Urology Research, 2026, Volume 4, Issue 2
http://ojs.bbwpublisher.com/index.php/UR
Online ISSN: 2981-8230
Print ISSN: 3083-4910

Research Progress on the Mechanism of LncRNA GAS5 in Regulating the Radiosensitivity of Prostate Cancer

Xiulong Ma

Department of Radiation Oncology, The Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an 710004, Shaanxi, China

Abstract: Prostate cancer is a prevalent malignant tumor in the male urogenital system. Radiotherapy, which uses high-energy radiation to kill cancer cells, serves as a cornerstone for local advanced and postoperative adjuvant treatment, yet tumor radioresistance, when cancer cells survive and adapt to radiation, significantly limits therapeutic efficacy. Long non-coding RNA (lncRNA) GAS5, a critical tumor-suppressive transcript, is commonly under expressed in prostate cancer and positively regulates radiosensitivity (the tendency of cells to be destroyed by radiation) through multiple mechanisms, including competing endogenous RNA (ceRNA, a process where RNAs regulate each other's expression by competing for shared microRNAs) regulation, DNA damage repair, cell cycle arrest, induction of apoptosis (programmed cell death), and interactions with signaling pathways. This review systematically summarizes the structural and functional characteristics of GAS5, its expression patterns in prostate cancer, and elucidates the molecular mechanisms underlying its regulation of radiosensitivity. Additionally, it explores clinical application prospects and existing challenges, providing theoretical evidence and novel insights for enhancing precision radiotherapy in prostate cancer.

Keywords: Long non-coding RNA; GAS5; Prostate cancer; Radiosensitivity; Molecular mechanism; ceRNA; DNA damage repair

Online publication: Jun 30, 3036

1. Introduction

Prostate cancer (PCa) is among the most prevalent malignant tumors in men worldwide. In China, its incidence is steadily rising due to population aging and increased screening, posing a significant threat to male health [1]. Radiotherapy plays a pivotal role across localized, locally advanced, and metastatic PCa stages. It effectively controls local lesions, reduces the risk of recurrence, and prolongs survival [2]. However, approximately 30–50% of patients develop primary or acquired radioresistance in clinical practice. This leads to local treatment failure, distant metastasis, and therapeutic failure, a critical challenge in prostate cancer

radiotherapy. Long non-coding RNAs (lncRNAs) are transcripts exceeding 200 nucleotides in length that do not encode or only encode short peptides. They are extensively involved in tumor proliferation, invasion, metastasis, and treatment resistance through epigenetic, transcriptional, and post-transcriptional regulation, as well as interactions with signaling pathways. Growth arrest-specific transcript 5 (GAS5) is located on human chromosome 1q25.1 and was initially identified for its high expression in growth-arrested cells. It functions as a tumor suppressor in various malignancies, including breast, lung, gastric, and prostate cancers. Its expression levels are closely correlated with tumor grade, stage, and prognosis [3]. Recent studies confirm that GAS5 is significantly under expressed in prostate cancer tissues and cell lines. Overexpression of GAS5 markedly inhibits proliferation, promotes apoptosis, and enhances radiotherapy-induced cytotoxicity. This positions it as a promising radiosensitizing target [4]. Current research has elucidated multiple key pathways through which GAS5 regulates radiosensitivity in prostate cancer. These include ceRNA networks, DNA damage response, cell cycle checkpoints, apoptotic pathways, and classical signaling axes. This review synthesizes recent domestic and international advances. It systematically outlines the molecular mechanisms by which GAS5 modulates radiosensitivity in prostate cancer and summarizes foundational and translational research findings, which inform the development of novel radiosensitization strategies.

2. Biological characteristics of LncRNA GAS5 and its expression pattern in prostate cancer

2.1. Gene structure and functional characteristics of GAS5

The GAS5 gene spans approximately 630 base pairs (bp) and comprises 12 exons. It generates multiple splice variants through transcription. Its core functional region contains a sequence highly homologous to the DNA-binding domain of the glucocorticoid receptor (GR). This enables competitive binding to GR and subsequent inhibition of its transcriptional activity. This mechanism regulates the expression of downstream genes involved in metabolism and proliferation [5]. GAS5 is widely expressed in normal tissues and is upregulated under conditions such as stress, growth arrest, DNA damage, and radiotherapy. It exerts tumor-suppressive functions by maintaining genomic stability, inhibiting abnormal proliferation, and promoting the clearance of damaged cells [6].

As a typical tumor-suppressive lncRNA, GAS5 primarily functions through several mechanisms.

(1) It acts as a competing endogenous RNA (ceRNA) to sequester miRNAs and relieve their inhibitory effects on target mRNAs [7]

(2) It directly binds to protein molecules to regulate their subcellular localization and activity.

