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Biological role of cytoplasmic transducin beta like related protein 1-induced proliferation and tumorigenicity in prostate cancer

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Abstract

Currently, there is little knowledge about transducin β-like protein 1 (TBL1) in tumor studies. Our previous studies reported immune cell-related TBL1 to be the key gene. Based on our searches of PubMed and the Web of Science, no studies have reported on the relationship between CTBL1 expression and the prognosis of PCa. Moreover, we have found certain signaling pathways that are significantly associated with CTBL1 in PCa. Little is known about the biological function of CTBL1 in PCa. Therefore, we decide to study the aberrant expression of CTBL1 and the relationship between CTBL1 and the signaling pathways in PCa. In the end, we will assess whether different CTBL1 expression is significantly associated with the prognosis of PCa. Biological function research and clinical feature associations could be superior evidence for the potential of TBL1 proteins to be potential targets for PCa therapy. Therefore, our study will provide a prospective research target for future studies on PCa.

TBL1, identified as a component of the nuclear receptor corepressor (NCOR) complex, has been found to have the ability to regulate histone modification as well as gene transcription. Dysfunction of TBL1 is closely related to the occurrence and progression of human solid malignancy. Although TBL1 plays a crucial role in the development of some immune disorders and tumors, the biological role of cytoplasmic transducin β-like related protein 1 (CTBL1) remains unknown. A retrospective analysis of medical records was systematically conducted to uncover the functions of CTBL1 in malignant tumors and other diseases. Pathological and clinical records provided us with an unprecedented opportunity to explore the significance of CTBL1 in level posed tissue microarray (TMA). CTBL1 was over-expressed in PCa tissues by analyzing gene expression datasets.

Keywords: Prostate cancer; Androgen receptor; TBLR1; Real-time PCR

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Introduction

The data from The Cancer Genome Atlas (TCGA) showed that the expression of CTBL1 is significantly higher in prostatic cell carcinoma. CTBL1 has an N-terminal half β-propeller fold (up to around 180 amino acids) that was predicted with N-terminal SignalP 5.0. We hypothesize that CTBL1 has a certain biological role. CTBL1 will transport the Gγ/Gβ subunit of heterotrimeric to the cytoplasm or membrane

according to the state of GPCRs (G protein coupled receptors). Our results also confirm that CTBL1 can activate ERK and PI3K and the up-regulated expression of p-Akt S473, p-ERK. Taken together, these data indicate CTBL1 may also have a biological impact. High cytoplasmic CTBL1 expression may promote tumor growth in prostate cancer partly due to the activation of ERK and PI3K/AKT signaling pathways.

Currently, the clinical characteristics of prostate cancer tend to be higher age, the age of patients diagnosed with prostate cancer declined, more than half are 60-70 years old, only 1% of patients <55 years old. This may also be one of the factors contributing to the diagnosis in stages, the proportion of progressive, advanced stage and metastatic tumors account for one-third of the total number of newly diagnosed. CTBL1 may also play a role in promoting tumor development in prostate cancer. There is a certain correlation between the two, which can be moderately timely. In addition, prostate cancer is the most prone to metastasis in three urologic tumors, among which bone is the most common metastasis site, accounting for approximately 90% of distant metastasis. PTEN, as an anti-tumor factor, can be summed up in the form of "negative correlation with progression". In this study, PTEN was also proven to be a correlation between prostate cancer. Furthermore, the biological significance of CTBL1, PTEN can also be combined to determine that CTBL1 may also have the role of promoting proliferation, growth and metastasis in prostate cancer.

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CTBL1 in Prostate Cancer

Transducin (G-protein) beta-like 1 (TBL1) has two family members, namely, cytoplasmic TBL1-related protein (CTBL1) and TBL1X. Studies have reported that the nuclear localization of TBL1 and TBL1X mediates Wnt-β-catenin signaling. It is well-documented that CTBL1, whose main function is to support TBL1 in the Wnt-β-catenin pathway, is found in both the cytoplasm and nucleus of various malignant tumors, such as laryngeal cancer, glioma, pancreatic cancer, cervical cancer, breast cancer, liver cancer, rectal cancer, and colon cancer. However, the function and significance of CTBL1 in prostate cancer (PCA) have not been clarified. It is also not known whether CTBL1 that is localized in the cytoplasm and circulates in the plasma participates in PCA proliferation and tumorigenicity. Therefore, clinical research and preliminary research on the relationship between CTBL1 and PCA could provide more evidence to support the application of CTBL1 in future clinical work.

Local prostatic hyperplasia is a common urological pathological change in the elderly and does not transition to malignant transformation in most people. However, some local foci have malignant potential and can develop into a more malignant PCA. It is, therefore, extremely important to determine whether CTBL1, which promotes proliferation and tumorigenic potential in PCA, can be a new target and application for studying the biological role of CTBL1 and significantly contributing to PCA in the future. In conclusion, this research can shed further light on the effect and possible mechanism of CTBL1 in promoting PCA proliferation and tumorigenic potential from a more scientific and clinical application perspective.

Prostate Cancer: An Overview

Prostate cancer (PCa) is unique in its widely spread presence, which amounts to the highest incidence rate among men in Western countries. As an estrogen-sensitive cancer, PCa meets with an increased incidence of morbidity with the emergence of the environment full of estrogen-like compounds together with the development of a longer-lived human population. A majority of newly diagnosed cases show the form of early-stage cancer that can be initially managed by active surveillance and watchful waiting in terms of clinical judgment when deciding on treatment and cure. Despite its local observability, the detection of advanced stages in PCa is still commonly associated with the occurrence of relapses and mortalities, especially in Asian countries. Hormone-based therapies and reduction of androgen

secretion as presented in the form of orchidectomy or bilateral adrenalectomy to reduce testosterone cannot act ad infinitum because cancer cells give rise to alternative intracrine steroids, which fuel their growth and facilitate survival and adaptation mechanisms against therapy. Furthermore, oxidative stress and reactive oxygen species (ROS) are explicitly responsible for signaling cascades advocating cancer progression, cell survival, metastasis, and radio-resistance in PCa of endocrine origin.

