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Review Article

Metabolic, autophagic, and mitophagic activities in cancer initiation and progression



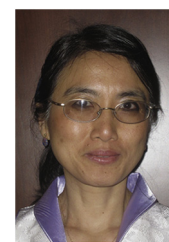
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ABSTRACT

Cancer is a complex disease marked by uncontrolled cell growth and invasion. These processes are driven by the accumulation of genetic and epigenetic alterations that promote cancer initiation and progression. Contributing to genome changes are the regulation of oxidative stress and reactive species-induced damage to molecules and organelles. Redox regulation, metabolic plasticity, autophagy, and mitophagy play important and interactive roles in cancer hallmarks including sustained proliferation, activated invasion, and replicative immortality. However, the impact of these processes can differ depending on the signaling pathways altered in cancer, tumor type, tumor stage, and/or the differentiation state. Here, we highlight some of the representative studies on the impact of oxidative and nitrosative activities, mitochondrial bioenergetics, metabolism, and autophagy and mitophagy in the context of tumorigenesis. We discuss the implications of these processes for cellular activities in cancer for anti-cancer-based therapeutics.

As the name suggests, reactive oxygen species (ROS) are molecules that contain oxygen and are highly reactive. ROS include hydroxyl radical, hydrogen peroxide, and superoxide. The reaction of superoxide and the free radical nitric oxide also produces peroxynitrite, a potent oxidant. The molecules are produced by specific enzymatic pathways including the mitochondrial electron transport chain NOX/

nicotinamide adenine dinucleotide phosphate oxidases and nitric oxide synthases [1–7]. These reactive species can act as cell signaling molecules and also cause nonspecific posttranslational modification of proteins if domain-dependent control of their action is lost [8–13]. Under such circumstances, the irreversible modification of lipid, DNA, and proteins can accumulate in the cell and inactivate the

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biological function of these macromolecules as well as the organelles with which they are associated [14,15]. The maintenance of a redox homeostasis is then critical to both reductive and oxidative stress occurring when regulation of these pathways is lost [16]. Also, cancer initiation and progression are significantly impacted by redox signaling as well as redox stress [17].

Cellular metabolism is essential to generate adenosine triphosphate to provide the energy needed for multiple cellular functions. Such functions include DNA replication, transcription, translation, protein transport, assembly of multi-molecule complexes and organelles, cell mobility, and enzymatic reactions. In addition, the metabolites generated are building blocks for synthesis of DNA, RNA, and other essential cellular constituents. Metabolic programs are controlled at the levels of uptake of nutrients from extracellular space, glycolysis, and mitochondrial respiration. These metabolic functions can be regulated by reactive species and can also, in turn, regulate cellular redox status.

Autophagy and mitophagy are lysosome-mediated degradation of intracellular lipids, proteins, and organelles [18–21]. This degradation can serve to clear reactive species-induced damage to these molecules and cellular compartments. The processes are highly regulated by more than 30 proteins and many signaling pathways [21], which can include redox signaling itself as well as cellular metabolic programs [22–33].

The integration of these cellular activities plays important roles in cancer initiation and progression and will be discussed in this review.

Reactive species, signaling, and stress in cancer initiation and progression

DNA damage by reactive species can be carcinogenic as represented by the link between cigarette smoking and increased risk of cancer [34–37]. Cigarette smoke contains reactive species such as nitric oxide, hydrogen peroxide, and peroxynitrite [34,35], and cigarette smokers exhibit increased oxidative damage as evidenced by elevated 8-hydroxy-2'-deoxyguanosine (8-OHdG) levels [36,37]. The involvement of ROS in transformation mediated by oncogenes or tumor suppressor loss has also been demonstrated. For example, exogenous expression of oncogenic, constitutively active H-RasG12V or Myc leads to ROS-dependent transformation or mitogenic activities [38–41]. Down-regulation of tumor suppressor genes such as p53 also leads to increased intracellular ROS, DNA oxidation, and mutation rate. Reactive nitrogen species also contribute to tumor growth as demonstrated by studies suggesting the importance of nitric oxide for cancer growth and tumor initiating cell maintenance [42–46]. In converse, antioxidant-related drugs and molecules have been shown to inhibit tumor initiation. For example, the antioxidant N-acetylcysteine attenuates lymphomas in p53 knockout mice [47,48]. A transcription factor, critical for upregulation of antioxidant

enzymes, nuclear factor (erythroid-derived 2) factor 2 (Nrf2), also attenuates cancer initiation similar to the antioxidant proteins it upregulates [49–56]. Together, these data suggest a pro-tumorigenic role for reactive species and a benefit for antioxidant-based therapies.

