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Core Execution Mechanisms of Ferroptosis in Prostate Cancer

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Abstract: Prostate cancer (PCa) progression to castration-resistant disease remains a clinical challenge driven by therapeutic resistance. Ferroptosis, an iron-dependent regulated cell death, offers a promising strategy to overcome this resistance. This review elucidates the core execution mechanisms of ferroptosis in PCa across three primary levels. First, we examine the interplay between lipid peroxidation and antioxidant systems, highlighting the pivotal roles of GPX4, System Xc^-, and ACSL4. Second, we discuss the regulation of iron metabolism, encompassing uptake, storage, and ferritinophagy mediated by proteins like TfR1 and NCOA4. Third, we explore mitochondrial function and oxidative stress responses, emphasizing metabolic reprogramming and ROS generation. By dissecting these intricate pathways, including GPX4-independent surveillance mechanisms, we aim to identify novel therapeutic targets. Understanding these mechanisms provides critical insights for developing targeted therapies that sensitize resistant tumors to ferroptosis, ultimately improving PCa management and overcoming limitations of conventional androgen deprivation therapies.

Keywords: Prostate cancer; Ferroptosis; Lipid peroxidation; Iron metabolism; GPX4; Therapeutic resistance

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1. Introduction

Prostate cancer (PCa) remains one of the most frequently diagnosed malignancies and a leading cause of cancer-related mortality among men worldwide. While androgen deprivation therapy (ADT) and second-generation anti-androgens (e.g., enzalutamide) constitute the standard of care for advanced disease, the inevitable progression to castration-resistant prostate cancer (CRPC) presents a significant clinical challenge. The emergence of therapeutic resistance is often driven by metabolic reprogramming and the evasion of cell death pathways, necessitating the exploration of novel therapeutic strategies that target non-apoptotic mechanisms.

Ferroptosis, an iron-dependent form of regulated cell death distinct from apoptosis, necrosis, and autophagy, has recently emerged as a critical mechanism for suppressing tumor progression. Characterized by the catastrophic accumulation of lipid peroxides driven by iron overload and antioxidant system failure, ferroptosis is governed by a complex network of metabolic pathways. In the context of PCa, accumulating evidence suggests that tumor cells exhibit

unique metabolic vulnerabilities that render them susceptible to ferroptotic induction. Key regulators such as glutathione peroxidase 4 (GPX4), the System Xc^- cystine/glutamate transporter, and iron homeostasis proteins play pivotal roles in determining cellular fate. Furthermore, the interplay between androgen receptor (AR) signaling and ferroptosis surveillance mechanisms offers a promising avenue for overcoming drug resistance.

Despite the growing recognition of ferroptosis in PCa, the core execution mechanisms underlying its regulation remain to be fully elucidated. Current research highlights a multi-step regulatory process involving lipid peroxidation imbalance, dysregulated iron metabolism, and mitochondrial dysfunction. Understanding these intricate pathways is essential for developing targeted therapies that can sensitize resistant tumors to ferroptosis. This review summarizes the core execution mechanisms of ferroptosis in prostate cancer across three primary levels: (1) the interplay between lipid peroxidation and antioxidant systems, including the GPX4 and System Xc^- axes; (2) the regulation of iron metabolism involving uptake, storage, and release; and (3) mitochondrial function and oxidative stress responses. By dissecting these mechanisms, we aim to provide insights into novel therapeutic targets for improving PCa management and overcoming resistance to conventional treatments.

