Review

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The Importance of STARD3 and Lipid Metabolism in Prostate Cancer

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Abstract

Prostate cancer is common in men and continues to pose a significant medical challenge. The primary feature of prostate cancer is hormone sensitivity. Prostate cancer cells become dependent on testicular androgen for survival. Steroidogenesis involves the synthesis of steroid hormones such as androgens from cholesterol. Tumor cells increase fatty acid production with androgens. Synthesized fatty acids contribute to membrane formation and support oncogenic signaling. Hormone-dependent tumors require cholesterol for proliferation. Cancer cells have higher intracellular cholesterol levels than non-tumor cells. STARD3, a member of the START protein family, is a transmembrane protein that facilitates cholesterol transport and resides in late endosomes. STARD3 stimulates steroidogenesis by inducing the motion of lysosomal cholesterol into mitochondria. High mitochondrial cholesterol levels can prevent apoptotic cell death in different cancer types, thereby triggering tumor progression. This review discusses recent studies on the relationship between cholesterol levels and prostate cancer risk, as well as the properties and activity of STARD3. To the best of our knowledge, this study is the first to comprehensively summarize the role and therapeutic potential of STARD3 in prostate cancer.

Keywords: Cancer, lipid, prostate, STARD3

Introduction

Prostate cancer is among the most prevalent malignancies affecting men worldwide. Approximately 1,6 million new cases and 366,000 deaths are reported annually (1). The majority of prostate cancers are identified through prostate-specific antigen (PSA) screening, subsequently confirmed by diagnostic biopsy, and further evaluated using imaging techniques to assess potential metastatic dissemination. Patients who cannot be treated with surgery or radiation are treated with drugs targeting the androgen receptor (AR), which is the main causative agent of prostate cancer, and androgen deprivation therapy. PSA testing was repeated after treatment to evaluate disease recurrence. However, only 25% of men with a PSA level >4.0 ng/mL are diagnosed with prostate cancer during biopsy. False negatives are also common (2). Despite recent advances, there are important medical problems in men due to the overtreatment of cancer and the undertreatment of metastatic prostate cancer (3).

The primary feature of prostate cancer is hormone sensitivity. Because the prostate cannot produce testosterone, prostate cancer cells become dependent on testicular androgens for survival. In steroidogenesis, steroid hormones such as androgens are synthesized from cholesterol (4). Androgens in prostate cells; promote proliferation, lipogenic enzyme expression, and differentiation but prevent apoptosis (5). Given the relationship between prostate cancer and androgens, tumor cells increase fatty acid production. Synthesized fatty acids contribute to membrane formation and support oncogenic signaling. Zadra et al. (6) reported that the simultaneous blockade of lipogenesis and AR signaling strongly reduced prostate cancer growth.

Several studies have established a relationship between dietary lipids and prostate cancer. Tamura et al. (7) demonstrated that prostate cancer cells utilize saturated very long-chain fatty acids as substrates for membrane synthesis and androgen production, thereby promoting tumor growth. Epidemiological data and preclinical animal studies further suggest that dietary

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fat intake is involved in the initiation and progression of prostate cancer (8). The presence of lipids in cancer cells supports the growth, spread, and survival of cancer. As tumors break down or metastasize, new lipid synthesis is triggered to prepare the tumors for future environmental conditions. Thus, the cycle of lipid synthesis and degradation increases tumor survival. Treatments targeting lipid synthesis and oxidation block AR synthesis inhibit prostate cancer growth (9).

Lipid and Prostate Cancer

Cholesterol is a fat-like substance necessary for cell membrane formation and hormone production. Intracellular cholesterol homeostasis is tightly regulated. This homeostasis is determined by the rate of cholesterol synthesis in the liver, its uptake, conversion to steroid hormones, and the rate at which it is excreted from the body as bile. Circulating cholesterol is transported by lipoproteins, which are primarily classified into two main categories: low-density lipoprotein (LDL) and high-density lipoprotein (HDL). Elevated levels of cholesterol, LDL, and low HDL, contribute to cancer progression by increasing inflammation, proliferation, intratumoral steroidogenesis, and altering membrane lipid structure (10,11). LDL ensures the storage of cholesterol in cells that require repair as well as the release of cholesterol and triglycerides for metabolism (12). HDL, on the other hand, acts to remove cellular cholesterol and exerts antioxidant and anti-inflammatory effects. With these effects, HDL can reduce oxidative stress, inflammation, and cholesterol content in tumor cells, thereby affecting cancer cell proliferation (13). Cancer cells can synthesize cholesterol or take it up as LDL. Hormone-dependent tumors, such as prostate cancer, require cholesterol for proliferation. Cholesterol plays a precursor role in the production of androgens, which affect prostate cancer growth (14).

