OPEN ACCESS
©NIJPP ONLINE ISSN: 2992-5479
Publications 2025 PRINT ISSN: 2992-605X

NEWPORT INTERNATIONAL JOURNAL OF PUBLIC HEALTH AND PHARMACY (NIJPP)

Volume 6 Issue 3 Page 59-63, 2025

https://doi.org/10.59298/NIJPP/2025/635963

Membrane Redox Potentials as Determinants of Cancer Cell Survival and Therapy Resistance

Mukisa Ian Mugaiga

Department of Pharmacology Kampala International University Uganda
Email:mugaiga.mukisa@studwc.kiu.ac.ug

ABSTRACT

Membrane redox potentials represent a critical yet underexplored dimension of cancer biology. These potentials, generated across mitochondrial and plasma membranes through electron transport and redox-active enzymes, tightly regulate bioenergetics, reactive oxygen species (ROS) signaling, and cell fate. In cancer, aberrant shifts in membrane redox states foster metabolic reprogramming, adaptation to oxidative stress, and evasion of apoptosis, ultimately conferring a survival advantage under hostile microenvironmental conditions. Moreover, altered redox potentials modulate ion channels, transporter activity, and redox-sensitive signaling pathways, contributing directly to resistance against chemotherapy, radiotherapy, and targeted therapies. This review integrates current knowledge on the role of membrane redox potentials in cancer cell survival and therapeutic resistance, emphasizing the interplay between redox biology, tumor heterogeneity, and treatment outcomes. We highlight advances in methodologies to measure membrane redox states, discuss novel small molecules and nanotechnology-based interventions aimed at redox modulation, and propose future directions for exploiting membrane redox vulnerabilities as precision oncology strategies.

Keywords: Membrane redox potential, Cancer metabolism, Therapy resistance, Reactive oxygen species (ROS), Mitochondrial dysfunction

INTRODUCTION

Cancer cells exist in a highly dynamic redox landscape shaped by both intrinsic metabolic reprogramming and extrinsic microenvironmental pressures [1]. Unlike normal cells, malignant cells must continuously adapt to fluctuating oxygen and nutrient levels, hypoxic niches, and the presence of reactive oxygen species (ROS) within the tumor microenvironment [2]. To survive and thrive under these conditions, cancer cells rewire their bioenergetic networks, particularly by modulating mitochondrial and plasma membrane redox potentials. These modifications are not merely passive consequences of altered metabolism but represent active adaptations that allow tumor cells to fine-tune signaling pathways, balance oxidative stress, and maintain proliferative capacity [3]. Mitochondrial redox potential shifts, often coupled with changes in electron transport chain activity, directly influence ROS generation and ATP production, linking energy metabolism to signaling cascades that control cell fate. Similarly, plasma membrane redox systems regulate extracellular electron transfer, antioxidant defenses, and communication with stromal and immune cells [4]. Collectively, these redox adjustments provide cancer cells with a survival advantage, enabling them to evade apoptosis, resist therapy-induced oxidative damage, and promote metastatic dissemination [5]. While the Warburg effect and glycolytic reprogramming have long dominated discussions on cancer metabolism, the concept of membrane redox potentials provides an additional layer of understanding, highlighting how electron flow across membranes integrates metabolic flexibility with stress adaptation [6,7]. This perspective underscores the importance of redox biology in cancer progression and resistance mechanisms, offering new opportunities to identify biomarkers of treatment response and design redox-targeted therapeutic strategies in oncology.

