

Perspective

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Bioelectromagnetic fields in prostate cancer: molecular mechanisms and therapeutic implications

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Abstract

Prostate cancer (PCa) remains a global health challenge, with emerging evidence implicating environmental electromagnetic fields (EMFs) as dual regulators of tumor progression and therapeutic innovation. This perspective synthesizes mechanistic insights into EMFs bioeffects through three interconnected axes: (1) Calcium signaling as a central biosensor, translating EMFs stimuli into oncogenic processes via piezoelectric and ionic mechanisms; (2) Extracellular vesicles (EVs)-mediated metastatic reprogramming through cargo remodeling (e.g., pro-inflammatory proteins) and dysregulation of oncogenic miRNAs; and (3) Ferroptosis, a frequency-modulated cell death pathway



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driven by calcium-iron-reactive oxygen species (ROS) crosstalk. Paradoxically, EMFs exhibit context-dependent duality: low-intensity fields exacerbate malignancy by rewiring calcium/EVs-driven tumor-microenvironment interactions, while high-intensity fields achieve tumor ablation via calcium overload, ferroptosis, hyperthermia, or electroporation. Novel strategies, such as PEGylated nanocrystals combined with intratumoral micromagnets, synergize ferroptosis with immunogenic cell death, demonstrating therapeutic potential with minimal toxicity. Our analysis underscores the critical need for parameter optimization (frequency, intensity, duration) to balance oncogenic risks against therapeutic precision. We propose that integrating biophysical targeting with electromagnetic engineering holds promise to redefine PCa management through mechanism-driven precision. This perspective aims to frame these insights and highlight their implications for future research and therapeutic development.

Keywords: Prostate cancer, electromagnetic fields, calcium signaling, extracellular vesicles, ferroptosis

INTRODUCTION

Prostate cancer (PCa) remains a major global health challenge, accounting for the second-highest cancer incidence and mortality among men worldwide^[1,2]. While established risk factors such as aging, genetic predisposition, and lifestyle variables (e.g., dietary patterns, obesity and tobacco/alcohol use) significantly contribute to its pathogenesis^[3], emerging evidence implicates environmental electromagnetic fields (EMFs) as critical epigenetic regulators of PCa progression^[4,5]. While epidemiological studies remain inconclusive regarding EMFs' carcinogenic potential^[6], mechanistic research increasingly reveals their capacity to bidirectionally reprogram tumor biology through multifaceted interactions with cellular pathways and highlights their potential as therapeutic instruments.

Notably, the dual role of EMFs manifests in their ability to induce pro-metastatic phenotypes under certain parameters^[7,8] while exhibiting therapeutic potential under others^[9-12] [Table 1]. Low-frequency fields induce apoptosis via reactive oxygen species (ROS)-dependent caspase-3 activation, aligning with observed cell growth inhibition despite unspecified intensity parameters^[9]. In contrast, high-frequency nanosecond pulses impair cell viability and mobility through membrane permeabilization^[10]. Paradoxically, while some rodent models show no tumorigenic initiation from EMF exposure^[17], preclinical PCa studies reveal context-dependent therapeutic effects. For instance, low-dose alternating electric currents suppress tumor growth in xenografts through NF- κ B pathway inhibition, correlating with reduced prostate-specific antigen (PSA) levels and adenocarcinoma regression^[11]. Magnetic nanoparticle strategies (e.g., intratumoral micromagnets with PEGylated nanocrystals) synergistically drive immunogenic cell death via ferroptosis with negligible systemic toxicity^[12]. Additionally, microwave ablation combined with pulsed electric fields^[13] reduces viability and impedes migration, while static high-intensity magnetic fields directly decrease PSA levels and induce tumor regression, underscoring a dose-response relationship^[15]. These findings collectively underscore the critical role of parameter optimization—from alternating magnetic fields enhancing radiotherapy^[14] to focused ultrasound-ethanol combinations suppressing metastatic phenotypes^[18]—in balancing oncogenic risks against therapeutic precision, highlighting the need for rigorous control of frequency, intensity, and duration. Beyond metastatic reprogramming, EMFs exhibit stemness-modulating capabilities. Specific parameters promote normal tissue regeneration via calcium signaling, while others suppress cancer stemness through ROS/pH modulation and HMGA2 downregulation^[19-21], further exemplifying context-dependent bioeffects. This is exemplified by modulated electro-hyperthermia (mEHT)^[22], which leverages cancer cells' distinct electromagnetic properties (e.g., membrane potential, impedance). Its impedance-matched 13.56 MHz signal with low-frequency modulation synergizes thermal metabolic disruption and non-thermal immunogenic cell death, demonstrating superior clinical outcomes over conventional hyperthermia. This paradoxical duality positions EMFs as both microenvironmental risk