Several studies have investigated the relationship between cholesterol levels and prostate cancer risk. Some studies have suggested that high LDL-C levels contribute to the development and progression of prostate cancer, whereas high HDL-C levels may have a protective effect. In their study, Ossoli et al. (13) HDL was shown to inhibit cell proliferation induced by LDL by reducing cholesterol content in prostate cancer cell lines. After monitoring 53,944 men and 24,475 women diagnosed with cancer, elevated ≥240 mg/dL total cholesterol levels were positively associated with an increased risk of prostate and colon cancer in men, as well as breast cancer in women, compared with levels below 160 mg/dL (15). Jamnagerwalla et al. (16) demonstrated that elevated total serum cholesterol was correlated with an increased risk of high-grade prostate cancer. In contrast, no significant association was observed between serum LDL levels and the risk of overall, low-grade, or high-grade prostate cancer. Interestingly, elevated serum HDL levels were linked to a higher risk of both overall and high-grade prostate cancer (16). In prostate cancer patients with a Gleason score of 8-10, men with low levels of cholesterol have a lower risk of prostate cancer than men with high cholesterol (17). In a study analyzing 438 prostate cancer cases, it was observed that men with cholesterol levels below 240 mg/dL had a reduced risk of developing high-grade prostate cancer compared with those with cholesterol levels exceeding 240 mg/dL (18). Farwell et al. (19) identified a significant correlation between prostate cancer risk and total serum cholesterol, reporting a 45% increase in the overall risk of prostate cancer and a 204% increase in the risk of high-grade prostate cancer. Similarly, another research group found a positive association between cholesterol levels and the incidence of high-grade prostate cancer (Gleason score ≥8) in a cohort of 650 men diagnosed with the disease (20).

Collectively, these findings indicate that elevated cholesterol levels are associated with an increased risk of prostate cancer. Accordingly, statins, which inhibit cholesterol biosynthesis, reduce serum cholesterol levels, and suppress prostate cancer cell proliferation, have been linked to decreased cancer progression (21). Although the correlation between cholesterol levels and prostate cancer remains a topic of ongoing research, it is clear that cholesterol, especially HDL and LDL, plays a role in affecting prostate health. Maintaining a healthy lifestyle and managing cholesterol levels can help reduce the risk of prostate cancer. As research continues, a deeper understanding of these connections will pave the way for future targeted preventive strategies and interventions.

STARD3 and Prostate Cancer

STARD3 is one of the 15 members of the StART family. STARD3 acts as a lipid transfer protein that directs sterols to endosomes and regulates cholesterol accumulation. The overexpression of STARD3 also affects cholesterol trafficking, leading to increased mitochondrial cholesterol content. Some cancers are associated with the misuse of cholesterol derived from late endosomes (LE) or lysosomes. Cancer cells have higher intracellular cholesterol levels than non-tumor cells. Cholesterol accumulation contributes to the formation of membrane micro-domains rich in sphingolipids, stimulating the progression and migration of cancer cells. STARD3 is an important candidate for cancer therapy, and the identification of selective STARD3 inhibitors represents an interesting yet undiscovered area of research (22).

START proteins represent a family of lipid transfer proteins (LTPs) implicated in diverse cellular functions, including non-vesicular cholesterol transport. This family comprises 15 members categorized into six subfamilies based on their amino acid sequences and ligand-binding characteristics. STARD3 is distinguished by its C-terminal START domain, central FFAT domain, and N-terminal MENTAL domain, which collectively facilitate lipid trafficking. Through its FFAT motif, STARD3 interacts with VAP-A and VAP-B (vesicle-associated membrane protein-associated proteins) localized in the endoplasmic reticulum (ER), thereby establishing membrane contact sites between the ER and other organelles. Additionally, STARD3 acts as a LTP that directs sterols to endosomes and promotes membrane formation inside endosomes. In other words, it regulates cholesterol accumulation in endosomes and mediates distribution between organelles (23-25). High STARD3 expression increases the accumulation of free sterols in the endosomal region (26) (Figure 1, Table 1).