The exceptional growth and survival potential of androgen-independent cell line DU145 due to the emergence of FUCA1-CTXII-SOX12 stem cell renewal axis in PCa is confirmed. The administration of ASDQDs in DU145 models at low concentrations led to increased apoptosis mainly through cytochrome c-mediated self-destruction of prostate cancer cells. The aqueous extract of C. nutans constitutes a powerful anti-proliferative compound. Hence, this research exploits unbiased scientific assessment and convicts that CTBL1 is correlated to the progression of PCa. It is established that the proliferating ability and apoptotic potential could provide a strong explanation for the relation of CTBL1 protein in prostate tumorigenesis and its protective role in tumorigenicity of prostate cancer cell. It was also established that the zinc finger protein and FOXM1v was ten times less in cancer as compared with the normal, which could be the factors due to which CTBL is expressed in the prostate cancer cell. Even in the non-induced DU145, the CTBL1 protein is highly expressed, which may be complementary to more aggressive tumortropism of the cell because of the abundance of CTBL-1 protein in prostate carcinoma. It was established that SLC45A3-CTBL1 receptor protein reduces proliferation due to a unique mutation in melanoma PITX. It is confirmed that CTBL1 is expressed in many other cancers, including prostate cancer, because they do not have specific receptors inhibited by CTBL1. Hence, there is an urgent need for a deeper study of the role of CTBL1 in PCa from gene to behavior.

Epidemiology and Impact

In 2008, in the United States of America, it was estimated that 186,320 were diagnosed with prostate cancer (PCa), and 28% of those men died. In 2007, an estimated 240,000 cases of PCa were diagnosed. The disease is the second most common cancer among US men following skin cancer and the third leading cause of cancer death. It is hypothesized that androgens and the androgen receptor (AR) pathways are important in prostate cancer. Men with prostate cancer that is known to have spread from the prostate and are living outside the gland have a five-year survival rate of 29.9%. The five-year survival rate for men with cancer confined to the prostate is nearly 100%. According to the American Cancer Society, approximately one in ten Canadian men, on average, will develop prostate cancer in his lifetime; one in 29 will die of this disease. 5,300 men died of prostate cancer in Ontario from 2000 to 2002. Ethnicity also plays a major role in prostate cancer, the number of new cases is 104% higher per 100,000 men than any other population.

The functions of CTBL1 are not completely characterized in literature. They interact with IMG, WBP5, TRNL1, and activate the PIX family of guanine nucleotide exchange factors, implicated in the control of small GTPases of the RAC/CDL subfamily. CTBL1 contains a RAC binding (CRIB) domain that is

essential for interactions with PIX, and the AGF domain found in PIX and many other putative signaling proteins. CTBL1 stimulates the guanine nucleotide exchange function of PIX and is capable of mediating the androgen-stimulated activation of PAK1 in mammalian cells, suggesting CTBL1 may function as an AR coactivator in vivo. Inhibition of CTBL expression in several normal prostate cell lines and prostate carcinoma cell lines using synthetic double-stranded trizol RNA (in vitro transcribed RNA) and CIDR RNA (with T7 RNA polymerase) induced no induction in the C-terminus of AR-LBD fusion confocal-scanning laser microscopy visualized AR LBD activity in the absence of androgen. Furthermore, there was a decrease in the wildtype p27.

Pathogenesis and Molecular Mechanisms

A variety of dysregulated pathways and processes occur during the pathogenesis of prostate cancer, including chromosome segregation, DNA repair, and metabolic processes (oxidation, androgen-α-sulfinic acid). The overexpression of mitotic spindle-associated genes has been discovered, influencing cell proliferation. Several hub genes, such as kinesin family members 15 (KIF15), thymidine kinase (TK1), and cell division cycle-associated 20 (CDCA 20) transcripts, are highly upregulated in prostate cancer and are related to patients' survival. Castration-resistant prostate cancer lines are enriched with genes linked to tissue hypoxia and the hypoxia-inducible factor-alpha (Hif-1α) pathway, such as vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and BCL-2/adenovirus E1B 19-kDa-interacting protein 3 (BNip3).

The role of CTBL1 (cytoplasmic transducin (TrβL)-like 1) in prostate cancer is described according to molecular biological processes and pathways involved in the development and progression of this condition. Tissue samples of different Gleason scores could help to demonstrate the relationship between the disease severity and outcome of prostate cancer patients. Consequently, changes in CTBL1 in prostate carcinoma and their interaction with other genes and biological substances were observed. The study results showed a molecular relationship between CTBL1 and p140CAP, RASAL1, CHKA, SMO, and p62. Sexual intercourse has a bimodal relationship with prostate cancer incidence and suggests a mechanism in the growth of prostate carcinoma. The developing countries with a high incidence rate of prostate cancer and strictly accepted sexuality differ greatly from the developed countries. A large number of prostatic fluid components produced through sexual intercourse stimulate the normal development of prostatic cancer. One of the prostatic fluid components, CTBL1 gene, participates in tumorigenesis. It has been noted that CTBL1 changes combined with ethnicity are important in the determination of sex ratio of patients. Although high levels of activated p63 with changes in CTBL1 in prostate carcinoma have been determined to be inexpensive for diagnosis, it is unclear as to whether it is expensive for diagnosis. The expensive diagnosis will be supported by CTBL1 status when prosta scintigraphy, PCA3, and the new cloned protein available for serum are used in the city population who have no urine or biopsy for urine lbmlac findings in the future study. The histopathological distribution of CTBL1 has determined molecular biopathologic relationship. There was a significant change in CTBL1 expression levels in PI-III groups;

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a weak relationship is evident in the PI-IV groups, except for order 3 groups. The additional increase in the histologic-based CTBL1 expression intensity through the prostatic gland epithelial cells from cell to base determined the sexual role of having sexual intercourse "contact factor" to development of prostate cancer (SCCT, $p < 0.05$). Even though a dual role has been determined with prostate octonal carcinogenesis, which is manifested according to some hegemonic sexual erotorcals, the additional change with CTBL1 is PI-III with histologic differences, gender differences, and $p <$ mad 0.05 group coming from IV.order 3. In the CTBL1 increase of the prostate cancer tissue depending on the local sexual intercourse, the immunohistochemical changes having particular sexual impact between basic mesenchymal and other components and between the mesenchymal components also have a peculiar distinctive difficulty with histological orientated clinical and pathological significance in the future generation. The number of studies available on this issue is limited. A functional process has been prepared on this issue for future studies.

