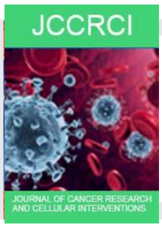

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Mini Review

Burning Within: The Dual Role of ROS Metabolism in Cancer Cell Survival and Death

Davison K, Schumaker L, Gansauge W, Naguro K, Troiano
Department of Animal Biotechnology, Korea

***Corresponding Author:** Gansauge W**,** Department of Animal Biotechnology, Korea

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Abstract

Reactive Oxygen Species (ROS) are central to the metabolic reprogramming of cancer cells, functioning as both signaling molecules that promote tumor progression and as toxic agents that can induce cell death. Cancer cells maintain a finely tuned redox balance, allowing them to exploit ROS for growth while avoiding oxidative.

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Introduction

Cancer is characterized by uncontrolled cell proliferation, metabolic reprogramming, and resistance to cell death. One of the hallmarks ofcancer metabolism is the dysregulation of redox homeostasis. Reactive Oxygen Species (ROS), traditionally viewed as harmful byproducts of cellular metabolism, are now recognized as key regulators of cancer cell signaling and survival

ROS include free radicals such as superoxide ($O_2\bullet^-$) and hydroxyl radicals (•OH), as well as non-radical molecules like hydrogen peroxide (H_2O_2). While normal cells maintain low ROS levels, cancer cells exhibit elevated ROS due to increased metabolic activity and oncogenic signaling. This altered redox state plays a crucial role in tumor initiation, progression, and response to therapy

Sources of ROS in Cancer Cells

Mitochondrial ROS Production

The mitochondria are the primary source of ROS in most cells. During oxidative phosphorylation, electrons may leak from the electron transport chain (ETC), particularly at complexes I and III, leading to the formation of superoxide. In cancer cells, mitochondrial dysfunction and altered metabolism enhance this leakage, increasing ROS production.**NADPH Oxidases (NOX Enzymes)**

NADPH oxidases are dedicated ROS-producing enzymes. Several NOX isoforms are overexpressed in cancer and contribute to sustained ROS generation, which supports proliferative signaling and tumor growth.

Peroxisomes and Endoplasmic Reticulum

Peroxisomes generate ROS during fatty acid oxidation, while the endoplasmic reticulum produces ROS during protein folding processes. These organelles further contribute to the oxidative environment in cancer cells.

External Factors

Environmental stressors such as radiation, toxins, and inflammation can also elevate ROS levels, further influencing cancer development.

Biological Roles of ROS in Cancer

ROS as Signaling Molecules

At moderate levels, ROS act as secondary messengers in intracellular signaling. They regulate pathways such as MAPK, PI3K/Akt, and NF-κB, promoting cell proliferation, survival, and differentiation. ROS can also modulate transcription factors like HIF-1α, enhancing angiogenesis under hypoxic conditions.

DNA Damage and Genomic Instability

ROS can cause oxidative damage to DNA, including base modifications, strand breaks, and mutations. This contributes to genomic instability, a key driver of cancer initiation and progression

. Tumor Progression and Metastasis

Elevated ROS levels promote epithelial-mesenchymal transition (EMT), cell migration, and invasion. ROS-mediated signaling also supports the remodeling of the tumor microenvironment.

Immune Modulation

ROS influence immune responses by affecting immune cell function. Cancer cells can exploit ROS to suppress anti-tumor immunity and evade immune surveillance

Antioxidant Defense Systems in Cancer Cells

To counteract excessive ROS, cancer cells upregulate antioxidant systems:

- **Glutathione (GSH):** A major intracellular antioxidant that neutralizes ROS and maintains redox balance.
- **Superoxide Dismutases (SOD):** Convert superoxide into hydrogen peroxide.
- **Catalase and Glutathione Peroxidase (GPx):** Detoxify hydrogen peroxide into water.
- **Thioredoxin System:** Regulates redox-sensitive signaling and protects against oxidative stress.

The transcription factor NRF2 plays a central role in regulating antioxidant gene expression, often being hyperactivated in cancer cells

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Redox Balance: A Double-Edged Sword

Cancer cells operate within a narrow window of ROS levels. While moderate ROS promote tumor growth, excessive ROS can trigger cell death pathways such as apoptosis, necrosis, and ferroptosis. This delicate balance is critical for cancer cell survival
Disruption of this balance—either by increasing ROS beyond tolerable levels or by inhibiting antioxidant defenses—can selectively kill cancer cells while sparing normal cells.

Therapeutic Targeting of ROS Metabolism

Pro-oxidant Therapies

Certain anticancer treatments aim to increase ROS levels to toxic thresholds. Chemotherapy agents and radiation therapy generate ROS to induce oxidative damage and kill cancer cells

Targeting Antioxidant Systems

Inhibiting antioxidant pathways, such as glutathione synthesis or NRF2 signaling, can sensitize cancer cells to oxidative stress.

Combination Strategies

Combining ROS-inducing therapies with inhibitors of antioxidant defenses enhances therapeutic efficacy and may overcome drug resistance.

Challenges and Limitations

While targeting ROS metabolism is promising, challenges include specificity, toxicity to normal cells, and adaptive resistance mechanisms in tumors.

Future Perspectives

Advances in understanding redox biology are paving the way for novel cancer therapies. Personalized approaches based on tumor redox status, along with the development of targeted ROS modulators, hold great potential. Further research is needed to fully exploit ROS metabolism for clinical benefit.

Conclusion

ROS metabolism in cancer cells represents a complex and dynamic system that supports both tumor survival and cell death. The dual role of ROS underscores the importance of maintaining redox balance in cancer progression. Targeting this balance offers a promising strategy for developing more effective and selective cancer therapies

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