While reactive species can be pro-tumorigenic, their contribution to tumor biology is diverse and needs to be carefully considered prior to the development of novel therapeutic approaches. Evidence indicates that the role of ROS and antioxidants can differ depending on cell type or disease state. For example, mouse embryonic fibroblasts expressing endogenous K-RasG12V have lower levels of ROS as detected in the dichlorofluorescein fluorescence assay [57]. In this model, another indicator of oxidative stress, the glutathione (GSH) disulfide (oxidized GSH) to GSH (reduced glutathione; GSH) ratio, is also decreased in Nrf2-dependent fashion [57]. In tumor cells, high levels of antioxidant production through mechanisms such as upregulation of Nrf2 can provide survival advantages and resistance to chemotherapy [17,56,58–63]. Indeed, dual inhibition of the antioxidants glutathione and thioredoxin synergistically decreases tumor cell growth in vivo [167]. Overexpression of the anti-apoptotic factor Bcl2 also causes lymphomas in mice and humans without altering the rate of peroxide generation while attenuating oxidative damage to lipid membranes [64]. These studies highlight the complexity of the role of reactive species in cancer, which may vary depending on the genetic, epigenetic, and microenvironmental variation present in tumors. Thus, it may be difficult to make broad conclusions regarding the use of antioxidants for cancer therapy in the context of the diverse initiation and progression mechanisms of the disease [17,55,56,62].

Metabolic programming in cancer initiation and progression

Obesity increases the risk for various cancers, consistent with a close link of whole body metabolism to cancer predisposition [65,66]. At the cellular level, it has been long noted that metabolic programs in cancer cells differ from normal cells [67]. Recent studies identified diverse mechanisms of metabolic plasticity in cancer cells. These include increased glucose uptake in most tumors [68–71], elevated glycolytic intermediates due to the expression of the pyruvate kinase M2 isoform [72–76], increased pentose phosphate pathway activities associated with transketolase isoform TKTL1 elevation [77,78], increased glutamine catabolism [79,80], and increased use of lactate as a fuel in selective tumors [81]. Signaling pathways and molecules, such as Akt and Myc that are known to play important roles in cancer, regulate the expression of glucose and glutamine transporters, glucose metabolism enzymes, glutamine metabolism, and mitochondrial biogenesis [82–92]. Thus, it is becoming increasingly apparent that the pro-survival and pro-proliferative roles of oncogenic signals are strongly linked to changes in cellular metabolism and mitochondrial

function. As an example, loss of the tumor suppressor p53 attenuates mitochondrial respiration and stimulates glycolysis with mechanisms including regulation of subunit I of cytochrome c oxidase, synthesis of cytochrome c oxidase 2, hexokinase 2, glucose transporters, phosphoglycerate mutase 1, and TP53-induced glycolysis and apoptosis regulator [93–98]. In human glioblastomas [99–101] and acute myeloid leukemia [102], somatic mutations of isocitrate dehydrogenases alter metabolism by converting α -ketoglutarate to 2-hydroxyglutarate, which in turn leads to a hypermethylation phenotype [103,168]. The causal relationship of altered metabolism in tumorigenesis has also been suggested by the finding that germline mutations of succinate dehydrogenase and fumarate hydratase cause hereditary tumors, likely mediated by multifaceted mechanisms including altered gene expression, altered cell signaling, increased mutagenesis, or upregulation of hypoxia inducible factor 1 alpha (HIF1 α) [104–107]. The data have led to increasing recognition that genetic mutations and metabolic changes in cancer are linked and required for the development and progression of the disease.