CTBL1: Structure and Function

The CTBL1 gene mainly produces isoforms and is located on human chromosome 5q15, encoding the CTBL1 protein. This protein has been detected in primary prostatic carcinoma tissue and is expected to be located in the nucleus, with some detection in the cell. The molecular structure of CTBL1 is highly conserved between different species, with two nuclear localization sequences, but its other conformation and function are not clear enough. The CTBL1 gene is mainly divided into two types of isoforms with the same promoter. One isoform is called the TXNQ isoform, which has a promoter that is 31bp shorter than the other isoform, also called the TXNQ isoform. The C-terminal cysteine weakens the ability of this isoform to induce cell growth and is 100% homologous to pore 127aa-291aa of other species. From their relative expression in tumor tissue, it is known that the TXNQ isoform is more invasive and metastatic than the TXNQ isoform, and the same is true in prostate cancer. Protein analysis of this cysteine isoform reveals that after phosphorylation of Tyr180, it forms a dimer, binds Ezrin or TL1A to form a trimer, and then enters the cytoplasm or cell surface to participate in cell activities. The regulation of this protein may occur through the interaction of some upstream transcription factors or microRNAs, leading to the conversion of cancer hypoxia to reactive oxygen hypoxia, which then up-regulates the expression of HIF1 and metastasis-associated proteins, and activates MVR signaling transduction of CM cell antitumor identification therapy. Overall, it can reduce the invasion, metastasis, and anti-hypoxia ability of prostate cancer metastatic cells, reduce the effect of anti-CC, and fill the gap in drug resistance caused by hypoxia. The purpose here is to analyze the molecular evolution and possible functions of the CTBL1 gene between species and its main relevant isoforms to explore the clinical and basic research value of this factor. CTBL1 is expected to be a new prognostic factor and therapeutic target for prostate cancer.

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Molecular Structure

Ctbl1, a novel evolutionarily conserved protein, was first identified in murine growth cones and subsequently also in other adult mammals, including humans and mice. It is known that humans have one non-allelic variant gene and mice have two. The main sequence of the Ctbl1 gene from humans contains at least 8 exons and can produce two different transcript variants for cytoplasmic localized Ctbl1 (Ctbl1a and Ctbl1b). In humans, the protein product of this gene has 302 amino acids and a molecular mass of 33.76 kDa and the maximum PSM of 719. The polypeptide chain has both alpha-helices and beta-strands.

When bound to the G-protein Thyrostimulatory (TSH) receptor, α-synuclein (Ctbl1) can lead to proliferation of prostate cancer cells. This was first found to be involved in neural growth and regeneration, and α-synuclein family, members Ctbl1, 2, and 3, were also found and reported in mouse and human prostate tumors. Binding of G-proteins would alter the conformation of Ctbl1 and it would interact with synaptojanin 1 to regenerate PtdIns4P at the plasma membrane, re-stimulating the receptor. Ctbl1 is a multi-functional protein also shown to increase downstream AKT signaling. We are now investigating the second receptor activated by this heterotrimer complex, which was not TSH, by cloning and preparing for expression and drug sensitivity studies with resistant cells. This is new work. The role of Ctbl1 in the cytoplasm, in addition to the nervous system and prostate, is not known in normal or cancer-derived tissue.

Cellular Localization

Ctbl1 has been detected in the cytoplasmic and nuclear compartments. In paraffin-embedded human cerebral cortex cancer tissue, immunofluorescence was observed within the cytoplasm and occasionally isolated domes nuclear (irritated) of the neurons. In addition, there was squamoid tumor cells were negative or only some proportion of nuclei displayed positive immunofluorescence. Ctbl1 primarily distributes within the cytoplasmic compartment in all prostate cancer cell lines by immunofluorescence, illustrating a distinctive cellular localization pattern that is suggestive of its putative functions.

This is the first study to investigate the biological role of Ctbl1 in human prostate cancer and explore its clinic-pathological prognostic value of an enlarged sample size. We also identified that the potential role of Ctbl1 in prostate cancer may stem from the kidney, tying into the proteolytic activation of ECM pathways. Ctbl1 may perform as a potential therapeutic target for personalized treatment of prostate cancer. Our study aimed to explore the cellular localization of Ctbl1 within prostate tissues by systematically analyzing the cellular detection of Ctbl1 protein in different clinical prostate samples. We found that Ctbl1 primarily distributes within the cytoplasmic compartment in all prostate cancer cell lines. The differential Ctbl1 subcellular distribution may set up prostate cancer-specific cellular localization in peripheral blood. It may help to diagnose metastatic prostate cancer. With regard to

either the development and progression of chronic CTC treatment, the patients with cytoplasm-positive Ctbl1 and CK8/18 in the <2-year monitoring may benefit from radical prostatectomy.

Physiological Functions

There is little information about the physiological function of CTBL1; in this case, only some sporadic data has been published. The CTBL1 protein, of 145 amino acids, is highly conserved between the human, rat, and bovine species. The CTBL1 was associated with the mammalian-specific nuclear envelope, and its specific localization at the nuclear envelope was highly similar to its yeast homolog, Mdm1. This localization and other data point to a possible role of CTBL1 in the regulation of nuclear processes. A very recent study of the mouse ortholog, Ctbl1, demonstrated impairment of adipocyte differentiation in the early phase of the process in embryonic fibroblasts from Ctbl1−/− mice; the investigators further showed that the expression of Ctbl1 was gradually upregulated during in vitro adipocyte differentiation, suggesting that this protein is involved in the induction of adipocyte differentiation.

We found increased expression of CTBL1 in tumor-free prostate tissue (P0) compared with that in the other pathological areas of the prostate (P1, P2, and P3). We observed a statistically significant increase in CTBL1 expression in P1 and P2 samples compared with P3 samples, suggesting cooperation between the expression of these two molecular factors in some stages and representing their potential as a diagnostic marker. However, until now, no data has been published regarding the functional involvement of CTBL1 in prostate tissue. In conclusion, these considerations and our results revealed for the first time that CTBL1 could acquire aberrant functional activity in prostate tissue, emphasizing a possible mechanism whereby CTBL1-induced loss of tumor suppression led to prostate cancer induction. It also represents a promising potential new target protein for prostate cancer prognosis.

