction of Trx2, which in its reduced state protects against elevated levels of ROS within the mitochondria [136]. It has been reported that TrxR2 expression is highly elevated in liver cancer [137], TrxR1 levels on the other hand, the cytosolic isoform, are upregulated in many different cancers including breast [138], thyroid [139], prostate [140], liver [141], melanomas [142] and colorectal, where strong overexpression of both TrxR and Trx may correlate with overall tumor aggressiveness [143], perhaps through the HIF-1 pathway[144]. The elevated level of the enzyme is an adaptation to the increased ROS production resulting from the higher metabolic activity of cancer cells [145]. The TrxRs have become an important molecular target in cancer treatment, since its inhibition results in an increased susceptibility in regards to cytotoxicity and cell death [146]. Single nucleotide polymorphism (SNP) in both TrxR1 and TrxR2 have been found to be associated with the risk of developing colorectal tumors [147,148].

Peroxiredoxins are a group of peroxidases that reduce peroxides with conserved cysteine residues [149]. Of the 6 mammalian isoforms, Prx3 and Prx5 (also found in peroxisomes) localize in the mitochondria [150]. Prx3, member of the Trx2/TrxR2/Prx3 axis, is the major target of the H_2O_2 generated in the mitochondrial matrix, and its inhibition has shown to sensitize cells to apoptosis [150]. Prx3's expression is upregulated in prostate[151], colon[152], and cervical[153] cancer, and some studies suggest it has an important role in the regulation of ROS-induced apoptosis in antiandrogen-resistant cells, which may convey its potential as a therapeutic target in prostate cancer[151]. Moreover, in a malignant mesothelioma cell line, it was established that Prx3 levels allowed cells to thrive in response to elevated mROS levels, and that any alteration in the redox activity of Prx3 impaired cell proliferation pausing the G2/M phase [154], showing that this important peroxidase allows for proper cell cycle dynamics in this particular cancer cell line.

Determination of ROS and antioxidant concentrations

As the balance between oxidative stress and the antioxidant systems play a crucial role in cellular homeostasis and cancer pathophysiology, the quantification of both ROS and antioxidant levels has become of increasing interest to scientists. As an example, in murine and human breast cancer models, cancer stem cells (CSC), unlike other cancer cell lines, display lower ROS levels than their corresponding non-cancerous cells. The low ROS burden in the CSC's is associated with increases in endogenous antioxidant systems and confers radiation-resistance that is reversed by pharmacologic depletion of antioxidants [155]. In this case, the quantification of ROS and the antioxidant systems in CSC's and their non-tumor counterparts proved pivotal in defining strategies to reverse limit their therapeutic resistance.

As indicated above, the redox properties greatly vary between different cancer types, which makes the quantification of ROS and the antioxidant system's activity a potentially useful parameter to determine each cancer type's response to determined therapies. We are not aware of any broad quantitative ROS profiling of tumor cells but our own studies and those of other groups indicate that the concentrations of steady-state [H_2O_2] (SS-[H_2O_2]) in select tumor cell studies range anywhere from 5-50 picomolar[156,157]. Metastastic bladder tumor cells display a near 2-fold (18-31 pM) increase SS-[H_2O_2] when compared to their non-metastatic parental counterpart[156]. It is possible that chemotherapeutic strategies which both augment metabolic H_2O_2 production and limit ROS detoxification may allow for SS-[H_2O_2] to exceed these picomolar quantities and drive tumor cell death.

The ability to develop chemotherapeutic strategies based on the intrinsic redox-state of a particular cancer is reliant on precise monitoring of cellular ROS levels. For this purpose, several direct and indirect methods are used to measure oxidative stress, and their advantages and disadvantages have been reviewed by Poljsak et al [158]. One of the disadvantages of direct quantification of free radicals is that the high reactivity and short half-life of such molecules, make it difficult to achieve steady concentrations of ROS in the micromolar range, limiting their accurate measurement with tools such electron spin resonance (ESR) in patients[158].