Autophagy and mitophagy in cancer initiation and progression

Autophagy senses cellular metabolic status, as well as various stress signals [29,108]. More than 30 proteins coordinate the autophagic processes, generating autophagosomes from essentially all membrane sources from the cell. Key signaling pathways include AMP-activated protein kinase (AMPK)-mammalian target of rapamycin (mTOR) pathways, Beclin-VPS34 complexes, ATG3, 4, 5, 6, 7, 8, 12, and 16 that are involved in autophagosomal formation, and adaptor proteins sequestosome 1 (SQSTM1)/p62 and NDP52 that recognize ubiquitinated targets. Perturbations of these pathways have been shown to contribute to tumorigenesis [109]. For example, mTOR inhibitors tuberous sclerosis complex-1/2 are tumor suppressors [110]. Beclin/ATG6 deficiency has been found to be associated with human breast, ovarian, and prostate tumors [111]; Beclin +/- mice develop tumors in endocrine tissues [112,113]. ATG4C, ATG5, and ATG7 genetic disruptions have also been found to develop liver adenomas or exhibit increased tumorigenesis in response to carcinogens in mice [114,115].

One regulator of autophagic flux associated with cancer is GABA(A) receptor-associated protein-like 1 (GABARAPL1). Lower levels of GABARAPL1 have been associated with poor outcome for liver and breast cancer patients [116,117], and GABARAPL1 is suggested to be a tumor suppressor through the inhibition of Wnt [118,119]. GABARAPL1 interacts with the Wnt/ β -catenin signaling activator segment polarity protein disheveled homolog Dvl-2 and plays an important role in Dvl-2 degradation. Data indicate that knockdown of GABARAPL1 in breast cancer cells promotes proliferation and invasion in association with decreased autophagic flux and decreased lysosome numbers [120]. Although the

requirement for Wnt in this effect is not known, Wnt signaling is well-established as a regulator of breast cancer initiation and metastasis [121,122], suggesting the attenuated GABARAPL1-mediated repression of Wnt signaling promotes breast cancer development and progression. Together, these data strongly suggest that a better understanding of the critical regulators of autophagy cellular transformation and tumor growth is important.

The above evidence indicates that autophagic deficits promote tumorigenesis as autophagy is required to guard against oxidative damage to the genome [23]. However, as multiple mechanisms are involved in both autophagy regulation and tumorigenesis, the connection between autophagy and tumor biology can be complex. For example, ablation of FIP200, a downstream target of mTOR inhibition and cofactor of ATG1-ATG13 activation, has been shown to inhibit mammary tumorigenesis [123]. In established tumors, autophagy may provide a survival advantage to the tumor cells in nutrient-deprived conditions and support chemoresistance [124]. Thus, autophagy inhibitors, such as chloroquine, have been tested in cancer therapy [125,126].

Mitophagy or autophagy of mitochondria is required to eliminate dysfunctional mitochondria to maintain appropriate metabolic and cell survival signals [32]. One key mediator of mitophagy linked to cancer is the putative tumor suppressor gene Parkin. Parkin is located at a chromosomal fragile site and loss is associated with tumors of the lung, breast, brain, ovary, pancreas, and colon [127–134]. In animal models, deletion of exon 3 of Parkin also promotes the development of spontaneous hepatic tumors [131]. The mechanisms through which Parkin acts as a tumor suppressor continue to be elucidated, but it is known that Parkin translocates to the mitochondria as a consequence of loss of membrane potential, leading to ubiquitination of mitochondrial proteins and recruitment of p62-LC3 and autophagosomes to the mitochondria [29,32,135–137]. It regulates the ubiquitination of multiple mitochondrial proteins [138] with important targets being identified as the mitochondria fusion regulator Mitofusin 2 [139] and the mitochondria migration regulator mitochondrial rhoGTPase (Miro) [140]. Recent evidence suggesting the potential involvement of these Parkin targets in cancer further demonstrates the importance of mitophagy and mitochondrial function in cancer [141–144].

