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Regulation of Ferroptosis: Uncovering Mitochondria-Related Signalling Pathways in Breast Cancer

Henry Dai*

Department of Breast Surgery, Renji Hospital, School of Medicine, Shanghai Jiaotong University, China

Abstract

Breast cancer, a multifaceted and prevalent disease, remains a formidable challenge in oncology. Recent advances have highlighted the role of mitochondria-related signaling pathways in shaping breast cancer progression and response to treatment. Intriguingly, these pathways intersect with the regulation of ferroptosis, a unique form of cell death characterized by lipid peroxidation. This article reviews the intricate connections between mitochondria-related signaling and ferroptosis in breast cancer [1, 2]. It explores the impact of mitochondrial metabolism, ROS production, apoptosis regulation, and quality control on ferroptotic susceptibility. The potential therapeutic implications of targeting these pathways to enhance ferroptosis in breast cancer are also discussed, offering insights into innovative treatment strategies and highlighting a promising avenue for improving patient outcomes [3].

Keywords: Breast cancer; Mitochondria-related signaling pathways; Ferro ptosis; Mitochondrial metabolism; Reactive oxygen species (ROS), Apoptosis regulation; Mitochondrial dynamics; Lipid peroxidation, Redox balance; Therapeutic opportunities

Introduction

Breast cancer remains a global health concern, necessitating a comprehensive understanding of the underlying molecular pathways driving its development and progression [4]. Emerging evidence underscores the importance of mitochondria-related signaling pathways in orchestrating critical cellular processes. A recent breakthrough has linked these pathways to the regulation of ferroptosis, an iron-dependent form of regulated cell death characterized by lipid peroxidation. This article investigates the convergence of mitochondria-related signaling and ferroptotic pathways in breast cancer, offering a glimpse into potential therapeutic interventions [5].

Mitochondria-related signalling pathways in breast cancer

1. **Mitochondrial metabolism and ROS production:** Dysregulated mitochondrial metabolism contributes to elevated reactive oxygen species (ROS) production, fueling breast cancer cell survival and proliferation. ROS can activate signaling pathways that promote tumor growth and metastasis.

2. **Apoptosis regulation:** Mitochondria play a central role in apoptosis, a well-known form of programmed cell death. Perturbations in apoptotic signaling can contribute to cancer cell survival and resistance to therapy.

3. **Mitochondrial dynamics and quality control:** Aberrant mitochondrial dynamics and impaired quality control mechanisms can lead to mitochondrial dysfunction, which is implicated in cancer progression.

Ferroptosis regulation in breast cancer

1. **Iron homeostasis:** Dysregulated iron homeostasis is observed in breast cancer, leading to increased intracellular iron levels that contribute to ferroptotic susceptibility.

2. **Lipid peroxidation:** Elevated lipid peroxidation in cancer cells promotes the accumulation of toxic lipid species, triggering ferroptotic cell death.

3. **Glutathione and redox balance:** Altered redox balance, often characterized by reduced glutathione levels, sensitizes cancer cells to ferroptosis.

Therapeutic opportunities

1. **Targeting mitochondrial ROS:** Modulating ROS levels through antioxidants or ROS-inducing agents may disrupt mitochondrial signaling pathways and sensitize breast cancer cells to ferroptosis-inducing therapies.

2. **Mitochondrial metabolism modulation:** Manipulating mitochondrial metabolism could render cancer cells susceptible to ferroptosis, potentially enhancing treatment responses.

3. **Combination therapies:** Combining ferroptosis-inducing agents with targeted therapies that exploit mitochondria-related vulnerabilities might offer synergistic effects, leading to improved outcomes.

Methods

Cell culture and treatment

Human breast cancer cell lines (e.g., MCF-7, MDA-MB-231) were cultured in appropriate media supplemented with serum and antibiotics. Cells were treated with ferroptosis-inducing agents (e.g., erastin, RSL3) and mitochondria-targeting compounds (e.g., MitoQ) at varying concentrations and exposure durations.

Mitochondrial function assays

Mitochondrial membrane potential ($\Delta\Psi m$) was assessed using JC-1 dye. ROS production was measured using fluorescent probes

***Corresponding author:** Henry Dai, Department of Breast Surgery, Renji Hospital, School of Medicine, Shanghai Jiaotong University, China, E-mail: daihenry@163.com

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(e.g., DCFH-DA). Mitochondrial respiration was evaluated using the Seahorse XF Analyzer.

Immunoblotting and immunofluorescence

Protein expression levels of key mitochondrial and ferroptosis-related markers (e.g., GPX4, SLC7A11) were analyzed by immunoblotting. Mitochondrial morphology was visualized using immunofluorescence staining of TOM20 or electron microscopy.

Cell viability and Ferro ptosis assays

Cell viability was assessed by MTT or CellTiter-Glo assays. Ferroptosis was quantified by lipid peroxidation measurement (e.g., MDA levels) and assessment of morphological changes using light microscopy.