Traditional indirect methods to quantify oxidative stress focus on detecting either more stable ROS intermediates or tracers of free radical damage in biomolecules[158,159]. Indirect methods include the measurement of total antioxidant status by colorimetric, enzymatic, fluorescent and immune methods, the measurement of endogenous enzymatic and non-enzymatic antioxidant systems[160], and the fingerprinting methods through high performance liquid chromatography, gas-liquid chromatography and colorimetric tests that are able to measure markers of oxidative DNA damage, lipid peroxidation and protein damage [158]. Markers of oxidative stress damage include 8-OHdG (8-hydroxyguanosine), double-strand DNA breaks, 4-HNE (4-Hydroxynonenal), MDA (Malondialdehyde), PCC (protein carbonyl content), 3-Nytrotyrosine, advanced glycation end products and others[158,161].

A new generation of redox-sensors include genetically encoded probes or direct chemical sensors. These novel sensors can provide sensitivity to monitor near picomolar fluxes in SS-[H_2O_2] and we refer the reader to detailed reviews on this topic[162,163].

The quantification of antioxidants and antioxidant systems in patients has its own challenges. The direct measurement of specific antioxidants is not only expensive but may fail to account for synergistic effects of antioxidants and leave many key antioxidants unmeasured[158]. Also, the changing values of oxidative stress markers over time and from patient to patient make it difficult to establish typical oxidative stress reference values [164,165]. Therefore, while there is a continued effort to improve and expand the methods to quantify the oxidative stress status in an effective, efficient, cost permissive and accurate manner, to date, there is not a single established preferred method that would prove useful in clinical settings.

Targeting mROS and anti-oxidant systems in anticancer therapy

Strategies which target mitochondrial metabolism has been shown to be effective in a number of different clinical cancer studies and these findings are reviewed in [166,167]. However, targeting mitochondria redox activity as a therapeutic cancer target is still in development. As discussed above, ROS can both assist or limit tumor cell proliferation. While tumor cell lines increase their production of ROS some cell lines engage antioxidant networks to ensure that ROS levels do not surpass a fatal threshold [27,52–55,168,169]. Therefore, it is not surprising that treatment of cancer with dietary antioxidants has been successful in some studies while ineffective or detrimental in others. For example, while supplementation with carotenoids may increase mortality in breast cancer patients [170], supplementation with vitamin C and E in the same patients was associated with reduced recurrence rate [170,171]. Vitamin C also potentiates the anti-proliferative effect of doxorubicin in breast cancer [172] while high vitamin D levels are associated with increased survival in colorectal cancer patients [173].

Despite these findings, when translated into human clinical trials, dietary antioxidants lack consistent beneficial effects [174–177], probably due to a generalized rather than a localized mROS targeting [166]. Alternate strategies include the use of synthetic mitochondria-targeted antioxidants to inhibit tumor cell growth and promote apoptosis. For instance, inhibition of cell proliferation and induction of apoptosis was achieved in pancreatic cancer cells with the mitochondrial antioxidants Mito-CP, and Mito-CP-Ac, by altering mitochondrial and glycolytic functions, and intracellular citrate levels [178]. In addition, Mito-Q and Mito-chromanol can selectively inhibit proliferation of different xenograft models of tumorigenesis as reported by Cheng et al [179]. Moreover, cell growth inhibition and apoptosis was induced by decreased mitochondrial superoxide via the mitochondria superoxide scavenger MitoTEMPO in melanoma cells, while sparing healthy fibroblasts [180], allowing for enhanced tumor cell killing while limiting cytotoxicity in healthy tissue. Furthermore, the mitochondria deacetylase SirT3, mentioned previously in this review, which increases SOD antioxidant activity by lysine deacetylation and HIF-1α stabilization [181], can also attenuate tumorigenesis in cancer cell lines [66].

Considering that the targeted inhibition of mROS has shown to be beneficial as anti-cancer therapy, it would be reasonable to conclude that enhancing the activity of the natural antioxidant mechanisms in the mitochondria would convey the same results. However, the elevated expression of the natural antioxidants TrxR, in particular the mitochondrial TrxR2, has been encountered in several types of cancer, and in some instances has been correlated to tumor aggressiveness [138–143]. Similarly, Grx2 has been shown to have an anti-apoptotic effect in tumor cells [28]. Moreover it has been established that decreases in glutathione levels in murine breast cancer do not impede tumor development but increase Trx activity as a compensatory shift to buffer ROS levels [168]. This latter observation suggests that cancer cells have the capacity to survive and adapt to glutathione inhibition by augmenting antioxidant function of the mitochondria. Targeting Trx2 has proven to be useful in inhibiting multiple myeloma growth by restricting proteasome function and promoting cytotoxic oxidative stress [182]. In addition, Grx2 down regulation can sensitize cells to the cytotoxic effects of chemotherapy [120].