OPEN ACCESS
ONLINE ISSN: 2992-5479
PRINT ISSN: 2992-605X

2. The Concept of Membrane Redox Potentials in Cellular Bioenergetics

Membrane redox potentials are determined by the balance between electron donors and acceptors across biological membranes, and they play a central role in maintaining cellular energy and signaling processes [8]. These potentials reflect the degree of reduction or oxidation occurring within cellular compartments and are critical for the regulation of metabolic flux, ion gradients, and reactive oxygen species generation [9]. The mitochondrial electron transport chain is the most prominent regulator of redox potential. It establishes proton gradients necessary for ATP synthesis while simultaneously influencing the rate and site of ROS formation. Subtle changes in the redox state of the electron transport [10] chain complexes can tip the balance between efficient energy production and oxidative stress. Plasma membrane oxidoreductases also contribute significantly by facilitating extracellular electron transfer, thereby maintaining redox communication between cells and their surrounding environment [11] These systems modulate antioxidant defenses, regulate cell-surface signaling, and help preserve redox equilibrium under stress conditions. In addition, ion channels and transporters often display sensitivity to redox changes. The oxidation state of cysteine residues or alterations in membrane potential can influence their activity, ultimately impacting calcium homeostasis, nutrient uptake, and signal transduction pathways [12]. In cancer cells, persistent alterations in these bioenergetic systems create a hyper-reduced membrane state [13]. This environment promotes rapid proliferation, supports metabolic plasticity, and enhances the ability of tumor cells to neutralize therapy-induced oxidative damage. However, it simultaneously establishes a foundation for resistance to treatment by reducing the effectiveness of apoptosis and oxidative stress-based therapeutic approaches [14].

3. Membrane Redox Potentials and Cancer Cell Survival Mechanisms

3.1. Regulation of Apoptosis and Cell Death Pathways

One of the most critical aspects of membrane redox regulation in cancer is its influence on programmed cell death. In healthy cells, mitochondrial membranes undergo redox fluctuations that can trigger cytochrome c release and initiate apoptosis [15]. In cancer, however, hyper-reduced mitochondrial membranes stabilize the inner membrane and prevent cytochrome c efflux, effectively blocking the intrinsic apoptotic pathway [16]. This shift protects malignant cells from chemotherapy or stress-induced cell death. Additionally, reactive oxygen species generated under altered redox potentials are not merely damaging byproducts but also act as second messengers that activate survival pathways such as NF-κB and PI3K/AKT. These pathways further enhance resistance to apoptosis and support proliferation [16].

3.2. Adaptation to Tumor Microenvironmental Stress

The tumor microenvironment exerts constant stress through hypoxia, nutrient deprivation, and inflammatory signals [17]. Under hypoxic conditions, stabilization of HIF-1α is tightly linked to altered membrane redox balance, which promotes glycolytic metabolism and reduces mitochondrial dependence. Cancer-associated fibroblasts, immune cells, and endothelial cells also exchange metabolites and signaling molecules that reshape plasma membrane redox states, reinforcing tumor survival and adaptability within hostile niches [18].

3.3. Stemness and Cancer Plasticity

Membrane redox remodeling contributes to the maintenance of cancer stem-like cells. These subpopulations rely on finely tuned redox potentials to balance self-renewal with resistance to oxidative stress [19]. By sustaining stemness, altered redox potentials enable tumors to regenerate after therapy, contribute to metastasis, and maintain long-term heterogeneity. This redox-driven plasticity poses a significant barrier to durable treatment responses [20].

4. Membrane Redox Potentials in Therapy Resistance

4.1. Chemoresistance

Altered membrane redox potentials are strongly implicated in resistance to chemotherapy [21]. Cancer cells frequently upregulate their antioxidant capacity, allowing them to neutralize the surge of reactive oxygen species that many cytotoxic drugs are designed to induce [22]. By maintaining a hyper-reduced state, tumor cells dampen oxidative signaling and prevent the initiation of apoptotic cascades. In addition, changes in lipid composition and peroxidation thresholds of cellular membranes influence the susceptibility of tumor cells to ferroptosis, a regulated form of cell death dependent on iron and lipid ROS. By modulating these thresholds, cancer cells gain protection against ferroptosis-inducing drugs, further reinforcing resistance [23].

4.2. Radioresistance

Radiotherapy relies heavily on the generation of ROS to damage DNA and induce cell death. However, tumor cells with highly reduced mitochondrial membranes exhibit increased resilience against radiation-induced oxidative stress [24]. The lowered redox potential stabilizes mitochondrial structures, reducing damage and apoptosis. Beyond mitochondria, plasma membrane redox signaling also contributes by promoting the activation of DNA repair pathways [25]. By accelerating the repair of radiation-induced DNA double-strand breaks, these cells effectively limit the efficacy of radiotherapy.