(3) It participates in DNA damage repair and cell cycle checkpoint regulation.

(4) It modulates the expression of apoptosis-related genes to initiate the intrinsic apoptotic pathway.

2.2. Aberrant expression of GAS5 in prostate cancer and its clinical significance

Multiple clinical samples and cellular experiments have confirmed that GAS5 expression is significantly lower in prostate cancer tissues than in adjacent normal tissues. It is even lower in castration-resistant prostate cancer (CRPC) cells, suggesting that its loss is associated with disease progression and enhanced malignant phenotypes [8]. Studies in cell lines, including LNCaP, DU145, and PC-3, show that GAS5 expression is markedly reduced compared to normal prostate epithelial cells. There is further downregulation in radioresistant cell lines, indicating that low GAS5 expression is an important molecular feature of

radioresistance in prostate cancer [9].

Clinical correlation analyses have demonstrated that low GAS5 expression is significantly associated with higher Gleason scores, advanced TNM stages, lymph node metastasis, and early postoperative recurrence in prostate cancer. It serves as an independent adverse prognostic factor [10]. Furthermore, GAS5 expression levels are closely associated with radiotherapy response. There is significantly higher expression in tumor tissues from radiosensitive patients than in those from resistant patients. This suggests that GAS5 may serve as a biomarker for predicting radiotherapy sensitivity in prostate cancer [11].

3. Core molecular mechanisms by which GAS5 regulates radiosensitivity in prostate cancer

3.1. Competing endogenous RNA (ceRNA) mechanism

The ceRNA mechanism is a central pathway through which GAS5 regulates radiosensitivity in prostate cancer. GAS5 sequesters specific miRNAs via sequence complementarity. This blocks their degradation or translational inhibition of target mRNAs, thereby restoring the expression of tumor-suppressive genes and reversing radioresistance [12].

miR-18a is overexpressed in prostate cancer and promotes proliferation and radioresistance by inhibiting tumor-suppressive genes, including PTEN and BIM [13]. GAS5 directly targets and inhibits miR-18a activity, upregulating PTEN expression and suppressing excessive activation of the PI3K/Akt pathway. It also enhances radiotherapy-induced DNA damage and apoptosis. α-Solanine exerts radiosensitizing effects by upregulating the GAS5/miR-18a axis [14].

GAS5 also sequesters miR-320a, relieving its inhibitory effect on RAB21. RAB21 inhibits proliferation and migration by regulating cytoskeletal dynamics and membrane trafficking. It also enhances radiotherapy-induced G2/M phase arrest and apoptosis. *In vitro* and *in vivo* experiments have confirmed that this axis significantly improves radiosensitivity in prostate cancer.

Additionally, GAS5 targets miR-103, miR-21, and others. It inhibits cell cycle progression and enhances apoptotic responses by modulating pathways such as AKT/mTOR and MAPK. In this way, it synergistically enhances radiotherapy sensitivity.

3.2. Regulation of DNA damage repair response to enhance radiotherapy-induced genomic damage

Radiotherapy exerts its cytotoxic effects by inducing DNA double-strand breaks (DSBs). Efficient DSB repair is a key mechanism of radioresistance [15]. GAS5 enhances radiosensitivity by inhibiting DNA damage repair through two mechanisms. First, it suppresses key DSB repair proteins, such as Rad51 and Ku70/Ku80, thereby inhibiting homologous recombination (HR) and non-homologous end joining (NHEJ). This prolongs the duration of γ-H2AX foci and exacerbates damage accumulation [16]. Second, GAS5 regulates DNA damage checkpoints. It activates the ATM/ATR-Chk1/Chk2 pathway, induces G1/S or G2/M phase arrest, and provides a window for failed DNA repair and the initiation of apoptosis. This prevents damaged cells from escaping proliferation.

Reprogramming cell cycle and apoptosis programs is an important pathway through which GAS5 enhances radiosensitivity [17]. GAS5 upregulates cyclin-dependent kinase inhibitors, including p21 and p27. It downregulates cyclins such as CyclinD1 and CDK4, thereby inducing G0/G1 or G2/M phase arrest. This

reduces the proportion of S-phase cells, which are more resistant to radiotherapy [18]. In regulating apoptosis, GAS5 upregulates pro-apoptotic proteins such as Bax and Cleaved Caspase-3/9. It also downregulates anti-apoptotic proteins such as Bcl-2, thereby activating the mitochondrial apoptotic pathway and lowering the apoptotic threshold [19]. Furthermore, GAS5 inhibits epithelial-mesenchymal transition (EMT) by downregulating N-cadherin and Vimentin while upregulating E-cadherin. This reduces invasive and metastatic capabilities and reverses EMT-mediated radioresistance.