Cholesterol contributes to the tight packing of membrane lipids, resulting in membranes with reduced water permeability and increased thickness due to the straightening of lipid chains. Cholesterol is predominantly synthesized in the ER and

subsequently distributed to other cellular membranes, including the mitochondria, where it undergoes irreversible conversion into bile acids or steroid hormones. After entering the limiting membranes of LE and lysosomes, LDL cholesterol is transported either to the plasma membrane via vesicular recycling or to the ER through non-vesicular mechanisms. Certain cancers are associated with dysregulation of cholesterol trafficking originating from LE or lysosomes. The cancer-associated LTP STARD3 is frequently localized in proliferative regions. STARD3 contains transmembrane domains that anchor it to endosomal membranes, mediating lipid transfer between endosomes and the ER. Furthermore, STARD3 overexpression disrupts cholesterol trafficking, leading to elevated mitochondrial cholesterol levels (27).

The prostate, an androgen-regulated organ, is one of the most common sites of malignancy in men. Androgens in prostate cells stimulate cell proliferation and differentiation while inhibiting apoptosis (28). The MLN64 protein, which is encoded from chromosome 17, contains a C-terminal START domain homologous to the StAR protein. The START domain harbors a hydrophobic tunnel that can bind a single cholesterol molecule, a feature crucial for regulating steroid biosynthesis (29). MLN64 increases steroidogenesis and regulates the transfer and conversion of cholesterol into pregnenolone (30).

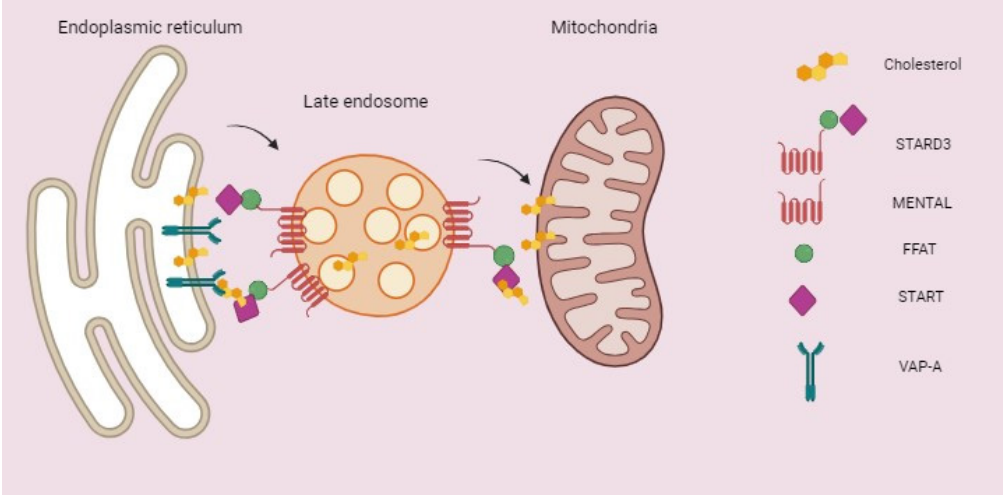

Figure 1. Cholesterol transport from the endoplasmic reticulum to late endosomes and mitochondria via STARD3

Table 1. Summary of the changes in the STARD3 protein and related molecules in diseases

No	Name	Disease	Function	Description	Year	Reference
1.	STARD1	Niemann-Pick type C	Cholesterol transport	The reexpression of ACDase in fibroblasts from patients with NPC disease lowers STARD1 expression and causes a decrease in mitochondrial cholesterol accumulation.	2021	(24)
2.	STARD3	Chronic obstructive pulmonary disease	Cholesterol transport	External cholesterol altered airway epithelial sensitivity of inflammation in response to cigarette smoke extract, through the regulation of STARD3-MFN2 pathway.	2022	(25)
3.	STARD3	HeLa cells	Cholesterol accumulation in endosomes	STARD3 is a cholesterol transporter scaffolding ER-endosome contacts and modulating cellular cholesterol repartition by delivering cholesterol to endosomes.	2017	(26)
4.	STARD3	Breast cancer	Over-expression of STARD3	The homology between the C-terminal part of STARD3 and the functional StAR domain (SHD) suggests that STARD3 and StAR may both play a role in steroidogenesis.	1997	(30)
5.	STARD3	Cell culture	Cholesterol transport	STARD3 participates in mobilization and utilization of lysosomal cholesterol by virtue of the START domain's role in cholesterol transport.	2002	(32)
6.	StAR	Cell culture	The ability of STARD3 to stimulate steroidogenesis	STARD3 stimulates steroidogenesis by virtue of its homology to StAR.	1997	(33)
7.	STARD3	Niemann-Pick type C	Mitochondrial cholesterol transport	A transport pathway for endosomal cholesterol to mitochondria requires STARD3 and that may be responsible for increased mitochondrial cholesterol in NPC disease.	2010	(34)