Table 1. EMF interventions and therapeutic applications in prostate cancer

Intervention method	Category	Treatment parameters	Efficacy measures	Effect classification	Ref.
60-Hz sinusoidal magnetic field	Extremely low	Frequency: 60 Hz	Cell growth inhibition, apoptosis	Potential adjuvant for radiation therapy	[9]
PEGylated nanocrystals + internal magnetic field	Extremely low	-	Ferroptosis, immunogenic cell death	Synergistic tumoricidal efficacy with low systemic toxicity	[12]
Pulsed EMFs (nanosecond pulses)	High	Frequency: 1 Hz-1 MHz; Intensity: 7,000 V/cm; Duration: 200 ns/pulse (23 pulses total)	Cell permeabilization, death, mobility loss	Applicable to nanosecond electroporation protocols	[10]
Microwave ablation + pulsed EMFs	High	Intensity: 72,800/56,600/1,450 V/m	Reduced cell viability, apoptosis, migration inhibition	Therapeutic intervention for PCa	[13]
Alternating magnetic field + radiation therapy	Low	Frequency: 160 ± 5 kHz; Intensity: 24 kA/m; Duration: 20 min	Tumor growth delay	Improved radiation therapy efficacy	[14]
Low-dose alternating electric current	Low	Frequency: 100 kHz; Intensity: 15/25 mA; Duration: 15/60 min	Tumor growth inhibition, PSA reduction	Minimally invasive treatment option	[11]
Static magnetic field (medicinal biomagnetism)	Extremely low	Intensity: > 1,000 Gauss	PSA reduction, adenocarcinoma regression	Alternative treatment for PCa	[15]
Low magnetic field exposure	Extremely low	Intensity: 20 nT; Duration: 4 h	Increased cancer aggressiveness and metastasis	Pro-carcinogenic	[7]
Terahertz wave	High	Frequency: 34.5 THz (wavelength: 8.7 μm)	Suppresses ferroptosis	Pro-carcinogenic (context-dependent)	[16]

EMFs: Electromagnetic fields; PCa: prostate cancer; CRPC: castration-resistant prostate cancer; PSA: prostate-specific antigen. Extremely low [<300 Hz]; low [300 Hz- 300 kHz]; high [>300 kHz].

amplifiers and emerging therapeutic instruments, demanding a coherent framework to resolve current controversies and harness therapeutic opportunities. Critically, the limitations of conventional cancer therapies-including efficacy-toxicity tradeoffs and therapeutic resistance-highlight an urgent need for innovative approaches where bioelectromagnetic strategies may offer transformative potential.

In this perspective, we integrate recent advances through three interconnected axes that bridge biophysical mechanisms with oncological paradigms [Figure 1] and propose a reconciling framework for EMFs' duality: (1) Calcium signaling as the central electromagnetic biosensor, where EMFs modulate ion flux to drive tumor aggressiveness or therapeutic vulnerability; (2) EV-mediated metastatic reprogramming, involving electromagnetic-sensitive cargo sorting and miRNA dysregulation; (3) Frequency-modulated ferroptosis, a therapeutic frontier leveraging EMFs-iron-calcium crosstalk. By integrating these dimensions, we propose an integrative framework that reconciles EMFs' dual roles in PCa pathobiology. In this paper, we not only elucidate how electromagnetic parameters dictate pro-tumorigenic versus tumor-suppressive outcomes but also establish calcium signaling as the nodal hub coordinating these effects. This perspective aims to guide the development of electromagnetic-based precision therapies while providing a mechanistic basis to mitigate potential microenvironmental risks in advanced PCa management.

ELECTROMAGNETIC-CA²⁺ CROSSTALK IN PROSTATE CANCER PATHOBIOLOGY

Calcium signaling drives the oncogenic progression of PCa through multifaceted mechanisms^[23]. Dysregulated calcium fluxes promote malignant progression by disrupting cell cycle regulation, inhibiting apoptosis, and facilitating epithelial-mesenchymal transition (EMT) and cytoskeletal remodeling^[23-27]. These processes are mediated by the compartment-specific dysregulation of calcium channel families.