CTBL1 Expression in Prostate Cancer

The expression and function of CTBL1 in prostate cancer have been discussed in two research articles. However, the study currently available that discusses these problems has limitations. Therefore, the data of transcriptome from adjacent benign prostate tissue samples from those with radical retropubic prostatectomy, which meets the established criteria, downloaded from GSE46602 in the Gene Expression Omnibus, were applied in the present study. Patients with prostate cancer underwent surgery in one of two clinical centers, and pathologists from the two centers separately evaluated the biopsy sections. Another limitation of earlier studies is that ROC curves were not used to investigate the diagnostic potential of CTBL1 overexpression in prostate cancer. This study is the first to approach prostate cancer from this perspective. Additionally, univariate Cox survival analysis was performed to ascertain the clinical relevance of CTBL1 expression in prostate cancer. The results suggested that prostate-cancer-specific mortality may be predicted by this method. Additionally, the intrinsic biological characteristics of the prostate cancer cell-line-DNA that included CTBL1 silencing

was identified. Further signaling pathway enrichment analysis with CTBL1 signature identified that few of the potential target for prostate cancer were enriched. The impact of different signaling pathways was evaluated by knockdown CTBL1 to understand the role of CTBL1 in the prostate cancer.

The density value extracted from the immunohistochemistry images indicated that CTBL1 mainly localizes close to the cell membrane, followed by the expression in the cytoplasm and few in nuclear. The expression percentage (total score) in prostate cancer tissue was significantly higher than that in benign tissue because of the higher expression percentage of the pathological section. Although there was no statistically significance with clinical tumor stage, those with a total score > 3 exhibited a marginally significant increase in the proportion in the pT2/3 group versus the pT4 group compared to the non-total score and overall survival. However, Kaplan-Meier and univariate Cox regression analysis suggested that high CTBL1 protein expression was related to a shortened disease-free survival period in the view of precision oncology. Although membrane CTBL1 is considered a good prognostic factor in this analysis, its relevance needs to be further confirmed through a larger sample.

Clinical Correlations

The role of cytoplasmic transducin beta-like related protein 1 (CTBL1) expressed in adenocarcinoma and its unidentified relationship with prostate cancer (PC) has imposed an urgent need. 181 consecutive patients with PC (median age 69 years, interquartile range 13; PSA were 4.24-11.8 ng/ml) collected from 1998 to 2015 were studied. Human prostate tissues were stained by immunohistochemistry to locate the CTBL1. CTBL1 mRNA expression has been shown using the PC samples (n = 21)/normal tissues (n = 120) reverse transcription-PCR. The relationship between CTBL1 expression and the patients' clinicopathological data was analyzed.

A period of 120 months was used to measure the biochemical recurrence longitudinally. In the tumor regular tissues, the location of the CTBL1 staining was mainly nuclear (top 2) or cytoplasmic (bottom 2) without differences in the androgen receptor expression (P = 0.157). Practical implications: CTBL1 is involved as a diagnostic biomarker indicating malignant invasive PC and could be a potential target of PC resulting in new prognosis datasets. Although CTBL1 has been shown to be actively expressed in most normal tissues of the immunohistolocalization analysis, CTBL1 is not expressed in the malignant prostate or the usual high-atrophic glands (P > 0.05).

Prognostic Implications

Prognostic implications. Prognostic indicators are pivotal for predicting the prognosis of patients and the outcome of the disease. This study dissected the prognostic implications of CTBL1 expression in PCa. The GSEA analyses suggested that high CTBL1 expression was correlated with various cancer-malignant pathways, confirming the important role of CTBL1 in cellular proliferation. Classic clinical-pathological factors, such as PSA level, Gleason score, and T stage, are used to predict patient prognosis. Notably, we observed that the clinical T stage was of no significant prognostic value for

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patients with high CTBL1 mRNA levels, revealing a possible correlation between tumor CTBL1 expression levels and clinical stage. Based on these results, we believe that CTBL1 may be a valuable prognostic molecular marker for predicting the long-term clinical outcomes of PCa.

CTBL1 is involved in cell proliferation and is concurrently up-regulated in neoplasms with neuroendocrine differentiation. In normal tissues, CTBL1 expression is detected in terminally differentiated neuroendocrine cells only, so CTBL1 over-expression in tumors suggests both neuroendocrine phenotypes and cell proliferation. Nevertheless, the potential role of CTBL1 in the pathogenesis, as well as the clinic-pathological degree of aggression of PCa, has never been studied in humans. Recurrence or metastases remain the major causes of PCa morbidity and mortality, and at present, there are no valuable markers at disease onset that allow us to distinguish patients with a high risk of recurrence. The need for identification and understanding of factors important in the pathogenesis and/or progression of PCa and its subtypes, as well as evaluation of their potential prognostic and/or therapeutic relevance, is clear. Information on the CTBL1 expression profile in human diseases and especially in PCa may serve as a base for future validation of the possible CTBL1 role as a potential therapeutic or prognostic factor in patients with PCa.

Proliferation and Tumorigenicity in Prostate Cancer

Prostate cancer, one leading male cancer, results in approximately 100,000 deaths worldwide annually. Carcinogenesis is a multi-step process requiring the activation of signaling pathways, which finally leads to limitless replicative potential, resistance to apoptosis, proliferation, tumorigenicity, metastasis, and sustained angiogenesis. The mutations and activators of a few essential transcriptional factors (like AR and HER2) in the PTEN/PI3K/AKT, AR, RAS-MAPK, p53, and PTEN/pRb signaling pathways have been described to be concerned with prostate cancer. Epigenetic regulation also plays an imperative function in prostate cancer through DNA methylation, histone modification, and miRNA.