4.3. Resistance to Targeted and Immunotherapies

Redox modulation extends to targeted therapies and immunotherapies. Many receptor tyrosine kinases, which are common targets in oncology, are redox-sensitive, and shifts in membrane redox potential can alter their conformations, affecting drug binding and downstream signaling cascades [26]. Furthermore, tumor immune evasion is closely linked to plasma membrane oxidoreductases. These systems regulate extracellular redox signaling that influences T cell activity, often suppressing immune responses and enabling tumors to escape immune surveillance even under checkpoint blockade therapies.

6. Therapeutic Targeting of Membrane Redox Potentials

6.1. Small Molecules and Redox-Active Drugs

Targeting cancer cell redox states with small molecules has emerged as a promising therapeutic strategy [27]. Pro-oxidant therapies such as arsenic trioxide and elesclomol are designed to push tumor cells beyond their redox tolerance, inducing lethal oxidative stress. These compounds exploit the heightened metabolic activity of cancer cells, which already operate close to their oxidative stress threshold [28]. On the other hand, redox-modulating antioxidants, including N-acetylcysteine and vitamin E derivatives, have shown dual and sometimes paradoxical effects. In some contexts, they suppress tumor progression by restoring normal redox signaling, while in others, they inadvertently protect cancer cells from oxidative stress, reducing treatment efficacy [29]. This duality highlights the importance of precision-based approaches when using antioxidant therapies.

6.2. Nanotechnology Approaches

Nanotechnology offers innovative solutions to selectively manipulate tumor redox states. Engineered nanoparticles can deliver redox modulators directly to tumor sites, minimizing systemic toxicity while enhancing therapeutic precision [30]. These particles can be designed to exploit tumor-specific characteristics such as hypoxia, high ROS levels, or acidic microenvironments. Redox-sensitive drug delivery systems are particularly promising, as they release therapeutic agents only when exposed to specific redox cues within the tumor, maximizing efficacy and reducing off-target effects [31].

6.3. Synthetic Biology and Gene Editing

Recent advances in synthetic biology and gene editing further expand opportunities to manipulate redox potentials. CRISPR-based approaches allow precise modulation of plasma membrane oxidoreductases or mitochondrial electron transport chain components, reprogramming cancer cells' redox landscapes [32]. Engineered redox-responsive bioswitches are also under development, designed to activate therapeutic genes or pro-drugs in response to altered redox states [33]. These approaches hold great promise for sensitizing tumors to conventional therapies while offering a new layer of precision in oncology.

7. Future Perspectives and Challenges

The therapeutic exploitation of membrane redox potentials presents both exciting opportunities and significant challenges in cancer treatment [34]. One of the foremost challenges lies in tumor heterogeneity. Redox states are not uniform across all cancer cells within a tumor; rather, they vary between regions, influenced by oxygen gradients, nutrient supply, and interactions with stromal and immune cells [35]. This spatial and temporal variability complicates the design of therapies that can target redox vulnerabilities consistently. Another major issue is selectivity. While altering redox potentials can effectively sensitize cancer cells to treatment, normal cells also rely on tightly regulated redox states for survival. Broad modulation of these systems risks systemic toxicity and damage to healthy tissues. This underscores the urgent need for therapies that can discriminate between malignant and non-malignant redox profiles. Biomarkers capable of accurately assessing membrane redox states in patients would be invaluable in guiding personalized treatment strategies.

Technological advancements will play a critical role in addressing these challenges. Multi-omics approaches that integrate redox biology with genomics, proteomics, and metabolomics hold promise for mapping tumor redox landscapes in unprecedented detail. Patient-derived organoids and advanced in vivo imaging tools could further refine preclinical models, allowing researchers to predict treatment responses more accurately. Artificial intelligence-driven redox mapping may also emerge as a powerful method for identifying therapeutic windows tailored to individual patients. Ultimately, the future of redox-targeted oncology will depend on bridging fundamental research with clinical translation. With continued innovation, membrane redox potentials may become both a biomarker of therapy response and a direct therapeutic target in precision medicine.