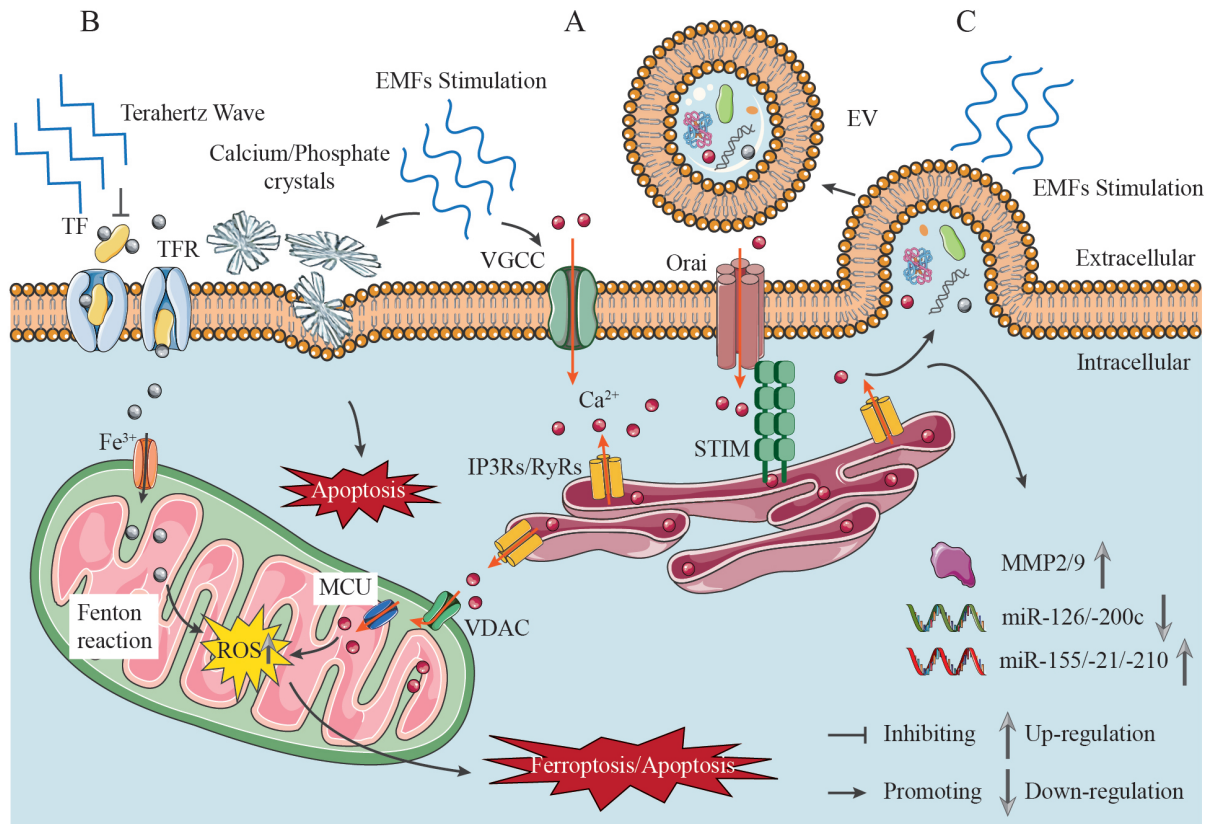


Figure 1. Mechanisms of EMF Regulation in Prostate Cancer: Calcium Signaling, Extracellular Vesicle Reprogramming, and Ferroptosis Modulation. (A) Calcium signaling as the central nodal effector. EMFs induce piezoelectric effects in prostatic calcium/phosphate crystals, generating mechanical stress that activates VGCCs, thereby initiating extracellular Ca^{2+} influx and intracellular signaling cascades, such as calcium-induced calcium release (CICR). EMFs (Low-Frequency) amplify this process, driving mitochondrial membrane depolarization and ROS overproduction, which synergizes with iron-dependent lipid peroxidation to potentiate ferroptosis; (B) Frequency-dependent ferroptosis modulation. EMFs (Low-Frequency) promote ferroptosis via the Ca^{2+} -ROS- Fe^{2+} axis, inducing lipid peroxidation and oxidative damage. Terahertz Waves (34.5 THz) suppress ferroptosis by inhibiting iron-transferrin binding; (C) EMFs-driven reprogramming of EVs to promote metastasis. EMFs (Low-Frequency) exposure triggers Ca^{2+} -dependent EV biogenesis and cargo sorting, enriching pro-metastatic proteins (e.g., MMP2/MMP9) and altering miRNA profiles (upregulate oncogenic miR-155/-21/-210 and suppress tumor-suppressive miR-126/-200c). These EVs enhance basement membrane invasion and metastatic dissemination through MMP-mediated extracellular matrix degradation and miRNA-driven epigenetic remodeling. VGCC: Voltage-gated Ca^{2+} channels; EMFs: electromagnetic fields; EV: Extracellular vesicle; TF: transferrin; TFR: transferrin receptor; ROS: reactive oxygen species; MMP: matrix Metalloproteinase.

Regulation of calcium channel families in PCa

Overexpression of ORAI calcium release-activated calcium modulator 3 (ORAI3) and its heteromerization with ORAI1 promote PCa cell proliferation by accelerating the cell cycle and inhibiting apoptosis^[28]. Elevated extracellular calcium activates the calcium-sensing receptor (CaSR), triggering Akt signaling to stimulate proliferation in skeletal metastatic PCa cells^[29]. TRP channels mediate PCa progression through the regulation of apoptosis and transient calcium accumulation. This facilitates metastasis by enhancing cytoskeletal dynamics and cellular invasiveness, particularly promoting bone metastases—a lethal characteristic of advanced PCa^[24,30]. The piezo-type mechanosensitive ion channel component 1 (Piezo1) regulates calcium flux, driving EMT and increasing metastatic potential^[31]. Furthermore, upregulation of voltage-gated Ca^{2+} channels (VGCCs), particularly $\text{CaV}1.3$, promotes resistance to androgen deprivation therapy (ADT) and the progression of castration-resistant prostate cancer (CRPC)^[32].