In general, while anti-oxidant cancer therapy is justified by ROS's role in cancer initiation, promotion and progression, pro-oxidant cancer therapy is also justified by ROS's role in inducing apoptosis and reversing chemo- and radio-resistance in tumors [183]. This paradox has raised the concern for the use of ROS- and antioxidant- targeted therapies, especially since effectiveness of this treatment seems to be dependent on the specific environment in which the cell exists, including its base oxidative stress status[183]. Some authors propose the creation of a "redox signaling signature", comprised of different parameters including redox status, expression of antioxidants, cell signaling and transcription factor activation profiles, as a reference to determine if anti-oxidant or pro-oxidant therapy would be effective in the treatment specific type of cancer[183]. This strategy would still prove challenging as ROS levels seem to vary even within the same type of cancer, and as previously discussed, the quantification methods still need to be improved[183].

In conclusion, to inhibit growth and induce apoptosis, both targeting the tumor's mROS and ROS-scavenging systems can elicit anti-cancer effects. Reducing the levels of mROS impedes survival signaling, while truncating the cancer's cell antioxidant armature induces cell death [182]. Therefore, in determining whether to take a pro-oxidant or anti-oxidant route for cancer therapy, the elucidation of a "redox signaling signature" may be critical in this decision making process. The development of accurate and specific reference parameters for determining the redox status of specific cancer types is still greatly needed.

Epitranscriptomic control of mROS

Recent work indicates that mitochondria are key to the regulation of cellular H_2O_2 consumption through Trx and glutathione dependent pathways, and that large changes in H_2O_2 efflux comes from altering the activity of mitochondrial matrix consumers[185,186]. The predominant matrix H_2O_2 consumers are the peroxiredoxins and glutathione peroxidases whose activity is indirectly or directly reliant on selenocysteine utilization, respectively[186]. Selenocysteine is the 21st amino acid and does not contain a dedicated codon. Selenocysteine incorporation during translation requires UGA-stop-codon recoding, which uses specifically modified tRNA for accurate decoding [187]. Dynamic changes in tRNA modification are an epitranscriptomic signal because they regulate gene expression post-transcriptionally (i.e., during translation elongation), (Figure 3). It has been shown that the stress-induced translation of many selenocysteine containing ROS detoxifying enzymes is dependent on the Alkbh8 tRNA methyltransferase and the tRNA modification 5-methoxycarbonylmethyl-2′-O-methyluridine (mcm^{5}Um) [188,189]. Alkbh8 enzymatically methylates the uridine wobble base on tRNA^{Selenocysteine} to promote UGA-stop codon decoding. Also, Alkbh8 protein, stop-codon recoding and Alkbh8-dependent uridine wobble base modifications are increased in response to ROS stress (H_2O_2 or rotenone) to improve the translation of selenocysteine containing GPx and TrxR enzymes[189]. Thus it has been demonstrated that regulation of the ROS response is under epitranscriptomic control. Loss of *Alkbh8*$^{-/-}$ decreases the levels of many GSH metabolizing selenoproteins, promotes increased ROS and DNA damage levels, and confers enhanced sensitivity to oxidizing agents [189]. Interestingly, over-expression of Alkbh8 has been identified in human bladder cancer models and invasive carcinomas, with *in situ* silencing of Alkbn8 suppressing invasion, angiogenesis and tumor growth in xenograft models [190]. As Alkbh8 is a key node

in the regulation of cytoplasmic and mitochondrial H_2O_2 via selenoprotein regulation, cancer cell addiction to increased selenoproteins may be a coping mechanism that could be exploited therapeutically.