CONCLUSION

Membrane redox potentials represent a fundamental determinant of cancer cell fate and therapy response. By shaping survival signaling, metabolic plasticity, and resistance mechanisms, these potentials occupy a central position in cancer biology. Emerging therapeutic strategies that modulate membrane redox balance hold promise for overcoming resistance and improving treatment efficacy, positioning redox-targeted interventions as a frontier in precision oncology.

OPEN ACCESS
ONLINE ISSN: 2992-5479
PRINT ISSN: 2992-605X

REFERENCES

1. Schiliro C, Firestein BL. Mechanisms of Metabolic Reprogramming in Cancer Cells Supporting Enhanced Growth and Proliferation. Cells. 2021 Apr 29;10(5):1056. doi: 10.3390/cells10051056. Erratum in: Cells. 2022 Nov 14;11(22):3593. doi: 10.3390/cells11223593. PMID: 33946927; PMCID: PMC8146072.
2. Lee H, Kim B, Park J, Park S, Yoo G, Yum S, Kang W, Lee JM, Youn H, Youn B. Cancer stem cells: landscape, challenges and emerging therapeutic innovations. Signal Transduct Target Ther. 2025 Aug 5;10(1):248. doi: 10.1038/s41392-025-02360-2. PMID: 40759634; PMCID: PMC12322150.
3. Qiu, X., Wang, A., Wang, J. *et al.* Mitochondrial metabolic reprogramming in colorectal cancer: mechanisms of resistance and future clinical interventions. *Cell Death Discov.* **11**, 375 (2025). https://doi.org/10.1038/s41420-025-02670-y
4. Yang, J., Shay, C., Saba, N.F. *et al.* Cancer metabolism and carcinogenesis. *Exp Hematol Oncol* **13**, 10 (2024). https://doi.org/10.1186/s40164-024-00482-x
5. Tasdogan A, Ubellacker JM, Morrison SJ. Redox Regulation in Cancer Cells during Metastasis. Cancer Discov. 2021 Nov;11(11):2682-2692. doi: 10.1158/2159-8290.CD-21-0558. Epub 2021 Oct 14. PMID: 34649956; PMCID: PMC8563381.
6. Xing F, Hu Q, Qin Y, Xu J, Zhang B, Yu X, Wang W. The Relationship of Redox With Hallmarks of Cancer: The Importance of Homeostasis and Context. Front Oncol. 2022 Apr 22;12:862743. doi: 10.3389/fonc.2022.862743. PMID: 35530337; PMCID: PMC9072740.
7. Brandl N, Seitz R, Sendtner N, Müller M, Gülow K. Living on the Edge: ROS Homeostasis in Cancer Cells and Its Potential as a Therapeutic Target. *Antioxidants*. 2025; 14(8):1002. https://doi.org/10.3390/antiox14081002
8. Alum EU, Uti DE, Offor CE. Redox Signaling Disruption and Antioxidants in Toxicology: From Precision Therapy to Potential Hazards. Cell Biochem Biophys. 2025 Jul 28. doi: 10.1007/s12013-025-01846-8.
9. Foyer CH, Noctor G. Redox homeostasis and antioxidant signaling: a metabolic interface between stress perception and physiological responses. Plant Cell. 2005 Jul;17(7):1866-75. doi: 10.1105/tpc.105.033589. PMID: 15987996; PMCID: PMC1167537.