Remodeling of calcium signaling is closely associated with the development of hormone-sensitive, castration-resistant, and highly aggressive PCa subtypes, directly regulating the responsiveness of PCa to anti-androgen therapies.

Electromagnetic influence on calcium channels in PCa

Electric fields influence cellular behavior through three primary mechanisms^[33]: modifying plasma membrane potentials, redistributing extracellular ions and ionic currents, and generating mechanical forces transmitted intracellularly via the cytoskeleton. VGCCs act as the primary electromagnetic effector, directly converting field-induced membrane depolarization into shifts in the extracellular Ca^{2+} gradient that initiate intracellular signaling cascades, such as calcium-induced calcium release (CICR)^[34] [Figure 1]. These mechanisms converge on calcium signaling as their nodal effector.

Mechanistic studies reveal that low-intensity magnetic fields (LMFs) regulate bioelectric properties through calcium ion flux modulation, altering intracellular calcium distribution to influence membrane polarization states and cell cycle regulation-key drivers of tumor aggressiveness^[35-37]. This calcium-electromagnetic interplay further coordinates tumor-microenvironment communication through surface biomarker remodeling^[36,38]. This calcium flux may not only mediate immediate bioelectric responses but also underpin EMFs' dual regulation of stemness, promoting normal stem cell differentiation while inhibiting tumor stemness via cell cycle control^[19,39,40].

The interplay between EMFs and calcium signaling constitutes a biomechanical axis in prostate carcinogenesis. Emerging evidence reveals that EMFs may induce piezoelectric effects within prostatic calcifications^[41], where mechanical deformation of calcium/phosphate crystals under EMF exposure could alter cellular behavior and potentially enhance expression of apoptosis-inhibiting genes [Figure 1].

Notably, calcium electroporation-a non-thermal ablation method-has shown efficacy in localized PCa treatment. This approach significantly reduces cancer cell viability by inducing calcium overload to promote apoptosis *in vitro*, while pulsed electric fields concurrently disrupt actin cytoskeletal integrity and impair cellular motility^[42]. Collectively, the electromagnetic-calcium crosstalk highlights calcium's dual role as both mediator and therapeutic target in PCa pathobiology. EMFs may drive malignancy through piezoelectric/ionic calcium dysregulation, while targeted electromagnetic interventions such as electroporation, VGCC channel modulation, and magnetic nanoparticle-mediated modulation^[43] can reverse this interplay to disrupt tumor progression. Adjunctive ER stress modulation (e.g., salubrinal) may reduce neuroinflammatory cascades exacerbated by EMF-driven calcium dysregulation^[44]. This central axis underscores the critical importance of electromagnetic parameter control to exploit calcium signaling therapeutically while mitigating its oncogenic potential.

ELECTROMAGNETIC REPROGRAMMING OF EXTRACELLULAR VESICLES AND MIRNA NETWORKS

Extracellular vesicles (EVs) are increasingly recognized as key mediators in the development and progression of PCa^[45]. They facilitate communication between cancer cells and their environment by transferring bioactive molecules (proteins, microRNAs, mRNAs, DNA, lipids), promoting tumor progression, angiogenesis, immune evasion, and metastasis^[46-48]. Notably, microRNAs (miRNAs) transferred via EVs orchestrate critical oncogenic programs. These small non-coding RNAs regulate approximately 30% of protein-coding genes involved in cell differentiation, growth, and apoptosis during PCa pathogenesis^[49-51]. By targeting key signaling pathways, including AR signaling, p53 networks, PTEN/PI3K/AKT, and Wnt/ β -catenin cascades, miRNAs modulate cancer stemness, cell cycle progression, apoptotic

resistance, and metastatic competence. Recent advances in EV engineering highlight their potential as precision nanocarriers for miRNA delivery in oncology, underscoring the clinical relevance of EV-mediated miRNA networks in pathological reprogramming^[52]. Their stability in biofluids positions EVs and miRNAs as promising non-invasive biomarkers for PCa diagnosis stratification and treatment response prediction.