Table 1. Continued

No	Name	Disease	Function	Description	Year	Reference
8.	STARD3	Niemann-Pick type C	Over-expression of STARD3	STARD3 expression is increased in NPC cells and plays a key role in cholesterol transport into the mitochondria.	2017	(35)
9.	StAR	Hepatocellular carcinoma	Mitochondrial cholesterol transport	StAR silencing by siRNA resulted in the net decrease of mitochondrial cholesterol levels.	2008	(36)
10.	STARD3	Breast cancer	Over-expression of STARD3	StARD3 over-expression may contribute to breast cancer aggressiveness by increasing membrane cholesterol and enhancing oncogenic signaling.	2015	(37)
12.	STARD3	Prostate cancer	Over-expression of STARD3	STARD3 expression seems to be correlated with high stage, high Gleason score and short relapse-free time in the prostate cancer patients	2007	(38)

Hormone-dependent tumors, such as prostate cancer, induce intratumoral steroidogenesis independently of circulating androgen. Cytochrome P450c17 plays a role in androgen biosynthesis, acting as both 17 α-hydroxylase and 17,20-lyase in steroid biosynthesis (28). The precursors of potent androgens facilitate the enzymatic conversion of progesterone and pregnenolone into the androgens androstenedione and dehydroepiandrosterone, respectively (31). The expression of the CYP17 and MLN64 genes, which encode key enzymes involved in androgen biosynthesis, is known to be upregulated in neoplastic tissues. Elevated MLN64 and CYP17 activity in prostate cancer tissues stimulates steroidogenesis by facilitating continuous cholesterol transport to mitochondria and enhances androgen production via the catalytic function of cytochrome CYP17. Prostate cancer is strongly affected by steroid hormones, and the regulation of these genes can significantly reduce the risk of developing cancer (28).

STARD3 is a transmembrane protein that plays a crucial role in cholesterol transport and is predominantly localized in LE. Additionally, STARD3 promotes steroidogenesis by facilitating the transfer of lysosomal cholesterol to mitochondria (32-35). Several studies have shown that high mitochondrial cholesterol levels can inhibit apoptotic cell death in different types of cancer, thereby triggering tumor progression (36,37). The overexpression of STARD3 in cancer potentially stimulates independent steroidogenesis, favoring the development of hormone-dependent cancers, such as prostate cancer. Elevated STARD3 levels in prostate cancer patients are associated with metastasis, local recurrence, and reduced overall survival. Consequently, STARD3 is a potential oncogene, for which the first inhibitor has recently been identified (22). In prostate cancer, a linear relationship has been identified between the expression of STARD3 and CYP17, which are integral to the steroid biosynthesis pathway. The co-expression of STARD3 and CYP17 in prostate cancer promotes steroidogenesis by facilitating continuous cholesterol transfer to mitochondria and enhancing androgen biosynthesis via the catalytic activity of cytochrome CYP17. Consequently, dysregulated STARD3 and CYP17 expression is linked to poor prognosis in prostate cancer patients (38). Although the precise molecular mechanism remains unclear, these findings imply that elevated STARD3 expression contributes to membrane cholesterol accumulation, potentially driving increased cancer aggressiveness (22). The application of the STARD3 inhibitor VS1 in breast and colon cancer cell lines has been shown to specifically target STARD3 and trigger its degradation (39). Investigations in this area are expected to advance the development of STARD3-targeted in silico approaches. Furthermore, the design of anti-STARD3 therapies has significant potential as a therapeutic strategy against cancer.

Conclusion

Some cancers are linked to the misuse of cholesterol derived from LE or lysosomes. Cancer cells exhibit higher intracellular cholesterol levels than non-tumor cells. This cholesterol accumulation contributes to the formation of sphingolipid-enriched membrane microdomains, which promote cancer cell proliferation, progression, and migration. StAR-associated MLN64 and CYP17 in prostate cancer tissue increase the activation of steroidogenesis and androgen biosynthesis through cholesterol transfer to the mitochondria. Prostate cancer is strongly affected by steroid hormones, and it is considered that regulating these genes can significantly reduce the risk of developing cancer. Within this context, it remains to be determined whether STARD3 alone or in combination with AR can trigger progression to prostate cancer. As a cholesterol-specific START protein, STARD3 is considered a molecular target for therapeutic interventions aimed at modulating the lipid metabolism of neoplastic cells by either correcting its dysregulated function or silencing its expression in cancer cells.

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