Ferroptosis Induced by the AR-SREBP1-FASN Axis in Prostate Cancer

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Abstract. Prostate cancer is one of the most common malignant tumors in men. Although traditional endocrine treatments such as androgen deprivation therapy are effective in the early stage, the emergence of castration-resistant prostate cancer (CRPC) has posed a severe challenge to clinical practice. Studies have shown that prostate cancer has a unique lipid metabolism dependence, and ferroptosis, as a novel type of programmed cell death, is closely related to the lipid metabolism state of tumors, providing a new research perspective for breaking through the resistance dilemma. This article focuses on the role of the AR-SREBP1-FASN axis in the lipid metabolism reorganization and ferroptosis regulation of prostate cancer, analyzes the molecular mechanism by which androgen receptor regulates SREBP1 through transcription and activates FASN to mediate de novo synthesis of fatty acids and triglycerides, discusses the pathological significance of this pathway, and summarizes the synergistic treatment strategy of second-generation anti-androgen drugs combined with ferroptosis inducers and their potential value in reversing resistance. The analysis indicates that targeting the AR-SREBP1-FASN axis to break the lipid metabolism defense barrier is expected to provide a new therapeutic breakthrough for CRPC patients. However, the dynamic changes characteristics of this pathway in different disease stages of the human body are still unclear, and the clinical translation of specific small molecule inhibitors targeting SREBP1 or FASN still faces many obstacles, which are the directions for future research.

Keywords: Prostate Cancer; AR-SREBP1-FASN axis; lipid synthesis; Ferroptosis.

1. Introduction

The latest global cancer data report indicates that prostate cancer (PCa) is the second most common malignant tumor among men worldwide, ranking first among male malignant tumors in European and American countries, and being the fifth leading cause of male deaths worldwide in 2022 [1]. Its causes are influenced by various factors such as geographical location, race, lifestyle, diet, and age [2]. As a male-specific disease, prostate cancer typically occurs in middle-aged and elderly men. A survey shows that 65% of newly diagnosed prostate cancer cases involve men over 65 years old, and 25% involve those over 75 years old [3].

Early localized PCa can be cured through radical surgery or radiotherapy, but patients in the middle and advanced stages still face high recurrence risks and complications related to treatment (such as sexual dysfunction and urinary incontinence). Traditional endocrine therapy includes androgen deprivation therapy (ADT), which blocks testosterone in the testicles, and anti-androgen therapy, which blocks testosterone in the adrenal glands [4]. These are currently the main treatment methods for advanced PCa in clinical practice. Although most patients initially respond well to ADT and anti-androgen therapy, due to the reactivation and abnormal activation of androgen receptors (AR), some patients eventually develop astration-resistant PCa (CRPC) [5], and new treatment options for PCa urgently need to be sought.

Unlike other tumors, PCa has unique lipid metabolism-dependent characteristics, manifested as abnormal activation of fatty acid de novo synthesis, continuous activity of cholesterol biosynthesis, and high dependence on mitochondrial fatty acid oxidation for energy supply [6]. In PCa, the oncogene MYC promotes enhanced fatty acid de novo synthesis by influencing the upregulation of fatty acid synthesis gene expression, thereby inducing PCa growth [7]. Studies have found that fatty acid synthase (FASN) is associated with the malignant proliferation, invasion, metastasis, and reduced radiotherapy sensitivity of PCa. Ferroptosis, as a type of cell death closely related to the

metabolic state of tumors, theoretically can avoid drug resistance caused by defects in cell apoptosis or abnormalities in anti-apoptotic pathways, and may be associated with the AR-dependent lipid metabolism network. Therefore, it has gradually become a research hotspot in the field of prostate cancer treatment [8]. This study focuses on the AR-SREBP1-FASN axis that can induce ferroptosis in prostate cancer, presenting a new idea for prostate cancer treatment.

2. The AR-SREBP1-FASN Axis and Lipid Metabolism Reprogramming

2.1. The Role of Androgen Receptors in Lipid Metabolism

Androgens are a class of sex steroid hormones mainly secreted by the testes of male animals. They play a crucial role in the maturation and maintenance of the male reproductive system and can regulate cellular energy metabolism and influence the de novo synthesis of lipids. Androgens mainly exert their effects through androgen receptors (AR). Under physiological conditions, the normal activation of the androgen-AR pathway is a key factor in maintaining metabolic homeostasis. In adipose tissue, AR signaling effectively inhibits the expression of core adipogenic transcription factors such as PPARγ and C/EBPα, thereby effectively preventing the differentiation and lipid storage of precursor adipocytes. At the same time, it can regulate the balance of adrenergic receptors and promote the breakdown of triglycerides into free fatty acids.