Experimental studies demonstrate that metastatic PCa-derived EVs enhance malignant phenotypes by stimulating cancer cell proliferation, migration, and invasion while suppressing apoptosis^[53]. They can also induce EMT via TGF β /androgen receptor signaling to promote invasion and drug resistance^[54,55]. These findings position EVs as multiparametric targets for precision diagnostics and therapy. Current therapeutic strategies focus on blocking EV production/uptake^[53], intercepting EV-activated pathways (MEK/ERK, TGF β)^[56], and disrupting EV-mediated microenvironmental reprogramming^[57]. Notably, engineered EVs show promise as biocompatible drug carriers to overcome therapeutic resistance^[53,54], with strategies like peptide-functionalized bacterial EVs demonstrating targeted miRNA delivery efficacy in bone diseases^[58], reinforcing the potential of engineered EVs to overcome therapeutic resistance. Combinatorial approaches targeting both EV signaling and conventional therapies may enhance treatment efficacy.

Recent studies reveal that short-term exposure (4 h) to LMFs (20 nT) significantly reduced cellular EV release and modified EV cargoes in PCa cells (specifically PC-3 cells), inducing pro-tumorigenic transformations and significantly enhanced invasiveness^[7]. Notably, LMF-induced calcium influx through voltage-gated channels may act as a trigger for EV biogenesis and cargo sorting, as calcium signaling is known to regulate vesicle trafficking and the matrix metalloproteinase (MMP) activation^[59-61] [Figure 1]. In LMF-exposed PC-3 cells, EVs exhibit enriched inflammatory and metastatic protein profiles, associated with 16 disease pathways and 95 human phenotypes linked to cancer aggression. This oncogenic reprogramming extends to miRNA dysregulation: LMF exposure markedly upregulates three critical oncogenic miRNAs (miR-155, miR-21, miR-210) while suppressing two tumor-suppressive miRNAs (miR-126, miR-200c), thereby promoting a metastatic profile. In contrast, the normal prostate epithelial cell line PNT2 exhibited reduced EV protein cargo following identical LMF exposure, with fewer associated functional enrichment pathways and minimal alterations in miRNA expression or invasion.

The pro-metastatic effects are further validated by LMF-induced upregulation of zinc-dependent matrix metalloproteinases (MMP2/MMP9)^[7] in PC-3 cells compared to PNT2 cells. These enzymes, which are critical for cancer invasion, demonstrate significantly elevated activity in patients with metastatic PCa and are associated with poor prognosis^[62,63]. Elevated MMP levels correlate with enhanced basement membrane penetration and metastatic dissemination, while the coordinated regulation of EV-mediated signaling and miRNA networks provides mechanistic evidence for LMF-driven metastatic progression specifically in malignant cells. In contrast, non-ionizing EMFs may impede metastasis by modulating the EMT pathway (VEGFR/PI3K/AKT/MAPK) and by inducing cadherin switching. Notably, amplitude-modulated radiofrequency EMFs have been shown to selectively suppress brain metastasis^[21,64,65]. Collectively, these findings establish electromagnetic fields as potent modulators of tumor microenvironment crosstalk, where reprogrammed EV release dynamics synergize with miRNA-driven epigenetic reprogramming to accelerate metastatic cascades in malignant cells like PC-3, while sparing normal counterparts such as PNT2. This electromagnetic-sensitive axis provides a compelling rationale for developing novel therapeutic strategies that specifically target these pathways in advanced PCa and highlights the critical influence of field parameters on metastatic reprogramming, demonstrating how changes in magnetic field exposures modulate EV-mediated and miR-regulatory processes in PCa metastasis.

ELECTROMAGNETIC FIELDS REGULATION OF FERROPTOSIS

Ferroptosis, a form of programmed cell death characterized by iron overload and lipid peroxidation, has emerged as a promising therapeutic strategy for PCa^[66]. Its induction exerts direct tumor-suppressive effects through iron-mediated oxidative damage, yet paradoxically drives pro-tumorigenic adaptations in the tumor microenvironment (TME), particularly in advanced PCa with dysregulated iron metabolism^[66,67]. Recent studies highlight the potential of ferroptosis in suppressing PCa metastasis and overcoming drug resistance^[66,68], while ferritin degradation may potentiate neurotoxicity through iron-mediated oxidative stress^[69]. ROS acts as a central hub connecting ferroptosis to PCa pathogenesis, amplified by inflammatory signals and redox-sensitive transcription factors (e.g., Nrf2, HIF-1 α) that either directly enhance oxidative stress or indirectly modulate ferroptosis susceptibility [Figure 2A]. Therapeutically, p53 activation dualistically regulates apoptosis and ferroptosis to suppress PCa growth, but ferroptosis-driven macrophage polarization in the TME may inadvertently promote tumor metastasis [Figure 2A], emphasizing the need for context-specific modulation to balance efficacy and paradoxical outcomes.