Preclinical studies suggest that drugs which affect glutathione metabolism can limit the most common renal malignancy, clear cell renal cell carcinoma [191]. Moreover, GSH biosynthesis is significantly enhanced in patients with a mutation in fumarate hydratase which is associated with a highly malignant form of renal cancer[192]. Gottlieb and coworkers demonstrated that adducts formed between fumarate and glutathione that are observed as a result mutations in the TCA cycle enzyme fumarate hydratase (FH) disrupt glutathione metabolism leading to oxidative stress and cellular senescence [192]. The FH mutation is commonly associated with a highly malignant form of renal cancer that was mimicked in mice dually deficient for FH and the senescence regulator p21, indicating that, in this model, senescence serves to restrict initiation of these renal cancers. Thus, it appears that disruption in mitochondrial GSH metabolism is met by engagement of the senescence which serves to restrict the emergence of cells with oncogenic potential. Future work will define whether epitranscriptomic defects in selenocysteine utilization leads to the engagement of the senescence and a shift in mitochondrial function, which would serve to restrict oncogenic activity and limit mROS production.

Conclusions

The metabolic state of the mitochondria has long been known to be altered in tumor cells relative to normal tissue because of the cancer cells limited access to both molecular oxygen and fuel sources. As outlined above it appears that the mitochondria also adapt to fluxes in ROS production which are either self-generated or from extra mitochondrial sources. It is not surprising that mitochondria through reactive thiols would serve as sentinels to any cellular redox changes as they are the primary sites for both generating and consuming the primary ROS signaling intermediate, H_2O_2. As a myriad of signaling networks have emerged as targets of ROS control it is very likely that in these many instances the mitochondrion is critical in signal regulation. The mitochondrion is a dynamic organelle and often juxtaposed intracellularly to regions of high energy demand. It is also likely that its cellular compartmentalization is dually purposed to engage coordinated redox-sensitive signaling nodules that are key for optimizing mitochondrial function. Under conditions where control of mitochondrial function and redox-signaling become discordant, as in response to an oncogenic or carcinogenic insult, the cell and mitochondria adapt by engaging protective response mechanisms that allow for cell survival and maintenance of cell function. The adaptive response often manifests itself as increases in antioxidant levels which confer a selective survival advantage that is often observed in aggressive metastatic cancers. Thus, it is not surprising that antioxidant-based cancer prevention strategies have shown poor therapeutic efficacy. Future therapeutic strategies might be directed at limiting global adaptions to mROS and ROS signaling. With the emergence of novel tumor mitochondria targeting strategies a new era in antioxidant based chemotherapeutic strategies is on the horizon.

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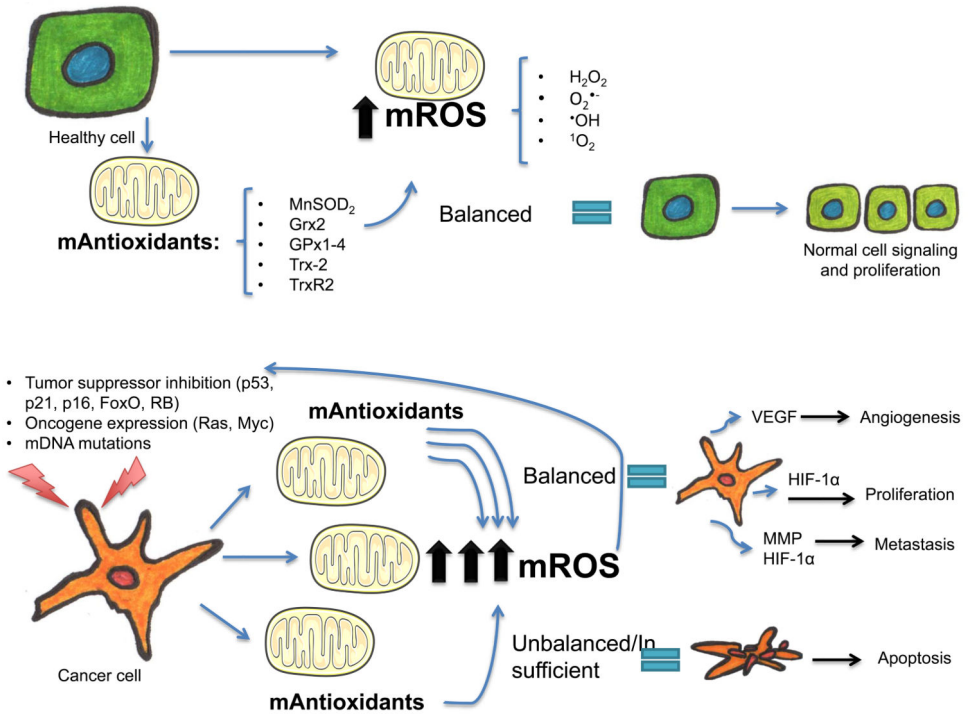