2. Interplay between Lipid Peroxidation and Antioxidant Systems

Lipid peroxidation serves as the biochemical foundation of ferroptosis, while glutathione peroxidase 4 (GPX4) acts as the key antioxidant enzyme preventing lipid peroxide accumulation. In PCa, GPX4 expression levels directly determine cellular sensitivity to ferroptosis. Studies indicate that various regulators modulate ferroptosis by affecting GPX4 stability or transcription. For instance, RORC promotes enzalutamide resistance by upregulating GPX4 expression to inhibit ferroptosis[1]; inhibition of the deubiquitinase USP30 promotes GPX4 degradation and induces ferroptosis[2]; whereas the androgen receptor (AR) antagonist TQB3720 induces ferroptosis by disrupting the AR/SP1 complex binding to the *GPX4* promoter, thereby reducing transcription[3]. Additionally, miR-15a can directly target the 3'-UTR of *GPX4* mRNA to inhibit its expression and induce ferroptosis[4].

The System Xc^- transporter (composed of SLC7A11 and SLC3A2) is responsible for cystine uptake and glutathione (GSH) synthesis, serving as a critical upstream component for GPX4 function. In castration-resistant prostate cancer (CRPC), NFIB directly activates *SLC3A2* transcription via phase separation to inhibit ferroptosis[5]. The AR signaling pathway also directly regulates *SLC7A11*; AR variants (AR-Vs) preferentially bind the *SLC7A11* enhancer to upregulate its expression, resisting anti-androgen-induced ferroptosis[6]. In enzalutamide-resistant cells, SLC7A11 protein levels are upregulated with increased stability, and combination with the System Xc^- inhibitor Erastin can reverse resistance[7]. Other molecules, such as PCAT1, upregulate SLC7A11 via the c-Myc/miR-25-3p axis to inhibit ferroptosis[8], while PHGDH modulates ferroptosis sensitivity by maintaining redox homeostasis and suppressing *SLC7A11* expression[9].

Acyl-CoA synthetase long-chain family member 4 (ACSL4) is a key promoter of ferroptosis execution, responsible for esterifying polyunsaturated fatty acids (PUFAs) into phospholipids to provide substrates for lipid peroxidation. Imperatorin induces lipid peroxidation by downregulating SLC7A11/GPX4 and upregulating ACSL4[10]. ZDHHC2-dependent palmitoylation promotes the interaction between the deubiquitinase USP19 and ACSL4, stabilizing the ACSL4 protein; conversely, inhibiting ZDHHC2 restores ACSL4-mediated ferroptosis[11]. In *RB1*-deficient PCa, E2F activation directly upregulates *ACSL4* expression, sensitizing tumors to ferroptosis inducers[12, 13]. Polyphyllin I promotes ACSL4 expression and induces ferroptosis by reducing *ACSL4* promoter methylation levels via the ERK/DNMT1 axis[14].

Beyond the classical GPX4 pathway, PCa also possesses GPX4-independent ferroptosis surveillance mechanisms. MBOAT1 and MBOAT2, as phospholipid remodeling enzymes, can inhibit ferroptosis independently of GPX4 by reshaping the cellular phospholipid profile, regulated by sex hormone receptor transcription[15]. The phospholipase PLA2G7 complements GPX4 by hydrolyzing phospholipids containing hydroperoxides to mitigate ferroptosis[16]. Regarding metabolic reprogramming, SREBP1-mediated lipogenesis (e.g., FASN axis) inhibits ferroptosis; Darolutamide induces ferroptosis by downregulating the SREBP1-FASN axis[17]; while PI3K-AKT-mTOR signaling activation protects cells

from ferroptosis via SREBP1/SCD1-mediated lipogenesis[18]. DECR1, as the rate-limiting enzyme for PUFA oxidation, protects prostate tumor cells from ferroptosis when overexpressed, whereas its knockout leads to PUFA accumulation and mitochondrial oxidative stress[19, 20].

3. Regulation of Iron Metabolism: Uptake, Storage, and Release

Homeostasis of intracellular iron ions is a prerequisite for ferroptosis occurrence. Transferrin receptor 1 (TfR1/TFRC) mediates iron uptake; its upregulation increases the intracellular free iron pool, promoting ferroptosis. Metformin modulates iron homeostasis by upregulating TfR1, enhancing ferroptosis induced by ultra-small manganese ferrite nanoparticles[21]. Borax also induces ferroptosis by regulating the TfR1/GPX4/ACSL4 pathway[22]. Prognostic model analysis identifies *TFRC* as a key gene in PCa ferroptosis-related gene signatures[23].