The regulatory role of EMFs in ferroptosis is increasingly recognized as a critical axis in PCa biology, with distinct effects dictated by frequency, intensity, and waveform parameters. This duality—where specific EMF parameters promote ferroptosis while others inhibit it—underscores the need for precise parameter control. Terahertz waves (ferroptosis-inhibiting EMFs, 34.5 THz) suppress ferroptosis through a direct mechanism targeting iron metabolism: they inhibit iron-transferrin binding, thereby reducing intracellular Fe²⁺ accumulation, lipid peroxidation, and malondialdehyde (MDA) levels^[16] [Figure 1]. This effect is frequency-specific. The high-energy terahertz range disrupts iron-transport protein interactions, reducing intracellular Fe²⁺ availability. By limiting the iron source for the subsequent lipid peroxidation reaction, it suppresses ferroptosis without relying on significant ROS production, thus highlighting a non-oxidative pathway for ferroptosis inhibition.

In contrast, extremely low frequency electromagnetic fields (ELF-EMFs, ferroptosis-promoting EMFs, operating at 50 Hz and with magnetic field density between 1 μ T and 1 mT $\pm$ 2%) act as potent ferroptosis promoters by triggering calcium-dependent oxidative stress. ELF-EMFs induce calcium influx and mitochondrial membrane depolarization, synergizing with iron-dependent lipid peroxidation through ROS overproduction^[38,70] [Figure 1]. Additionally, electromagnetic exposure-induced calcium influx may destabilize membranes and promote nanopore formation, potentially exacerbating iron-dependent oxidative damage^[60,71]. This calcium-ROS interplay disrupts mitochondrial-endoplasmic reticulum coupling, impairing metabolic adaptation and amplifying ferroptosis vulnerability.

Radiotherapy resistance in advanced PCa arises from multifactorial mechanisms, including enhanced DNA repair, cancer stem cell (CSC) persistence, immunosuppressive TME, and metabolic reprogramming^[72,73]. These converge to promote ferroptosis suppression (e.g., GPX4/SLC7A11 upregulation) and apoptotic evasion. EMF-based strategies, such as combining ionizing radiation (IR) with ferroptosis inducers^[74] or magnetic nanoparticle-guided iron delivery^[12,75], utilize electromagnetic bioeffects to selectively sensitize resistant PCa. They achieve this by synchronizing ferroptosis activation with tumor biology while minimizing off-target toxicity.

IR is another electromagnetic stimulus that promotes ferroptosis through ROS-mediated MAPK/Nrf2 signaling and p53-dependent regulation of iron metabolism^[74] [Figure 2B]. Unlike terahertz waves, ionizing radiation generates ROS directly. EMF-based therapeutic strategies leverage these mechanisms to enhance PCa treatment. Specifically, IR induces ferroptosis through ROS generation and ACSL4 (a key enzyme in lipid peroxidation) upregulation. When combined with inhibitors of ferroptosis suppressors (SLC7A11/

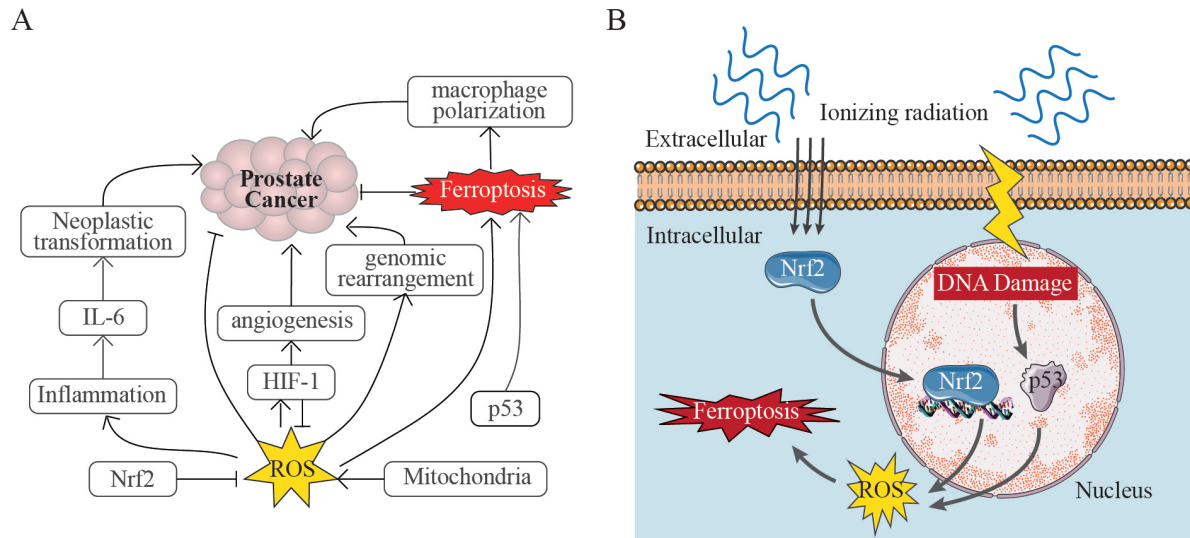


Figure 2. Dual Roles of Ferroptosis in Prostate Cancer. (A) Ferroptosis directly suppresses prostate cancer (PCa) through iron-dependent lipid peroxidation, while paradoxically promoting tumor progression via macrophage polarization in the tumor microenvironment (TME). Key molecular regulators include p53, ROS, Nrf2 and HIF-1; (B) Ionizing radiation triggers ROS overproduction, which activates MAPK/Nrf2 pathways to amplify oxidative stress, while simultaneously engaging p53 to dysregulate iron homeostasis. This dual action synergistically drives lipid peroxidation and ferroptotic cell death. ROS: Reactive oxygen species.