Figure 1. Mitochondrial redox control in healthy and cancer cells

ROS produced in the mitochondria, when balanced by the mitochondrial mediated antioxidant system, have several roles in healthy cell signaling pathways and cellular proliferation. An altered gene expression is seen in cancer cells, that have both an increased production of mROS, and an active antioxidant system to maintain a steady proliferative rate. In cancer cells a balanced production and scavenging of mROS allows the cell to perpetuate and induce more altered gene expression, and induce cellular mitosis, angiogenesis and metastasis through mROS mediated mechanisms, all in favor of cancer cell survival. In contrast, when the oxidant scavenging system is overpowered by mROS production in cancer cells, an oxidative-induced apoptosis occurs.

mROS-mitochondrial reactive oxygen species, H_2O_2—hydrogen peroxide, $O_2^{\bullet-}$ - superoxide, $^{\bullet}OH$-hydroxyl radical, $^1O_2$-singlet oxygen, mAntioxidants-mitochondrial antioxidants, $MnSOD_2$-manganese superoxide dismutase, Grx2-Glutaredoxin-2, GPX1-4-Glutathione peroxidases 1 and 4, Trx-2- thioredoxin 2, TrxR2-thioredoxin reductase, RB-retinoblastoma gene, mDNA-mitochondrial DNA, VEGF-vascular endothelial growth factor, HIF-1α-hypoxia inducible factor 1α, MMP- matrix metalloproteinase.