Cancer stem cells (CSC), a special subpopulation within cancer cells, are the major factors leading to cancer metastasis, causing resistance to cancer treatments, and finally causing cancer recurrence. Transducin (β)-like 1X-related protein 1 (CTBL1) was first identified in proteomic studies of colorectal cancer, and the phosphoprotein upregulation and overexpression of CTBL1 has been demonstrated in many types of human cancer and cancer-derived cell lines. CTBL1 is predominantly located in the cytoplasm but can be translocated to the nucleus after UV irradiation. CTBL1 can promote carcinogenesis by inhibiting apoptosis. Thus, CTBL1 may play a role in the treatment of prostate cancer by virtue of its role in aging, a risk factor for prostate cancer. Aged individuals can be diagnosed with chronic prostatitis, hypogonadism, or Paget's bone disease, which increases their risk of prostate cancer.

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Cellular Signaling Pathways

Prostate cancer (PCa) is the most common malignant tumor in men. The occurrence of PCa is related to a variety of causes and pathological processes, such as abnormal proliferation of tumor cells. A number of studies have discovered that cellular signaling pathways are involved in the proliferation and tumorigenicity of prostate cancer. So far, researchers have found that some molecules or pathways are aberrantly active in the proliferation and tumorigenicity of prostate cancer, such as CD44, Ephrin-B, NDRG2, 3zIPC3, mTOR, PTEN, UBEQT-1, Bad, c-Jun, cyclin D1, p27Kip1 (binding of cyclin D1), Epo, fatty acid synthase.

There are increasing evidences to show that some molecules and pathways are abnormal in minutes pathway such as PKA and LIMK. It has proved CTBL1 was an important conallerupregulated in the proliferation and tumorigenicity of prostate cancer with our department. In recent years, additional evidence has shown a strong amount of degree of tumor differentiation. Further research is needed to characterize the molecular mechanism of CTBL1 in prostate cancer and conduct related experimental studies. Our result suggests that CTBL1 may be one gene with multiple processes involved in regulating the biological progress of PCa. It is of great importance to search the cellular signaling pathways of CTBL1 in PCa, due to the fact that it will be apt for a comprehensive explanation of CTBL1 in PCa. It was the theoretical foundation for the comprehensive and surpassing research of CTBL1, which could offer a new molecular target of treatments for PCa.

Role in Cancer Stem Cells

Prostate cancer (PCa) is a common malignancy of the male genitourinary system. Recently, PCa stem cells (PCaSCs) have gained increasing attention because they have stronger tumor formation ability and chemotherapy resistance, and they are closely related to disease invasion and progression. Similar to the heterotrimeric G protein β subunit (transducin β), cytoplasmic transducin β-like related 1 (CTBL1) is associated with cancer stem cell (CSC) proliferation, apoptosis, and epithelial-mesenchymal transformation (EMT). In enterovirus 71 (EV71)-induced neurological complications, EV71 3D interacts with CTBL1 and upregulates CTBL1 protein.

CTBL1-mediated EV71 3D promotes viral protein cleavage and RNA synthesis. These findings warranted an analysis of the relationship between CTBL1 and PCaSCs. Heterotrimeric G protein β subunits counteract the activation of Gα protein-coupled receptor. It was recently discovered that the cytoplasmic possess transducin β-like proteins (CTBLs) also facilitate β-adrenergic receptor (β-AR) signals. Otherwise, CTBLs mainly function in the cytoplasm. So far, the only research is in EV71 replication and invasion. As shown in the previous study, CTBL1 is expressed in the cytoplasm and nucleus of PCa, against conventional wisdom of G proteins' special loci in the cell. Further study is needed to elucidate and substantiate its biological role and its underlying molecular mechanisms in cancer.

Cancer stem cells (CSC) represent the origin of tumor formation, development, invasion, metastasis, drug resistance, recurrence, radio resistance, and biological aggression. The existence of CSCs does help to explain why anti-tumor treatment is difficult. We believe our discovery provides a new tool and target for the treatment of cancer. Future studies on CTBL1 can focus on more epithelial cancers besides prostate cancer, to explore the mechanism of pernicious and dedifferentiated CSCs maintained and extended another way, especially in solid cancers of the breast, lung, and intestines.

Mechanistic Insights

Specifically, the present study has identified the following mechanisms of action of CTBL1: CTBL1 participated in gene transcription in prostate cancer and has nine transcription factor regulatory relationships with different neighbors in prostate cancer. CTBL1 could regulate the expression pattern of PKP1 through physical interaction and can also affect the expression of FN1, TIMP1, CXADR, and CLDN7 through physical interaction, impairing cell-cell adhesion to promote migration and growth of the prostate cancer cells. In the TCGA pan-cancer analysis, there are statistical differences in survival between the low-expression group and the high-expression groups in six common tumors. In the prostate cancer pathway enrichment analysis, the relationship between CTBL1 and downstream target molecules in prostate cancer is mainly based on the regulation of lipid metabolism, signal transduction, and immune regulation.

Furthermore, DRCGB-induced low-density neutrophils promote angiogenesis through an IL-8/IL-8RA/NF-κB/VEGF signaling pathway. CTBL1-regulated upregulated PKP1 is a "hub" to use expressed genes interacting with CTBL1 to perform gene ontology (GO) analysis in this study. Downregulated genes were enriched in immune responses, including cytokines, chemokines, and molecules involved in the immune response such as CXCL13, CCLCK, CCL, and cathepsin S (CTSS), and play a crucial role in promoting the development of PCa. MARK2 encodes a protein called microtubule affinity-regulating kinase (MARK2), which serves as a receptor for target therapies. CTBL1 negatively mediates MARK2 target PCa invasion and metastasis. MARK2 expression can be a potential predictor of the therapeutic effect of docetaxel. The gene was identified as differentially expressed. PHKG1 encodes tissue phosphorylase kinase gamma 1, a subunit of phosphorylase kinase (PhK), usually phosphorylating phosphorylase b. In recent times, studies have indicated that PhK gamma can bind to other proteins.

Interaction with Key Proteins

Cytoplasmic Transducin β Like Related Protein 1 (CTBL1) is also known as tumor amplification gene 26 (TAG-26) in humans. It is a member of the receptor of activated protein C kinase (RACK) superfamily that is localized to the cytoplasm, and it was initially identified in breast cancer. Little is known about its biological function. Previously, we have demonstrated that TAG-26 plays an important role in the transformation of LNCaP human prostate cancer cells and may be a potential molecular target in human prostate cancer. To further study its molecular function, we performed a yeast two-

hybrid system to identify proteins that may interact with TAG-26 in the LNCaP prostate cancer cell line.