10. Liu CG, Qin JC, Lin YH. Fermentation and Redox Potential [Internet]. Fermentation Processes. InTech; 2017. Available from: http://dx.doi.org/10.5772/64640
11. Nordzieke DE, Medraño-Fernandez I. The Plasma Membrane: A Platform for Intra- and Intercellular Redox Signaling. Antioxidants (Basel). 2018 Nov 20;7(11):168. doi: 10.3390/antiox7110168. PMID: 30463362; PMCID: PMC6262572.
12. Das P, Sen P. Relevance of Oxidoreductases in Cellular Metabolism and Defence [Internet]. Biochemistry. IntechOpen; 2024. Available from: http://dx.doi.org/10.5772/intechopen.112302
13. Nadine Hempel, Mohamed Trebak,Crosstalk between calcium and reactive oxygen species signaling in cancer, Cell Calcium, 2017, 63:70-96. https://doi.org/10.1016/j.ceca.2017.01.007.
14. Liu S, Liu J, Wang Y, Deng F, Deng Z. Oxidative Stress: Signaling Pathways, Biological Functions, and Disease. MedComm (2020). 2025 Jul 1;6(7):e70268. doi: 10.1002/mco2.70268. PMID: 40599237; PMCID: PMC12209598.
15. Li, B., Ming, H., Qin, S. *et al.* Redox regulation: mechanisms, biology and therapeutic targets in diseases. *Sig Transduct Target Ther* **10**, 72 (2025). https://doi.org/10.1038/s41392-024-02095-6
16. Pace M, Giorgi C, Lombardozzi G, Cimini A, Castelli V, d'Angelo M. Exploring the Antioxidant Roles of Cysteine and Selenocysteine in Cellular Aging and Redox Regulation. *Biomolecules*. 2025; 15(8):1115. https://doi.org/10.3390/biom15081115
17. Waterhouse NJ, Goldstein JC, von Ahsen O, Schuler M, Newmeyer DD, Green DR. Cytochrome c maintains mitochondrial transmembrane potential and ATP generation after outer mitochondrial membrane permeabilization during the apoptotic process. J Cell Biol. 2001 Apr 16;153(2):319-28. doi: 10.1083/jcb.153.2.319. PMID: 11309413; PMCID: PMC2169468.
18. Celsi F, Pizzo P, Brini M, Leo S, Fotino C, Pinton P, Rizzuto R. Mitochondria, calcium and cell death: a deadly triad in neurodegeneration. Biochim Biophys Acta. 2009 May;1787(5):335-44. doi: 10.1016/j.bbabio.2009.02.021. Epub 2009 Mar 4. PMID: 19268425; PMCID: PMC2696196.
19. Matsuyama, S., Reed, J. Mitochondria-dependent apoptosis and cellular pH regulation. *Cell Death Differ* **7**, 1155–1165 (2000). https://doi.org/10.1038/sj.cdd.4400779
20. Chen T-H, Wang H-C, Chang C-J, Lee S-Y. Mitochondrial Glutathione in Cellular Redox Homeostasis and Disease Manifestation. *International Journal of Molecular Sciences*. 2024; 25(2):1314. https://doi.org/10.3390/ijms25021314