2.2. Molecular Regulatory Role of the AR-SREBP1-FASN Axis in Lipid Synthesis

Among the numerous pathways regulated by androgens in lipid metabolism, the AR-SREBP1-FASN axis is regarded as an important molecular pathway connecting endocrine signals with fatty acid de novo synthesis. This pathway integrates the transcriptional regulation mediated by androgen receptors with the process of fatty acid de novo synthesis and participates in the regulation of lipid accumulation and secretion functions in various male reproductive-related tissues. After androgens bind to AR, they can affect the expression of various lipid metabolism-related genes through the classical nuclear receptor transcriptional regulation mechanism. Srebf1 is one of the target genes of androgen receptors, and its protein product, sterol regulatory element-binding protein 1 (SREBP1), as a transcription factor, mainly regulates the expression of multiple key enzymes involved in fatty acid and triglyceride synthesis, thereby participating in the regulation of the lipid biosynthesis process [9,10]. The overexpression of SREBF partner (SCAP) enhances nuclear SREBP1 translocation and can upregulate the expression of the fatty acid synthase (FASN) gene. FASN plays an important role in the de novo synthesis of triglycerides, and as a multi-enzyme complex, the knockdown of the MAT gene in its functional domain can reduce the triglyceride and medium-chain fatty acid contents in cells.

Under the stimulation of androgen signals, the activated AR can directly bind to the androgen response element (ARE) in the promoter region of the SREBP1 gene, thereby regulating the expression level of this gene and influencing its downstream lipid metabolism-related target genes. Recent studies have shown that under androgen treatment, AR can combine with the mammalian target of rapamycin (mTOR) at the promoter region of SREBP1, synergistically promoting the expression of SREBP1 and inducing its translocation from the cytoplasm into the nucleus, ultimately promoting lipid synthesis [11]. In the prostate cancer model, inhibiting AR activity can lead to a decrease in SREBP1 expression, and further inhibit the transcriptional level of its key downstream target gene FASN, thereby limiting lipid synthesis. In prostate cancer cells, AR inhibitors-mediated phospholipid remodeling induces ferroptosis through the SREBP1-FASN axis.

Among the multiple downstream targets regulated by SREBP1, acetyl-CoA carboxylase 1 (ACC1) plays an important role as a rate-limiting enzyme in the pathway of fatty acid and triglyceride synthesis. Once ACC1 is activated, it directly drives the de novo synthesis process of fatty acids and triglycerides within the cell, completing the key steps of lipid production. Fatty acids, as long-chain aliphatic carboxylic acids, are the main components of lipids such as fats, phospholipids, and glycolipids. They are not only important components of cell membranes but are also considered the

main energy source of animals. Fatty acids are mainly stored in the form of triglycerides (TAGs) in lipid droplets (LDs) in adipose tissue in animals [12]. Triglycerides are synthesized by exercising three fatty acid molecules with one glycerol molecule. In the cytoplasm, ACC1 catalyzes the carboxylation of acetyl-CoA to generate malonyl-CoA, initiating triglyceride synthesis. At the same time, the elongation of the carbon chain of fatty acids occurs on FASN, with the core being the acyl carrier protein, which converts malonyl-CoA and acetyl-CoA through condensation, reduction, dehydration, and re-reduction processes into saturated fatty acids.

3. The Association between Lipid Metabolism and Ferroptosis in Prostate Cancer Cells

3.1. Ferroptosis

Ferroptosis is an iron-dependent form of programmed cell death characterized by the accumulation of lipid peroxides and excessive production of reactive oxygen species (ROS). Unlike traditional cell death mechanisms (such as apoptosis, necrosis, and autophagy), ferroptosis exhibits unique features in biology, chemistry, and genetics. Its mechanism primarily involves disruption of iron metabolism, accumulation of lipid peroxides, and failure of the antioxidant system [13]. During ferroptosis, iron ions within the cell catalyze lipid peroxidation through the Fenton reaction, leading to cell membrane rupture and cell death. The regulatory mechanisms of ferroptosis involve multiple signaling pathways, which affect the occurrence of ferroptosis by regulating the redox state and lipid metabolism within the cell [14].

3.2. Excessive Generation of Lipid Peroxides

The excessive generation of lipid peroxides is one of the key events in ferroptosis. Within cells, the production of lipid peroxides mainly results from the oxidation of polyunsaturated fatty acids (PUFAs), which play a significant role in cell membranes. Iron ions, by promoting lipid oxidation reactions, lead to the accumulation of lipid peroxides, thereby triggering oxidative stress in cells and ultimately causing cell death [14,15]. Studies have found that the accumulation of lipid peroxides is not only a marker of ferroptosis but also an important factor in the progression of various diseases (such as diabetes, cardiovascular diseases, and cancer) [16]. In PCa, inducing lipid metabolic reconfiguration in prostate cancer cells through drugs to cause lipid disorders in these cells is an extremely feasible treatment approach.