Reprogramming of the cell cycle and apoptosis (programmed cell death) pathways is an important mechanism by which GAS5 enhances radiosensitivity [17]. GAS5 upregulates cyclin-dependent kinase inhibitors such as p21 and p27 (proteins that block cell division) while downregulating cyclins such as CyclinD1 and CDK4 (proteins that promote cell division), thereby inducing G0/G1 or G2/M phase arrest (points where the cell can pause before duplicating its DNA or dividing) and reducing the proportion of S-phase cells, which are more resistant to radiotherapy [18]. In regulating apoptosis, GAS5 upregulates pro-apoptotic proteins such as Bax and Cleaved Caspase-3/9 (which promote cell death) and downregulates anti-apoptotic proteins such as Bcl-2 (which prevent cell death), thereby activating the mitochondrial apoptotic pathway and increasing the likelihood of apoptosis [19]. Furthermore, GAS5 inhibits epithelial-mesenchymal transition (EMT, a process where cancer cells gain the ability to move and invade by losing cell adhesion), by downregulating N-cadherin and Vimentin (proteins associated with cell movement) while upregulating E-cadherin (a protein that promotes cell adhesion), reducing invasive and metastatic capabilities, and reversing EMT-mediated radioresistance.

3.3. Regulation of key signaling pathways to synergistically enhance radiosensitivity

GAS5 also achieves synergistic radiosensitization by modulating core tumor signaling pathways. The PI3K/Akt/mTOR pathway is frequently hyperactivated in radioresistant tumors; GAS5 inhibits this pathway by upregulating PTEN via the ceRNA mechanism, reducing cellular proliferation and repair capacity [20]. The MAPK/ERK pathway regulates cell proliferation and anti-apoptotic signaling; GAS5 suppresses ERK phosphorylation, blocking pro-survival signals and enhancing radiotherapy-induced apoptosis. The NF-κB pathway is associated with inflammation and treatment resistance; GAS5 inhibits p65 nuclear translocation, reducing the transcription of downstream anti-apoptotic genes and lowering tumor cell radioresistance.

4. Issues and prospects

Significant progress has been made in research on the regulation of radiosensitivity in prostate cancer by GAS5, yet clinical translation still faces numerous challenges. GAS5 is widely expressed in normal tissues and lacks tumor specificity, making tumor-targeted delivery and minimizing impacts on normal tissues critical challenges. The poor in vivo stability and susceptibility to nuclease degradation of lncRNAs necessitate the development of more efficient delivery systems. Prostate cancer exhibits significant molecular heterogeneity, with variations in GAS5 regulatory pathways across subtypes, necessitating clarification of the mechanisms underlying GAS5 regulation in each subtype for precise regulation. Current research is predominantly based on foundational experiments and lacks validation through large-sample, prospective clinical studies of its effectiveness as a biomarker and target.

Future research should focus on four directions: exploring functional differences among GAS5 splice

variants to develop specific radiosensitizing tools; constructing tumor-targeted delivery systems for efficient and controlled release; conducting clinical cohort studies to establish GAS5-based predictive models for radiotherapy sensitivity; and investigating combination strategies involving GAS5 with immunotherapy and PARP inhibitors to establish multimodal treatment systems. With advancements in mechanistic research and technology, GAS5 holds promise as a crucial target for precision radiotherapy in prostate cancer, offering new avenues to improve patient prognosis.

5. Conclusion

LncRNA GAS5 is under expressed in prostate cancer and is closely associated with disease progression, poor prognosis, and radioresistance, serving as a core molecule in regulating radiosensitivity. GAS5 positively enhances radiosensitivity and reverses resistant phenotypes in prostate cancer through multiple mechanisms, including ceRNA networks, inhibition of DNA damage repair, reprogramming of the cell cycle and apoptosis, and regulation of tumor signaling pathways. Radiosensitizing strategies targeting GAS5 have demonstrated favorable effects in in vitro and in vivo experiments, possessing significant clinical translation potential. As research progresses, GAS5 will emerge as a new target for radiosensitization in prostate cancer, facilitating the development of precision radiotherapy and improving patient survival.

Funding

Molecular Mechanism of Long Non-Coding RNA GAS5 in Regulating Radiosensitivity of Prostate Cancer (Project No.: 2025SF-YBXM-005)

Disclosure statement

The author declares no conflict of interest.

References

[1] Wang H, Wang N, Chu D, 2023, Research Progress and Market Analysis of Androgen Receptor Antagonists for Prostate Cancer. Progress in Pharmaceutical Sciences, 47(08): 617–625.

[2] Zhan W, Zhang Y, 2026, The Impact of Apalutamide Treatment After Radical Prostatectomy on Disease Recurrence. Journal of Primary Medicine Forum, 30(05): 106–108.