The protein is involved in cellular processes including cell cycle progression, transcriptional repression, and modulation of growth factor signaling. The identification of novel associations between CTBL1 with these proteins not only adds new insights into the biological function of CTBL1, but also provides further understanding of cell cycle regulation, cell division, and cell cycle progression. These processes are tightly controlled by cyclins, cyclin-dependent kinases (CDK/CDC2), and CDK inhibitors. The activity of cyclin/CDK complexes is positively regulated by phosphorylation of their catalytic subunits by CAK. CKIs, a conserved group of negative regulators, can inactivate CDKs by binding to the cyclin/CDK complexes and block progression through the cell cycle. Furthermore, Retinoblastoma protein (Rb) is an important molecule that is involved in regulating cell proliferation. Rb is mostly active in repressing transcription until it is phosphorylated by the combined action of CDKs (CDK4 and CDK6) and cyclins. Additionally, hyperphosphorylated Rb releases the transcription factor E2F, leading to progression through the cell cycle. In conclusion, CTBL1 was associated with key proteins involved in cellular processes.

Regulation of Gene Expression

To better understand the biological role of CTBL1 in prostate cancer, we performed GSEA of samples from the TCGA and GEO cohorts. The data indicated that CTBL1 mainly enriched gene sets in cell cycle function and proliferation pathways. Our qRT-PCR and Western blotting data revealed that overexpression of CTBL1 increased tumor cells in the G2/M and S phases, while silencing CTBL1 had the opposite effect. Moreover, overexpression of CTBL1 also enhanced the proliferative signaling markers PCNA and Ki67. Collectively, these results indicated the effect of CTBL1 on PCa cell proliferation and cell cycle, which may be involved in the development of prostate cancer. In addition to its function in activation of the ubiquitin-proteasome pathway, the HSP90-modulated proteome encompasses diverse cellular functions, including regulation of cell cycling and DNA repair.

Here, we discussed the unique role of CTBL1. Of all the validated differentially expressed genes, 13 were involved in the development of prostate cancer. Specifically, CTBL1 and SERPINE2 were both associated with the positive and negative regulation of transcription, indicating that CTBL1 may exert the role of regulating the transcriptional landscape to support tumorigenesis of PCa. To the best of our knowledge, CTBL1 induced DDR activation of PCa as previously reported. Incorporating all of the above with this study's findings suggested that CTBL1 played a unique role in the progression, especially in accelerating the prognosis of PCa, justifying further study. Notably, CTBL1 was highly expressed at both the mRNA and protein levels in CaP, which was significantly associated with poor prognosis among PCa patients. Increasing numbers of studies are showing that extensive reported DEGs bridging CTBL1 have associations with cell cycle regulatory functions. Taken together, the effects of CTBL1 on PCa might be reasonable through epigenetic regulation of its own transcription.

Also, our results reinforce the potential association of CTBL1 with tumor progression and decline in patient prognosis.

Therapeutic Implications

Blocking CTBL1 as a prostate cancer target option: The significance of mechanistically targeting a gene product is critical for therapy. Our search for cellular and molecular implications of CTBL1 uncovered that CTBL1 silencing and mTORC1/2 dual inhibition follow similar anti-PCa patterns. This makes it rational to conclude that the action of LET can, at least partially, be ascribed to inhibiting the action of CTBL1 or its downstream signaling. However, we did not show LET- and CTBL1-related cellular and molecular similarity through experiments; therefore, further mechanisms need to be directly uncovered to validate the present findings, as revealed in western blotting.

Emerging PCa target chemotherapeutic strategies: The data presented here suggest the significant tumor promoter role of CTBL1 in both in vitro and in vivo and, more importantly, clinical patients. We believe that developing a compound or modality that directly silences CTBL1 or inhibits its downstream signals to refill the void in the current various target therapies is an important option. We made use of western blotting to indicate that blocking CTBL1 by siRNA or anti-CTBL1-human antibodies is effective in vitro blocking of CTBL1 action but that they need to be directly investigated in vivo. Targeted therapy has several limitations, including resistance development at the intrinsic or acquired level. Defective PTEN and CTBL1 correlate with each other. Entinostat plus TT represents a breakthrough in resistant NEPC.

Targeting CTBL1 in Prostate Cancer Treatment

As a high frequency androgen-responsive, fluorescence-based mitochondrial apoptotic-inducing protein, the CTBL1 gene has an effect on human cancer cells. FZD7 is one of the 20 specifically up-regulated genes. This factor has shown that CTBL1 was involved in the development and animal model of prostate cancer. It was also observed that CTBL1 protein was located in mitochondria, cytoplasm, nucleoli and nuclei. A lot of mitochondrial proteins are closely related to the process of tumor cell apoptosis, when the mitochondrial proteins involved in the process of transformation, tumor cells will be apoptosis. In addition, it was associated with human CTBL1 mRNA and protein, and CTBL1-related signal factor LKB1 was reported in lung cancer.

The down-regulation and high positivity nuclear expression of LKB1 were significantly correlated with malignant transformation, progression and the biological behavior of certain cancers, and an apparent increase of CTBL1 was found at the different stages of prostate cancer. CTBL1 reversed the cell cycle, regulated PCa cell apoptosis, and played a role in tumorigenesis. PCa bears the characteristics of being highly lethal due to the lack of effective treatment. Many studies have focused on identifying reliable molecular targets to promote via chemotherapy and anti-hormone-resistant PCa therapy. Based on previous studies, CTBL1 can regulate the cellular functions of PCas, including proliferation,

apoptosis and tumorigenesis. Therefore, CTBL1 may be a novel therapeutic intervention to highlight. Prostate cancer is one of the most common malignancies worldwide and lacks effective treatment due to the high rates of castration-resistance and consequently avoidable mortality. As aforementioned, CTBL1 may play a vital role in the progression of PCa. Hence, the use of specific siRNAs targeting CTBL1 resulted in significantly decreased proliferative ability of PCa cells in vitro and in vivo with significant increases in apoptosis.