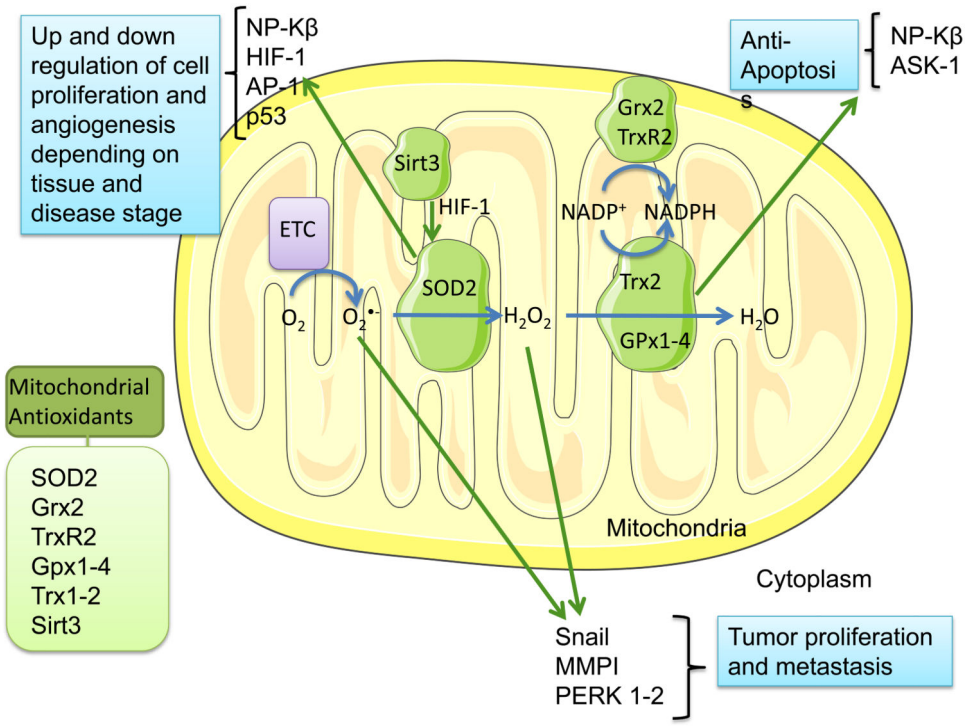

Figure 2. Mitochondrial detoxification systems in cancer

The normal activity of the mitochondria's electron transport chain (ETC) produces reactive oxygen species (ROS), in particular O_2^-, whose conversion into the less reactive H_2O_2 is catalyzed by the mitochondrial superoxide dismutase 2 (SOD2). Both O_2^- and H_2O_2 can promote tumor proliferation and metastasis via Snail, MMPI and Perk1-2 regulation, thus other mitochondrial oxidant scavenger systems area activated to decrease the damaging effects of ROS. For this purpose, Gpx 1 and 4, and Trx 2, metabolize H_2O_2, while Grx2 prevents Trx2's oxidation, allowing its detox activity. Trx2 via NP-Kβ and ASK-1 can have an anti-apoptotic effect in cancer cells. SOD2's antioxidant activity is increased by Sirt3 via HIF-1 stabilization and lysine deacetylation. SOD_2 is also involved in the regulation of cell proliferation, transformation, and angiogenesis by mediation of the transcriptional factors NP-Kβ, HIF-1, AP-1 and p53, which can have varying and contrasting effects depending on cancer type and stage of the disease.

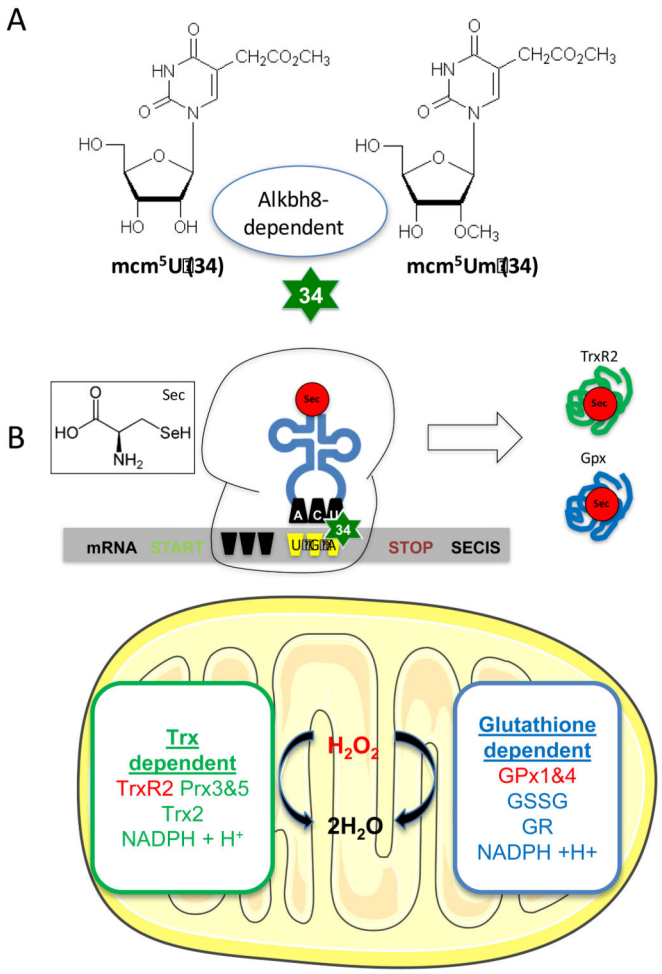

Figure 3. Epitranscriptomic control of mitochondrial ROS detoxification systems

A. The mcm^{5}U and mcm^{5}Um modifications on the wobble position (34) of tRNA^{Sec} are dependent on the methyltransferase activity of Alkbh8. **B.** Sec does not have a dedicated codon for use during translation, and its incorporation into a growing peptide utilizes the process of UGA stop codon recoding. The translation of selenoproteins requires transcripts with an internal UGA codon and a 3′ untranslated region (UTR) that contains a selenocysteine insertion sequence (SECIS). The Alkbh8 dependent mcm^{5}Um modification has been shown to be increased in response to H_2O_2 exposure with mitochondrial specific TrxR2 and Gpx H_2O_2 detoxification protein levels dependent on Alkbh8 activity [171].