Parkin recruitment to promote mitophagy can be regulated by Bcl2/adenovirus E1B 19 kDa-interacting protein 3 (BNip3), and very recent evidence demonstrates that BNip3 integrates mitophagy and apoptosis signaling in cancer [145,146]. BNip3 utilizes its BH3 domain to inhibit pro-survival Bcl2 family members, and thereby activating apoptosis while also increasing mitophagy by binding autophagosomes through an LC3 interacting region. BNip3 loss has been associated with progression of breast cancer to metastasis through a mechanism thought to involve retention of dysfunctional mitochondria [147]. BNip3 loss prevents normal mitophagy, leading to elevated levels of ROS. In this breast cancer model system, increased ROS resulted in elevated levels of HIF1 α and its target genes. The

activation of HIF signaling resulted in increased glycolysis, consistent with a Warburg effect. Thus, the data directly linked loss of BNip3 regulated mitophagy to changes in metabolism promoting cancer progression. As BNip3 itself is a well-known HIF target gene, these data also demonstrate the complex interactions between the pathways regulating and being regulated by mitophagy [148].

On the other hand, in established tumors, an increased mitophagy associated with an increased autophagy may also provide a survival advantage to the tumor cells in nutrient deprived or hypoxic conditions and support chemoresistance. However, it is unclear whether increased mitophagy without increasing general autophagy occurs in advanced tumors, and whether specific inhibition of mitophagy sensitizes established tumors to chemotherapies.

Integration of reactive species, metabolic programs, and autophagy in cancer

The relationship between reactive species and metabolic programs and its role in cancer have been extensively studied. Reactive species modification of DNA, lipids, or protein clearly impacts cell metabolism and proliferation [149–151]. Examples include the oxidative modification of mitochondrial DNA and mitochondrial proteins, as well as the induction of cell signaling and transcription pathways that are tumorigenic [41,152,153]. Conversely, mitochondrial dysfunction plays a direct role in modulating cellular redox status [154,155] as well as generation of NADH and reduced GSH by the pentose phosphate pathway [153].

The relationship between reactive species and autophagy is also emerging as being important in cancer biology [156]. Reactive species regulation of autophagy has been demonstrated by thiol modification of ATG4 cysteines and signaling through the ataxia-telangiectasia mutated-liver kinase B1-AMPK-mTOR pathway [157,158]. Reactive species modification of Kelch-like ECH-associated protein 1 (KEAP1) leads to upregulation of the antioxidant regulating transcription factor Nrf2 and increased levels of autophagy adaptor protein SQSTM1/p62 [159]. Conversely, autophagy regulates KEAP1 levels and homeostasis of the KEAP1-Nrf2 pathway, thereby regulating cellular redox status [160].

The interactions among reactive stress, metabolism, and autophagy in cancer initiation and progression are complex. Strong evidence indicated these interactions in cancer. For example, the major nutrient-sensing Akt-AMPK-mTOR pathway is regulated by reactive stress and is a direct regulator of autophagy [158]. In pancreatic ductal adenocarcinoma cells, increased nuclear import of microphthalmia/transcription factor E family of transcription factors enhances autophagy-lysosomal catabolic function, maintains intracellular amino acid pools, and thereby supporting cell proliferation [161]. The tumor suppressor gene p53 has been shown to be activated by nutrient and oxidative stress while its activation also plays a role in metabolic

homeostasis and autophagy by a variety of transcriptional as well as cytosolic mechanisms [162]. Recent studies also suggested that the covalent attachment of N-acetylglucosamine (O-GlcNAc) is not only involved in nutrient sensing and cancer metabolism [163], but may also play a role in regulating autophagy [164–166]. These data demonstrate that there are multiple cross regulation mechanisms for ROS, autophagy, and metabolic signals in cancer.

Conclusion

Existing evidence supports the general concept that cancer initiation can be facilitated by changes in reactive species, autophagy, and metabolism. These changes may include increased reactive species modification of mitogenic signaling, reactive damage to DNA and proteins, decreased autophagic and mitophagic clearance of damaged macromolecules and organelles, and altered metabolic substrate availabilities and usages. Tumor cells with established genome mutations or rearrangements are highly dependent on metabolic plasticity to sustain proliferation, antioxidants, autophagy, and mitophagy to gain survival advantages. Cross-regulation of reactive species production and elimination, mitochondrial bioenergetics and glucose metabolism, and autophagy and mitophagy add additional complexity of the biology of tumorigenesis. Detailed or individualized mechanisms in specific tumors and specific stages of tumorigenesis and progression can be diverse and are still being intensively investigated. Studies on the regulation of mitochondrial bioenergetics, metabolism, autophagy and mitophagy, and how reactive species integrate these regulations in different cancers will continue to provide important insights into cancer biology and therapeutics.