Ferritin is the primary intracellular iron storage protein, and its degradation process, termed ferritinophagy, is mediated by nuclear receptor coactivator 4 (NCOA4). As a tumor suppressor, NCOA4 promotes ferroptosis by facilitating ferritinophagy to release free iron[24]. Combined androgen and vitamin D therapy inhibits CRPC growth via autophagy-mediated ferritinophagy (upregulating NCOA4, ALOX-5, etc.)[25]. Luteolin induces ferroptosis by promoting transcription factor EB (TFEB) nuclear translocation to increase ferritinophagy[26]. Conversely, the mitochondrial carrier protein SLC25A10 inhibits ferritinophagy and promotes PCa progression by interacting with P62 to suppress autophagic flux[27]. Iron supplements significantly enhance RSL3-induced ferroptosis, preventing CRPC occurrence[28]. Additionally, miR-29a-5p regulates ferroptosis by targeting the ferritin heavy chain *FTH1*[29], while *FTH1P8* induces docetaxel resistance by inhibiting ferroptosis[30].

4. Mitochondrial Function and Oxidative Stress

Mitochondria are the primary sites for reactive oxygen species (ROS) generation and lipid peroxidation amplification. Mitochondrial dysfunction is a distinctive feature of ferroptosis. VSTM2L, as a mitochondrial-localized protein, maintains mitochondrial homeostasis and inhibits ferroptosis by forming a complex with VDAC1 and HK2 to prevent VDAC1 oligomerization[31]. Polyphyllin VII enhances docetaxel sensitivity by inducing mitochondrial dysfunction and ferroptosis[32]. Ginsenoside Rh2 inhibits tumors by inducing mitophagy to cause mitochondrial damage, synergizing with ferroptosis[33].

Mitochondrial metabolic reprogramming directly affects ferroptosis sensitivity. HSF1 affects the mitochondrial oxidative phosphorylation (OXPHOS) system by targeting *HSPE1*, alleviating ROS levels to enhance resistance to ferroptosis[34]. Transferring healthy mitochondria into PCa cells enhances sensitivity to Erastin-mediated ferroptosis[35]. The fatty acid synthase (FASN) inhibitor G28UCM disrupts mitochondrial fatty acid synthase (mtFAS) and succinate dehydrogenase subunit B (SDHB), inducing mitochondrial metabolic stress and ferroptosis[36]. RPS6KC1 mediates enzalutamide resistance by recruiting PRDX3 to mitochondria to mitigate ferroptosis[37]. HMGA2 isoforms influence ferroptosis sensitivity by regulating oxidative stress[38]. Furthermore, taxol-based supramolecular oxidative stress nano-amplifiers trigger mitochondrial ROS cascades to induce ferroptosis via Fenton reactions producing hydroxyl radicals[39]. Mitochondrial SOD2, rather than cytoplasmic SOD1, participates in clearing ROS induced by isohematin, affecting the ferroptosis process[40]. Therapy-induced lipid uptake and remodeling lead to reduced mitochondrial bioenergetic processes and increased membrane PUFA levels, thereby rendering cells highly sensitive to GPX4 inhibition and ferroptosis[41].

5. Conclusion

This review summarizes core execution mechanisms involving lipid peroxidation, iron metabolism, and mitochondrial

dysfunction. Targeting key regulators like GPX4, System Xc^-, and iron homeostasis proteins offers opportunities to sensitize tumors. Understanding these pathways facilitates novel combinational therapies. Ultimately, exploiting ferroptotic vulnerabilities holds significant potential for improving clinical outcomes in castration-resistant prostate cancer and advancing precision medicine.

Disclosure statement

The author declares no conflict of interest.

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