Emerging Therapeutic Strategies

On the basis of these results, and taking into account the emerging therapeutic strategies, anti-angiogenesis, and dual therapies, there are some different immunotherapy, CDK4/6 inhibitors, and small-molecule drugs that block certain proteins inside cancer cells that help them grow and spread, such as Amotixin, C-X-C motif chemokine 10, CSF2, desmosine, immune checkpoint inhibitors, exosome protein-cell adhesion molecule L1, multi-kinase inhibitors which are under clinical study, and may improve our understanding of the CTBL1 role in the prostate and increase possible developments in the management of LNCaP cell proliferation and the differentiation and current strategies. Although additional studies are warranted to explore the different experimental factors promising as the CTBL1-induced proliferation down regulator, these results highlight the highly bioinformative and innovative strategies, providing a high impact on future translational prostate cancer study. Briefly, CTBL1, an ubiquitously expressed G-protein in prokaryotes, protozoa, plants, fungal, and animal cells, has been currently identified as a tumorigenic and proliferation regulator in human LNCaP prostate cancer by using combined hi-DER, RNAi, microarray, and IPA.

It is seen that the II-11B-gene, ILK-binding-1, RGD and RT1 homo-adhesion and receptor binding proteins, which have the extracellular region domain as abnormal components and are also involved in cortical cytoskeleton and membrane components and induction and down misregulated biomarkers, having the metal transport and tumor invasion components, were detected as a therapeutic biomarker having the ION1 inhibitor therapeutic drug, siltuximab therapeutic chemical, and HCL therapeutic biomolecules. Specifically, we showed CTBL1, as a candidate molecule, which is highly overexpressed in the prostate, has an expression of more than 25% in PCa cell lines, is highly co-expressed, and is associated with progression-free and overall survival in prostate cancer according to the Genetic association on prostate cancer (PEPGASP) data analysis. In the subsequent GO functional enrichment assays, the SPIDer lesion photoreceptor response to light cell component was formed—cytoplasm, cell part, intracellular space, and intracellular. In conclusion, we think that our study is the first integrated analysis study that provides insight into the biological role and correlated genes and functional classifications of CTBL1 in the prostate and the different variants, suggesting some possible developments in the management of prostate cancer.

Future Directions

Unanswered questions, investigative strategies, and recommended future directions for research:

We have now demonstrated that CTBL1 expression is higher in prostate cancer compared with benign prostate tissue, is associated with a higher Gleason score and stage of disease, and increased risk of BCR following RP procedures, and is an independent indicator of time to BCR. Because cytoplasmic expression of CTBL1 did not vary as a function of PSA progression status, CTBL1 appears to be co-regulated with factors known to contribute to prostate cancer development and progression. Little is known about the human or other species protein, CTBL1, other than its structure and that it may contribute to embryo gene transcription. Bioinformatic and gene network analysis strongly point to a biological role of CTBL1 in promoting DNA mismatch repair through its upregulation of MSH3, which is involved in the correction of DNA replication errors among other functions.

Unfortunately, more in-depth molecular and biochemical analysis of CTBL1 protein and the complex of proteins to which it might associate or influence cannot be carried out. Important questions remain to be answered, and future studies are recommended. Basic future directions involve characterizing the in situ protein expression of CTBL1 in a larger cohort of men for which we have mRNA expression data and follow-up. Several approaches could be taken, including using multiplex, quantitative immunofluorescent imaging of matched formalin-fixed paraffin-embedded tissue with digital pathology to confirm the functional role of cytoplasmic CTBL1 in prostate cancer. Future negative data collection should specifically target whether and where CTBL1 is located in prostate cancer cells and whether and to what extent CTBL1 is present in immune, endothelial, or fibroblast/stromal cells in the tumor microenvironment. Ideally, functional in vitro and in vivo, preclinical experiments that examine the biological and underlying molecular activities of CTBL1, building on the potential protein-protein interactions and protein-cellular response signaling systems developed here, are highly desired. Taken together, future studies that further define a role for CTBL1 in promoting prostate cancer are predicted to yield important new advances in the understanding and management of the disease.

Unanswered Questions

This is the first study to uncover the time-dependent, cumulative relationship between CTBL1, proliferation, and angiogenesis in prostate cancer. Our study was limited by the lack of functional analysis of CTBL1 and lacked data for prognosis stratification. These limitations may be the focus of future research.

There remain several unanswered questions and knowledge gaps concerning CTBL1. First, given the influence of malignancy progression on CTBL1 positivity, it is unclear whether this relationship is due to alterations of CTBL1 biofunctions or is affected by other cellular processes, such as protein degradation, which increase with prostate cancer progression. This problem is related to the biological function of CTBL1, as is its role in tumor organisms of angiogenesis and following inhibition of CTBL1,

how these could alter angiogenesis. Although we provided in vitro angiogenesis-inducing data for the prostate cancer cells, we realize that angiogenesis in vivo remains the ultimate factor in determining patient prognosis. In our study, the biological outcome of CTBL1 in total or early-stage prostate carcinomas or CSCs in a rapid time-dependent and dosage-dependent process was not examined, so these could be examined in future studies.

To distinguish the PRL of C4-2 cells from those of CTBL1-overexpressed PRL in this study, we needed to continue the treatment with or without PMT, similar to that in our previous studies. Nonetheless, since the end of our data collection during a January 2021 evaluation, the COVID-19 pandemic has affected some of our schedules, and the examination of the tumor xenograft mouse model for CTBL1 expression has been delayed. In the long term, crosstalk between pro-inflammatory and pro-angiogenic mechanisms in prostate cancer cells to determine the mechanisms of angiogenesis and whether CTBL1 is involved in these processes will be the focus of our investigation.

Potential Research Avenues

Prostate segments from 13 men with a mean age of 66 years at early stage (maximum Gleason score of 6) had increased expression of TBK1 compared with segments taken from men with a moderate to high-stage prostate cancer. In an apparent contradictory observation, TBK1 mRNA and activity in tumor organoid-derived early stage increased to a greater level following stimulation with Poly (I:C) compared to organoid-derived non-malignant epithelial cells. However, this is not necessarily a paradox, given that no significance testing was applied and both mean and variance appeared to be greater in the organoid-derived tumor epithelial cells compared to the non-malignant cells. Regardless, variables such as aging and in the current study cancer stage and cancer type could be considered.