3.3. The AR-SREBP1-FASN Axis and Influence on Ferroptosis

As mentioned earlier, the AR-SREBP1-FASN axis can affect the synthesis of fatty acids and triglycerides. Previous studies have found that this pathway can reduce the incidence of ferroptosis, mainly through FASN, and its inhibition can reduce the generation of lipid peroxides. Additionally, this study has discovered that the AR-SREBP1-FASN axis may have another pathway to lower the incidence of ferroptosis. Specifically, FASN can promote the elongation of the carbon chain of fatty acids, while ACC1 can initiate the de novo synthesis of triglycerides. Both of them simultaneously promote the increase of triglycerides. The increase of triglycerides will promote the synthesis of fatty acids, reduce the level of PUFAs, decrease lipid peroxides in cell membranes, and ultimately lower the incidence of ferroptosis.

4. Therapeutic Approaches Targeting the Resistance of Prostate Cancer Cells to Ferroptosis

In recent years, reducing the expression of SREBP1 to inhibit the transcription of FASN and thereby triggering lipid peroxidation and ferroptosis has become one of the main treatment methods for prostate cancer. First, AR inhibitors can indirectly break the lipid protective barrier by relieving

the transcriptional drive of the SREBP1-FASN axis. Among them, enzalutamide is a second-generation AR inhibitor, which has a higher affinity compared to traditional anti-androgen drugs. Apalutamide is another AR inhibitor, and it has a higher affinity for AR than enzalutamide. Currently, apalutamide is indicated primarily the treatment of non-metastatic castration-resistant prostate cancer and metastatic hormone-sensitive prostate cancer.

Second, ferroptosis inducers can specifically trigger lipid peroxidation. The commonly used strategies for inducing ferroptosis currently mainly involve inhibiting the cystine or glutamate re-transport system to cause depletion of GSH or directly inhibiting GPX4 to lead to uncontrolled lipid peroxidation. The recognized ferroptosis inducers Erastin and RAS-selective lethal 3 (RSL.3) play a crucial role in the treatment of prostate cancer. Studies have shown that Erastin or RSL3 not only significantly inhibit the growth and migration of refractory PCa cells in vitro, but also significantly delay the tumor growth of refractory PCa in vivo [17].

Furthermore, in the prostate cancer model, ferroptosis inducers can effectively inhibit tumor cell growth, and when used in combination with second-generation anti-androgen drugs, they can produce a synergistic effect. This suggests that the lipid metabolism disorder triggered by the inhibition of the AR signaling pathway may provide a more suitable substrate and redox microenvironment for ferroptosis to occur. Qin et al. recently synthesized AR antagonists containing isothiocyanates, which can downregulate AR and its spliceosome [18]. Reasonably combining them with the GSH synthesis inhibitor buthionine sulfoximine (BSO) can promote lipid peroxidation and ferroptosis in PCa cells. The occurrence of androgen resistance may be closely related to the ferroptosis-inhibiting genes, such as ribosomal protein S6 kinase C1, which is a key gene related to enzalutamide resistance. FTH1P8 and ABCB1 can regulate the occurrence of docetaxel resistance by inhibiting ferroptosis in prostate cancer [19]. The use of inhibitors targeting these genes in combination with ferroptosis inducers and second-generation anti-androgen drugs is expected to alleviate the resistance of advanced prostate cancer. Additionally, some natural products and existing drugs have sensitizing effects on ferroptosis, such as kinnarubin, palbociclib, flubendazole, and iron supplements, which can all promote ferroptosis, and their combination with ferroptosis inducers can further enhance clinical efficacy.

5. Conclusion

The AR-SREBP1-FASN axis plays a crucial role in the lipid metabolism reprogramming and iron death regulation of prostate cancer. As a transcriptional regulator of lipid metabolism, AR can directly bind to the androgen response elements in the promoter region of the SREBP1 gene, thereby driving its expression upregulation and activating downstream lipid synthesis key enzymes such as FASN, promoting the de novo synthesis of triglycerides. This pathway not only provides necessary lipid raw materials for the malignant proliferation of prostate cancer cells but also weakens the substrate basis for lipid peroxidation, thereby inhibiting the occurrence of iron death.

Based on this, therapeutic strategies targeting the AR-SREBP1-FASN axis can be carried out from two aspects: inhibiting AR and inducing iron death. The second-generation AR inhibitors include enzalutamide, apalutamide, and iron death inducers include Erastin and RSL3. Moreover, the two can also be used in combination to jointly destroy the lipid protection barrier of tumor cells and enhance the iron death sensitivity of cells, providing a new intervention direction for the treatment of prostate cancer. This article redefines the androgen signal-driven lipid metabolism adaptation as an iron death defense mechanism, suggesting that lipid metabolism disorder is not only a concomitant phenomenon of tumor growth but also a key strategy for tumor resistance to iron death. However, current research in this field is mostly focused on the cellular and animal model level, and the dynamic changes of the AR-SREBP1-FASN axis in different prostate cancer progression stages in the human body and their clinical correlations still need to be further verified.

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