GPX4), synergistic effects are observed, enabling reduced radiation doses^[76]. In addition, magnetic fields improve the precision of targeting tumors by directing iron-based nanoparticles to them. These nanoparticles release $\text{Fe}^{2+}/\text{Fe}^{3+}$ in acidic lysosomes, thereby inducing ferroptosis^[77]. When combined with magnetic field-driven ROS or ELF-EMFs-mediated calcium signaling, this approach enhances tumor suppression in preclinical models. For resistant PCa, PEGylated manganese-zinc ferrite nanocrystals combined with intratumoral micromagnets can enhance drug accumulation and induce ferroptosis. Under external magnetic guidance, they synergize with cGAS-STING-mediated immunogenic cell death to achieve tumoricidal efficacy^[12,75]. The efficacy of this strategy has been validated in PCa mouse models fed a high-fat diet^[75], highlighting its translational potential.

However, challenges persist. These include addressing resistance mechanisms, optimizing EMF parameters (for example, determining the appropriate ELF frequency and intensity for safe ferroptosis induction, as well as the proper terahertz dosing to avoid unwanted inhibition), and validating combinations with anti-androgen agents. Resolving these challenges will be crucial for harnessing the EMFs-ferroptosis axis as a transformative PCa therapy.

SAFETY CONSIDERATIONS

Although emerging studies highlight the therapeutic potential of EMF-based interventions, their safety profile requires careful consideration, particularly regarding normal tissue toxicity and potential carcinogenic risks from chronic exposure. Strategies including microwave ablation with pulsed EMFs^[13], static high-intensity magnetic fields^[15], low-dose alternating electric currents^[11], and focused ultrasound-ethanol combinations^[18] demand strict parameter optimization to avoid off-target thermal or electrical damage. Techniques like high-intensity focused ultrasound or other focal approaches may minimize collateral damage to surrounding normal tissues by confining thermal or electromagnetic energy to a highly localized area. This precision can reduce off-target toxicity and spare critical organs from potential harm. Incorporating real-time imaging guidance further enhances the ability to selectively target

malignant lesions, thereby lowering treatment-related morbidity.

Beyond therapeutic settings, concerns persist regarding the potential carcinogenic risk of prolonged EMF exposure, especially at certain frequencies and intensities. While the International Agency for Research on Cancer has classified some EMFs as possibly carcinogenic in certain contexts, epidemiological studies remain inconclusive or show mixed results^[6,17,78]. Nonetheless, it is prudent to recognize the necessity of long-term monitoring and well-designed cohort studies to clarify any causal relationship, particularly given the latency periods of cancers. A nuanced understanding of safe exposure thresholds and patient-specific susceptibility factors will be critical to ensure that EMF-based modalities do not inadvertently heighten the risk of secondary malignancies or other adverse outcomes.

Furthermore, balancing the therapeutic window requires integrating pharmacologic co-therapies, carefully calibrated frequency-intensity matrices, and longitudinal safety surveillance, particularly in advanced cases such as castration-resistant disease. Through systematic *in vitro*, *in vivo*, and clinical investigations that document both efficacy and normal tissue responses, EMF-based therapies may be refined to maximize anti-tumor activity while minimizing unintended toxicity.

CONCLUSIONS

This perspective delineates the parameter-dependent dualistic role of EMFs in PCa pathobiology and therapy through three interconnected axes [Table 2]. First, calcium signaling acts as the central orchestrator, converting electromagnetic stimuli into oncogenic signaling via piezoelectric and ionic mechanisms. Second, EV-mediated communication serves as an electromagnetic amplifier, coupling cargo remodeling with miRNA network dysregulation to drive metastatic progression. Third, the EMFs-ferroptosis axis reveals frequency-dependent therapeutic potential, where calcium signaling may bridge electromagnetic exposure to iron-mediated cell death. Innovatively, this paper provides the first integrative framework bridging calcium signaling, EV, and ferroptosis under electromagnetic regulation. By revealing how EMFs spatiotemporally coordinate these axes [Figure 1], we redefine a new therapeutic paradigm: exploiting electromagnetic bioeffects to simultaneously disrupt oncogenic circuits (e.g., Ca²⁺-driven stemness, EV-mediated TME reprogramming) while activating tumor-selective death pathways (ferroptosis). Crucially, clinical translation requires stringent safety protocols to minimize off-tissue damage and long-term risks, including focal targeting and parameter optimization. This approach distinctively overcomes limitations of single-pathway targeting and offers precise, mechanism-driven control unattainable with conventional therapies.