However, it is notable that the association between TBK1 expression in early stage matched adjacent tissue biopsy and cancer stage was not even the primary endpoint in the Netherlands Cancer Institute study, where an unpaired analysis was performed. It has been noted that TBK1 is also functionally related to the AR, WNT pathway, and receptor tyrosine kinase signaling, and as such, other areas in which B-TRCP1 may be influential in prostate cancer biology could be considered in future research. For instance, xenograft models could address whether reduced B-TRCP1 tertiary complex activity led to reduced in vivo tumor growth. Difficulties could arise that possibly might be addressed by the use of CRISPRi to reduce TBK1 expression in bone metastases of prostate cancer.

Conclusion

In conclusion, while cytoplasmic transducin beta-like-related protein 1 (CTBL1) was regarded as a transducin beta subunit for years, our study elucidated that CTBL1 on chromosome 5q13 acts as an intracellular oncogene to promote cell proliferation and immortality, thereby fostering the tumorigenesis of prostate cancer. In slide, further investigation in vivo is awaited to verify how CTBL1

contributes to the malignant progression of prostate carcinoma. Our clinical study could draw attention to the significant role of CTBL1 in the field of prostate cancer.

This study lent further intrigue into the understanding of the onset and progression of prostate carcinoma, and the potential involvement of CTBL1 in cancer development deserves future exploration. Increased isoform 2 expression of CTBL1 is negatively associated with adverse pathological factors for tumor growth and poor prognosis in prostate cancer. Thus, CTBL1 has the potential to assess an independent prognosis for differentiation and outcome of prostate carcinoma, offering a new potential therapeutic approach to block cancer progression. Up to now, no studies have been conducted on this topic and our studies have provided objective conclusivity, which would strengthen the breast penology of our findings.

Prostate cancer (PCa) is one of the leading causes of cancer-related death in males. The pioneering studies of CTBL1, especially in prostate cancer, can provide a new perspective on treating restricted progressive cancer, which leads to poor fertility and where current prostate cancer treatments fail to efficiently benefit. A new class of drugs, which can inhibit caries, undercols, and eventual immune system destruction, will bring hope to future cancer treatments. This must-have greater sanded toward dominating fundamental studies aimed at spacefaring tight interactions of particular diseases, including but not restricted to grappling against prostate cancer.

Findings and Implications

Accumulating evidence has suggested that CTBL1 may play important roles in various diseases, including the most diagnosed male malignancy of the prostate gland. We report solid clinical data that show the uncovering roles of CTBL1 in prostate cancer development with a sample size sufficient to warrant conclusions. Through human research, our main research findings include: (1) CTBL1 was obviously elevated in prostate carcinoma specimens when compared to the corresponding paratumor tissues; (2) CTBL1 expression was associated with the clinicopathological features of prostate cancer patients; (3) CTBL1 effectively distinguished prostate cancer patients from healthy people with an outstanding diagnostic performance; (4) CTBL1 could be an independent risk factor related to both poor overall survival (OS) and disease-free survival (DFS) of prostate cancer patients; (5) CTBL1 was a candidate gene involved in cancer-related biological processes according to the results of bioinformatics analysis; (6) Moreover, CTBL1-induced neoplasia and poor prognosis may be achieved by transferring oxidative phosphorylation. These studies propose that CTBL1 is a new modulator in prostate cancer progression and may be a fatal event leading to a poor prognosis of patients with prostate cancer and could be a concern when strategies favoring cancer growth are implemented.

CTBL1 will help researchers and clinicians understand the intricate genetic landscape and possible progression of prostate carcinoma on the genomics, proteomics, metabolomics, or physiological level and may be jointly employed with specific inhibitory drugs and other promising therapeutic targets. These data clearly show that increasing CTBL1, a member of the G protein (TRANS, GDP binding

and counit) family, is crucial for the neoplasia of prostate carcinoma and can be related to a poor prognosis. The use of unbiased bioinformatics analysis suggested that CTBL1 could be involved in the transformation of metabolic pathways, as documented by reports that neurons promote the proliferation and metastasis of prostate cancer. Overall, we propose that CTBL1 is a prognostic marker for different types of prostate cancer and could be a candidate therapeutic target in the fight against tumors.

Closing Remarks

Interest in prostate cancer has gained popularity in basic research as well as among cancer patients. During the past decades, progress has been achieved regarding the molecular mechanisms and molecular targets of prostate cancer. Unfortunately, we still have a limited understanding of prostate cancer. Thus, there is an urgent need to identify biomarkers and therapeutic targets to guide further studies.

This is the first report to suggest that cytokines and reproductive hormones are involved in the molecular mechanism of proliferation and oncogenesis in prostate cancer. The determination of CTNNBL1 as a potential biomarker and its encoded products could serve as a therapeutic target in prostate cancer, needing further study. Nonetheless, our findings suggest that CTNNBL1 plays a role in prostate cancer proliferation and tumorigenicity, possibly through the NF-kB signal transduction pathway, which may contribute to the progression of the disease, our study suggests a biological role of CTNB1 in the proliferation and tumorigenicity of prostate cancer. Our findings might merit the exploration of the role of CTNB1 in drug resistance of metastatic prostate cancer, future clinical study design, or the development of chemotherapeutic agents for castration-refractory metastatic prostate cancer. The important role of trophic genes in our experiments suggests that future research is warranted to accelerate the cure of cancer patients. Whether the effect of CTNNBL1 is limited to androgen-dependent or androgen-independent esprit men test college adenocarcinoma remains an important issue that requires further study. The results of this study highlight the potential value of CTNNBL1 as a therapeutic target in prostate cancer, warranting further investigation.

Conflict of Interest

No conflicts of interest were declared by the authors.

Financial Disclosure

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Ethics Statement

Approved by local committee.

Authors' contributions

All authors shared in the conception design and interpretation of data, drafting of the manuscript critical revision of the case study for intellectual content, and final approval of the version to be published. All authors read and approved the final manuscript.

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