21. Liu Y, Li Q, Zhou L, Xie N, Nice EC, Zhang H, Huang C, Lei Y. Cancer drug resistance: redox resetting renders a way. Oncotarget. 2016 Jul 5;7(27):42740-42761. doi: 10.18632/oncotarget.8600. PMID: 27057637; PMCID: PMC5173169.
22. Chaiswing L, St Clair WH, St Clair DK. Redox Paradox: A Novel Approach to Therapeutics-Resistant Cancer. Antioxid Redox Signal. 2018 Nov 1;29(13):1237-1272. doi: 10.1089/ars.2017.7485. Epub 2018 Feb 21. PMID: 29325444; PMCID: PMC6157438.
23. Kim E-K, Jang M, Song M-J, Kim D, Kim Y, Jang HH. Redox-Mediated Mechanism of Chemoresistance in Cancer Cells. *Antioxidants*. 2019; 8(10):471. https://doi.org/10.3390/antiox8100471
24. Tufail, M., Jiang, CH. & Li, N. Altered metabolism in cancer: insights into energy pathways and therapeutic targets. *Mol Cancer* **23**, 203 (2024). https://doi.org/10.1186/s12943-024-02119-3
25. Bahar E, Kim J-Y, Yoon H. Chemotherapy Resistance Explained through Endoplasmic Reticulum Stress-Dependent Signaling. *Cancers*. 2019; 11(3):338. https://doi.org/10.3390/cancers11030338
26. Khan, S.U., Fatima, K., Aisha, S. *et al.* Unveiling the mechanisms and challenges of cancer drug resistance. *Cell Commun Signal* **22**, 109 (2024). https://doi.org/10.1186/s12964-023-01302-1
27. Alum EU. AI-driven biomarker discovery: enhancing precision in cancer diagnosis and prognosis. *Discov Onc* **16**, 313 (2025). https://doi.org/10.1007/s12672-025-02064-7
28. An, X., Yu, W., Liu, J. *et al.* Oxidative cell death in cancer: mechanisms and therapeutic opportunities. *Cell Death Dis* **15**, 556 (2024). https://doi.org/10.1038/s41419-024-06939-5
29. Chehelgerdi M, Chehelgerdi M, Allela OQB, Pecho RDC, Jayasankar N, Rao DP, Thamaraikani T, Vasanthan M, Viktor P, Lakshmaiya N, Saadh MJ, Amajd A, Abo-Zaid MA, Castillo-Acobo RY, Ismail AH, Amin AH, Akhavan-Sigari R. Progressing nanotechnology to improve targeted cancer treatment: overcoming hurdles in its clinical implementation. Mol Cancer. 2023 Oct 9;22(1):169. doi: 10.1186/s12943-023-01865-0. PMID: 37814270; PMCID: PMC10561438.
30. Nwuruku, O.A., Ugwu, O.P.-C., Uti, D.E., Edwin, N.: Harnessing nature: plant-derived nanocarriers for targeted drug delivery in cancer therapy. Phytomedicine Plus. 5, 100828 (2025). https://doi.org/10.1016/j.phyplu.2025.100828
31. Uti, D.E., Alum, E.U., Atangwho, I.J., Ugwu, O.P.C., Egbung, G.E., Aja, P.M. Lipid-based nano-carriers for the delivery of anti-obesity natural compounds: advances in targeted delivery and precision therapeutics. *J Nanobiotechnol* **23**, 336 (2025). https://doi.org/10.1186/s12951-025-03412-z
32. Wang, B., Hu, S., Teng, Y. *et al.* Current advance of nanotechnology in diagnosis and treatment for malignant tumors. *Sig Transduct Target Ther* **9**, 200 (2024). https://doi.org/10.1038/s41392-024-01889-y
33. Ammar, M.M., Ali, R., Abd Elaziz, N.A. *et al.* Nanotechnology in oncology: advances in biosynthesis, drug delivery, and theranostics. *Discov Onc* **16**, 1172 (2025). https://doi.org/10.1007/s12672-025-02664-3
34. Venturini, J., Chakraborty, A., Baysal, M.A. *et al.* Developments in nanotechnology approaches for the treatment of solid tumors. *Exp Hematol Oncol* **14**, 76 (2025). https://doi.org/10.1186/s40164-025-00656-1
35. Ailioaie LM, Ailioaie C, Litscher G. Fighting Cancer with Photodynamic Therapy and Nanotechnologies: Current Challenges and Future Directions. *International Journal of Molecular Sciences*. 2025; 26(7):2969. https://doi.org/10.3390/ijms26072969
36. Tan, E.W., Singh, S.K., Dua, K. *et al.* Cancer stem cells: mitochondria signalling pathway and strategies for therapeutic interventions. *Mol Biol Rep* **52**, 671 (2025). https://doi.org/10.1007/s11033-025-10748-0
37. Iqbal, M.J., Kabeer, A., Abbas, Z. *et al.* Interplay of oxidative stress, cellular communication and signaling pathways in cancer. *Cell Commun Signal* **22**, 7 (2024). https://doi.org/10.1186/s12964-023-01398-5
38. Jiang, J., Wang, K., Chen, Y. *et al.* Redox regulation in tumor cell epithelial–mesenchymal transition: molecular basis and therapeutic strategy. *Sig Transduct Target Ther* **2**, 17036 (2017). https://doi.org/10.1038/sigtrans.2017.36

CITE AS: Mukisa Ian Mugaiga (2025). Membrane Redox Potentials as Determinants of Cancer Cell Survival and Therapy Resistance. NEWPORT INTERNATIONAL JOURNAL OF PUBLIC HEALTH AND PHARMACY, 6(3):59-63. **https://doi.org/10.59298/NIJPP/2025/635963**