[3] Zhang C, Yan Y, Liang J, et al., 2021, Research Progress on the Role of Long Non-Coding RNAs in Liver Fibrosis. Medical Journal of the Chinese People's Liberation Army, 46(02): 186–192.

[4] Li X, Mo R, Jia J, et al., 2026, Research Progress on the Combination Therapy of Chimeric Antigen Receptor Natural Killer Cells for Prostate Cancer. Journal of Difficult and Complicated Cases, 25(03): 374–379.

[5] Yan N, He Z, Xu H, et al., 2017, Research Progress on Long Non-Coding RNAs in Breast Cancer. Journal of Shanghai Jiao Tong University (Medical Science), 37(01): 122–127.

[6] Sun S, Jiang P, Zhang W, 2026, Research Progress on the Regulation of Interactions Between Tumor-Associated Fibroblasts and Tumor Cells by Long Non-Coding RNAs in Gastrointestinal Tumors. Chinese Journal of Medical Frontiers (Electronic Edition), 18(01): 95–105.

[7] Song C, Kang L, Zheng D, et al., 2026, Research Progress on the Mechanism of NEAT1 in Regulating miRNAs in Lung Cancer. Chinese Journal of Respiratory and Critical Care Medicine, 25(03): 223–228.

[8] Wei L, Chen M, 2024, Research Progress on Potential Therapeutic Targets for Prostate Cancer. Chinese Journal of Medicine and Clinic, 24(14): 945–952.

[9] Luo B, Yang L, Li Y, et al., 2021, Screening of lncRNAs Related to the Human BLM Gene and Analysis of Their Expression in Different Prostate Cancer Cells. Journal of Agricultural Biotechnology, 29(05): 924–932.

[10] Qin Y, Lu B, Xie Y, et al., 2026, High Expression of MRE11 Promotes Malignant Progression and Indicates Poor Prognosis in Prostate Cancer. Journal of Shenyang Medical College, 28(02): 131–139.

[11] Zhang Q, Liu J, Ma H, 2025, LncRNA GAS5 Inhibits Epithelial-Mesenchymal Transition and Autophagy in Lung Cancer Cells by Targeting miR-21 Through the PI3K/Akt/mTOR Signaling Pathway. International Journal of Laboratory Medicine, 46(05): 568–574.

[12] Yang W, Xu Y, Zhuo S, et al., 2021, Progress in Epigenetic Modifications Related to Long Non-Coding RNAs in Cancer. Chinese Journal of Biotechnology, 41(08): 59–66.

[13] Li S, Liang Y, Yang X, et al., 2025, Research Progress on the Role of miRNAs in Prostate Cancer and Traditional Chinese Medicine Interventions. China Journal of Chinese Materia Medica, 50(10): 2619–2630.

[14] Zhang S, Chen H, Luo Q, et al., 2020, Effects of Natural Extracts Targeting the PI3K-AKT-mTOR Pathway on Proliferation, Apoptosis, and Autophagy in Leukemia Cells. Chemistry of Life, 40(01): 80–85.

[15] Qi Z, Wang L, Wu L, et al., 2025, Research Progress on the Mechanisms of Endocrine Therapy Resistance in Prostate Cancer. Medical Innovations, 35(04): 452–460.

[16] Chen M, Lu X, Zhang S, 2014, RNA Interference of DNA Repair Enhances Radiosensitivity in Tumor Cells. Chinese Journal of Cancer Biotherapy, 21(02): 227–230.

[17] Ma Q, Li H, Li Q, et al., 2026, Silencing LncRNA NORAD Inhibits Docetaxel Resistance in Castration-Resistant Prostate Cancer Cells by Suppressing TRIP13 and Increasing Autophagy. Hebei Medical Journal, 32(01): 46–55.

[18] Pan J, Shang F, Ma R, et al., 2023, Research Progress on the Regulatory Mechanisms of Cyclins, Cyclin-Dependent Kinases, and Related Kinase Inhibitors in Cell Cycle Progression. Chinese Journal of Biotechnology, 39(04): 1525–1547.

[19] Wang X, Liu J, Wen J, et al., 2022, Astragaloside IV Promotes Apoptosis of Synovial Fibroblasts in Rheumatoid Arthritis by Regulating the LncRNA MIR22HG and Caspase-3 Pathways. Journal of Guangzhou Medical University, 50(02): 9–17.

[20] Li W, Song Z, Huang S, et al., 2026, Research Progress on the Involvement of Non-Coding RNAs in the Occurrence and Development of Triple-Negative Breast Cancer Through the Regulation of the PI3K/AKT/mTOR Signaling Pathway. Acta Physiologica Sinica, 1–27.