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Review Article

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

Anita Hjelmeland [a,b], *Jianhua Zhang* [b,c,d,*]

[a] *Department of Cell, Developmental and Integrative Biology, University of Alabama at Birmingham, Birmingham, AL, USA*
[b] *Center for Free Radical Biology, University of Alabama at Birmingham, Birmingham, AL, USA*
[c] *Department of Pathology, University of Alabama at Birmingham, Birmingham, AL, USA*
[d] *Department of Veterans Affairs, Birmingham VA Medical Center, Birmingham, AL, USA*

Dr. Jianhua Zhang

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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

* *Corresponding author*. Department of Pathology, University of Alabama at Birmingham, Biomedical Research Building II, 901 19th Street South, Birmingham, AL 35294, USA. Tel.: +1 205 9965153; fax: +1 205 9347447.
E-mail address: zhanja@uab.edu (J. Zhang).
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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

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