Normal cells are dependent on reactive species for cell signaling, mitochondria and glycolysis for energy, metabolites for biosynthesis, and autophagy for clearance of excessive or damaged macromolecules and organelles. Dysregulated reactive species generation and deficient autophagy contribute to tumorigenesis by enhancing mutagenesis and genome instability. Once tumors are established, tumor cells with upregulated autophagy and Nrf2-mediated antioxidant production may gain a survival advantage in low nutrient and hypoxic conditions. In addition, metabolic activities, such as mitochondrial biogenesis, glycolytic activities, and glutamine utilization, are upregulated to help sustain the energy demand for tumor growth. Understanding the coordination of these activities during tumorigenesis and progression is important for the prevention and management of cancer [Fig. 1].

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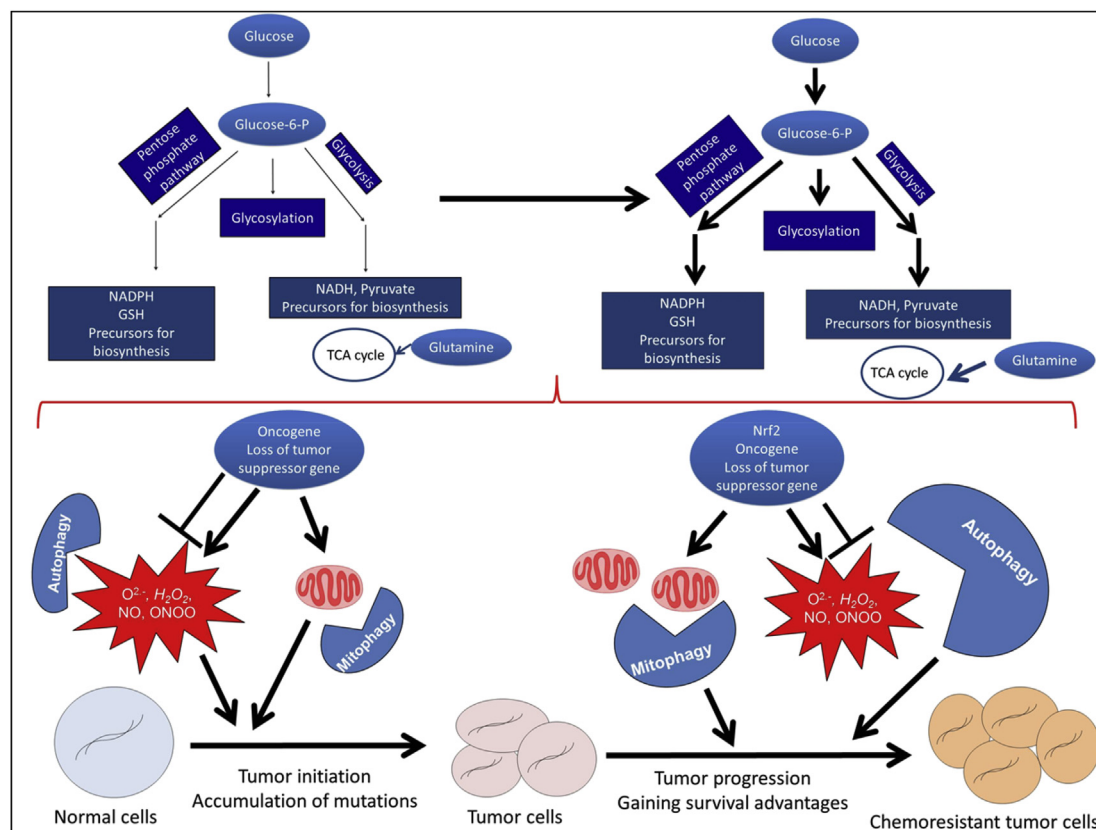


Fig. 1 – Redox regulation, metabolic programming, autophagy, and mitophagy in cancer initiation and progression.

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Conflicts of interest

There are no conflicts of interest.

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