Additionally, sex hormones (particularly androgens) drive PCa progression by activating oncogenic signaling pathways like AR-dependent transcription. Emerging evidence suggests that EMFs may indirectly modulate PCa biology through sex hormone fluctuations, though effects are context-dependent. In male workers, chronic low-frequency EMF exposure correlates with declining testosterone trends^[79,80], while pulsed EMFs elevate testosterone in male mice^[81]. EMFs also inhibit testosterone release in porcine endometrial models^[82] and suppress testosterone in male rats^[83]. Critically, no direct evidence links EMFs to prostaglandin alteration, which is a key mediator of PCa-associated inflammation and angiogenesis. Thus, EMFs' hormonal influence remains an underexplored dimension in PCa pathobiology. Notably, there has been no research directly focusing on how EMFs regulate the androgen receptor (AR) signaling pathway in PCa. Considering the pivotal role of androgens in driving AR-mediated oncogenesis, it is plausible that EMFs could also exert significant effects on AR signaling. However, elucidation of the underlying mechanisms requires further experimental validation.

Table 2. EMF-mediated mechanisms in cancer pathobiology

Axis	Key molecules /pathways	Effects of EMFs	Pathological outcome	Ref.
Calcium signaling	- VGCC - Orai/STIM - Piezo1 - TRPV6	- Induce Ca ²⁺ influx - Modulate membrane polarization and EMT - Generate piezoelectric effects	↑ Proliferation ↑ Therapy resistance ↑ Metastatic	[19-22] [23-28] [34-37]
EVs-mediated metastasis	- EVs release and cargo - miR-155/21/210 - miR-126/200c - MMP2/MMP9	- Alter EVs release patterns and cargo - Upregulate oncogenic miRNAs - Suppress tumor-suppressive miRNAs - Activate MMPs	↑ Inflammatory signaling ↑ Basement membrane invasion	[7] [38-46] [50-51]
Ferroptosis regulation	- Fe ²⁺ /Fe ³⁺ - ACSL4/GPX4 - MAPK/Nrf2 - p53	- Promote ferroptosis via ROS - Inhibit iron-transferrin binding (Terahertz) - Enhance lipid peroxidation	Context-dependent: ↑ Ferroptosis and tumor suppression (ELF-EMFs/IR) ↓ Ferroptosis (Terahertz)	[16] [52-62]

VGCC: Voltage-gated Ca²⁺ channels; EMT: epithelial-mesenchymal transition; EMFs: electromagnetic fields; EVs: extracellular vesicles; ELF-EMFs: extremely low frequency electromagnetic fields; IR: ionizing radiation; MMPs: matrix metalloproteinases; ROS: reactive oxygen species.

Future progress will require: (1) Parameter optimization studies: Systematic *in vitro* screening of frequency-intensity matrices to identify tumor-selective windows using calcium flux/ferroptosis biomarkers; (2) Multimodal validation: Testing EMFs-nanoparticle combinations in patient-derived organoids or CRPC murine models with bone metastasis; (3) Clinical translation: Integrating mEHT with anti-androgens while monitoring EV miRNA dynamics (e.g., miR-21/miR-200c ratios) and ferroptotic susceptibility; (4) Investigating EMFs' hormonal influence, such as prostaglandin-EMF crosstalk; (5) Investigating EMFs' role in modulating radiotherapy resistance mechanisms, including CSC regulation, TME reprogramming, and DNA damage response; (6) Determining whether EMFs might suppress AR-driven oncogenesis through testosterone downregulation, enhance androgen-deprivation efficacy, or modulate next-generation AR antagonists. Integrating electromagnetic bioeffects with molecular profiling will enable stage-adaptive therapy to overcome radio resistance. By transcending conventional approaches, electromagnetic engineering offers a transformative path toward stage-adaptive PCa therapy-where biophysical targeting synchronizes with tumor biology to maximize efficacy and minimize toxicity.

DECLARATIONS

Authors' contribution

Writing - original draft, investigation, conceptualization, and funding acquisition: Wang LY

Writing - review and editing: Fan MY, Jiang XY, Bing KJ, Wang YJ, Zhang H

Writing - review and editing, supervision: Wang KS, Huang YM

Availability of data and materials

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Conflicts of interest

Wang KH serves as a Junior Editorial Board member of *Journal of Cancer Metastasis and Treatment*. Wang KH was not involved in any steps of editorial processing, notably including reviewer selection, manuscript handling, or decision making. The other authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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