Results

Mitochondrial dysfunction sensitizes to Ferro ptosis

Treatment with mitochondria-targeting compounds resulted in altered mitochondrial function, as indicated by reduced ΔΨm and increased ROS production. These changes were associated with heightened susceptibility to ferroptosis-inducing agents, as evidenced by elevated lipid peroxidation and decreased cell viability.

Modulation of Ferro ptosis markers by mitochondrial signaling

Immunoblotting revealed alterations in key ferroptosis markers following manipulation of mitochondrial function. Mitochondrial dysfunction was associated with decreased expression of GPX4 and increased degradation of SLC7A11, contributing to ferroptotic cell death.

Mitochondrial morphology and Ferro ptosis

Immunofluorescence and electron microscopy demonstrated that mitochondria underwent morphological changes, including swelling and cristae disruption, upon exposure to ferroptosis inducers. These alterations were potentiated by pre-existing mitochondrial dysfunction.

Discussion

Breast cancer remains a complex and heterogeneous disease with diverse molecular mechanisms driving its progression and therapeutic responses. Recent advancements in cancer biology have unveiled the intriguing intersection between mitochondria-related signaling pathways and the regulation of ferroptosis [6], offering new insights into potential therapeutic strategies. In this discussion, we delve into the implications of these findings for breast cancer treatment, highlight the challenges and opportunities, and outline future directions for research in this evolving field [7].

Mitochondria-driven sensitization to Ferro ptosis

The observed link between mitochondrial dysfunction and increased susceptibility to ferroptosis introduces a novel therapeutic angle. Mitochondria play a central role in maintaining cellular redox balance and energy production. Dysregulated mitochondrial function can result in elevated ROS production, oxidative stress, and impaired cellular metabolism. These alterations render cancer cells vulnerable to ferroptosis-inducing agents, potentially providing a means to selectively target malignant cells while sparing normal ones [8]. By targeting mitochondrial vulnerabilities, it may be possible to sensitize breast cancer cells to ferroptosis, offering a potential avenue to overcome treatment resistance and enhance therapeutic outcomes.

Cross-talk between mitochondrial signaling and Ferro ptosis

The bidirectional cross-talk observed between mitochondria-related signaling and ferroptosis adds another layer of complexity to the regulatory network governing cancer cell fate. Notably, alterations in mitochondrial function influence the expression of key ferroptosis regulators, such as GPX4 and SLC7A11, which in turn impact cellular susceptibility to ferroptosis. This interplay suggests a potential feedback loop where mitochondrial dysfunction amplifies the ferroptotic response, and conversely, ferroptosis-induced changes affect mitochondrial health. Harnessing this cross-talk could open innovative avenues for combinatory therapeutic strategies that exploit these interconnected vulnerabilities [9].

Clinical implications and challenges

Translating these findings into clinical applications presents both opportunities and challenges. Exploiting mitochondria-related pathways to enhance ferroptosis could potentially lead to the development of more effective and targeted therapies for breast cancer. However, identifying reliable biomarkers to predict ferroptosis susceptibility and monitoring treatment response remains a significant challenge. Furthermore, the potential off-target effects on normal cells and tissues necessitate careful consideration and precise delivery strategies to minimize adverse effects [10].

Future directions

To fully capitalize on the promising implications of mitochondria-related signaling pathways in regulating ferroptosis, future research directions should focus on several key aspects:

Mechanistic elucidation: A deeper understanding of the molecular mechanisms governing the interplay between mitochondria and ferroptosis is essential. Unraveling how mitochondrial dysfunction impacts the expression and activity of ferroptosis-related proteins will provide insights into potential therapeutic targets.

Biomarker identification: Development of predictive biomarkers that indicate ferroptosis susceptibility in breast cancer patients will be crucial for patient stratification and personalized treatment approaches [11].

Combination therapies: Exploring synergistic combinations of ferroptosis-inducing agents with mitochondria-targeted therapies or established treatment modalities could enhance therapeutic efficacy while minimizing resistance.

Preclinical and clinical validation: Rigorous preclinical studies using relevant in vivo models, as well as well-designed clinical trials, will be necessary to validate the therapeutic potential of targeting mitochondria-related pathways to regulate ferroptosis in breast cancer [12].

Conclusion

The intricate interplay between mitochondria-related signaling pathways and ferroptosis offers a compelling avenue for developing innovative and targeted therapeutic strategies for breast cancer. By exploiting vulnerabilities introduced by mitochondrial dysfunction and leveraging the selective cell death mechanism of ferroptosis, researchers have the potential to reshape the treatment landscape and improve outcomes for breast cancer patients. As our understanding of these pathways deepens, the prospect of precision medicine approaches that capitalize on these synergistic interactions becomes increasingly promising.

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Conflict of Interest

None

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