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WT1 and Prostate Cancer

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ABSTRACT

WT1 plays a critical role in biological functions including cell growth, differentiation, survival and apoptosis. WT1 possesses functional complexity due to the presence of numerous isoforms which play diverse functions in the cells. Moreover, the activity of WT1 is largely dependent on specific WT1 interactive proteins such as p53 and Par4. Therefore, the role of WT1 was shown to be cellular context specific. The established cellular functions of WT1 are mediated by transcriptional regulator as a transcription factor and post-transcriptional control through protein-protein interaction. WT1 alterations were found in certain developmental disorders and several human cancers. The role of WT1 in prostate cancer is implicated due to the potential role of WT1 in regulation of critical genes involved in tumor development and progression including growth factors and growth factor receptors. Moreover, WT1 has been shown to be able to transcriptional regulate E-cadherin and VEGF, the proteins critically involved in cancer progression and metastasis. These data support the role of WT1 in prostate carcinogenesis and the analysis of WT1 alteration in clinical samples is warranted. The information obtained from clinical study would be the foundation for the development of molecular-based therapy, new diagnostic and prognostic indicator for prostate cancer.

Keyword: WT1; Prostate Cancer

Abbreviations: AR: Androgen Receptor; IGF-R1: Insulin-Like Growth Factor Receptor1; EGFR: Epidermal Growth Factor; IGFII: Insulin-Like Growth Factor2; EGF: Epidermal Growth Factor; TGF: Transforming Growth Factor-Beta; FGF: Fibroblast Growth Factor; EMT: Epithelial to Mesenchymal Transition

Introduction

Prostate cancer is the second commonly diagnosed malignancy in men worldwide and the fifth leading cause of cancer death among men worldwide [1]. The incidence of prostate cancer greatly varies up 25 folds between races and geographic populations [2]. However, the mortality rate varies about 10-fold across the countries [3]. The incidence of prostate cancer has increased due to sensitive screening procedures. Current estimates suggest that as many as 40% of American men over the age of 50 years have histologically detectable prostate cancer. However, only 8% of these prostate cancer patients will develop clinically significant tumors. Unfortunately, about 10% of newly diagnosed prostate cancer patients already have metastatic lesions. Once metastases develop, the median survival of these patients is limited to 6-12 months [4]. Although prostate cancer is initially hormonally responsive, the subsequent development of hormone refractory phenotype in the majority of prostate cancer patients will limit the efficacy of this therapeutic measure. As prostate cancer becomes the major health problem worldwide, research work that can provide a better insight into the prostate carcinogenesis will be urgently required for the development of better tumor marker and prognostic indicators as well as the more effective treatment of patients.

Molecular Alterations in Prostate Cancer

Analysis of molecular characteristics of prostate cancer showed that several gene mutations are required for cancer development and progression. This process involves oncogenic activation and tumor suppressor genes inactivation. The common molecular changes include *p53* mutation [5-8] *Bcl2* overexpression [9-11], Androgen Receptor (AR) alteration [12-14], c-*Myc* amplification [15-17], *MMCAI/PTEN* down regulation [18,19] and loss of heterozygosity at specific loci. As the growth-signaling pathway has been shown to be critical in malignant transformation, characterization of the deregulation of this

pathway has been intensively investigated. Among the major growth factors and growth factor receptors involved in prostate cancer development are IGF-R1 (insulin-like growth factor receptor 1), EGFR (epidermal growth factor), IGFII (insulin-like growth factor 2), EGF (epidermal growth factor), TGF β (transforming growth factor-beta) and FGF (fibroblast growth factor) [20,21]. Self-sufficient growth signaling pathway initiated by autocrine loop has been implicated in the prostate cancer tumorigenesis as well as the androgen-independent phenotype. The salient example of this phenomenon is the binding of TGF β to EGFR as an autocrine fashion [22]. Moreover, the change from androgen dependent to androgen independent phenotype has been shown to be related to the activation of growth factor signaling pathway as an alternative mechanism. This scenario is supported by the finding that the crosstalk between both pathways was demonstrated [23-28]. Further studies to dissect molecular mechanism underling the castration-resistant phenotype are ongoing.

Biological Function of WT1

WT1 (Wilms' tumor 1) was originally identified as a tumor suppressor gene, which played a causative role for a subset of Wilms tumors. Expression of the wild type WT1 gene is necessary for normal urogenital development [29,30]. The surway of WT1 expression and mutation in various human cancers showed frequent WT1 alterations in Wilms tumor [31], mesotheliomas [32], leukemias [33,34] and breast cancer [35]. Moreover, overexpression of WT1 was shown to be the indicator of aggressive clinical course in acute leukemia [36]. The Wilms' tumor 1 gene (WT1) is located on chromosome 11p13. It spans about 50 kb, contains 10 exons, and transcribes a 3.1 kb mRNA [37,38]. WT1 protein is a transcription factor whose C terminal domain consists of four (Cys)2-(His)2 zinc fingers [39,40]. The N-terminus of WT1 consists of two major functional domains: repression domain (residual 85-124) and activation domain (residual 181-250). WT1 can form homodimer, in which the first 182 residues are responsible for this interaction [41,42]. There are at least 24 isoforms of WT1 that have been detected, developed by alternative splicing, alternative translational start sites and RNA editing [43-46]. Moreover, a novel WT1 transcript was detected in an experimental model of human prostate cancer progression [47]. The truncated WT1 transcript is about 2.1 kb in size. This transcript consists of the coding region of WT1 encompassing exon 6-10 of WT1, combined with a portion of intron 5 at its 5' end. Subsequently, another novel truncated called Ex4a (+) WT1 isoform was detected in myeloid leukemia cells and certain solid cancer cells [48].

The overexpression of Ex4a (+) WT1 suppressed transcription of Bcl-xl gene and resulting mitochondrial damage and apoptosis. This truncated isoform likely interacted with major WT1 alternatively spliced isoforms and modulated the functions of these wild type WT1 proteins [48]. Several target genes for WT1 have been increasingly discovered and modulation of the WT1 target gene expression by WT1 is likely underlying mechanism for WT1-mediated biological functions including cellular proliferation, differentiation, survival and apoptosis. Among these, the growth factor (IGF-II) and growth factor receptor genes (IGF-1R and EGFR) have been shown to be the physiologically relevant targets of WT1. The biological functions of WT1 were shown to be modified by the mutational status of binding partners including p53 [49] and PAR-4 [50]. Recently, WT1 was shown to play a role in gene expression modulation at epigenetic level. The molecular pathway underlying this function has been elucidated. Modification of histone protein and chromatin modifying enzymes by WT1 was demonstrated as WT1 was able to recruit DNA methyltransferase, DNMT1 and polycomb group protein protein enhancer of zesta homolog 2 (EZH2) and CREB-binding protein (CBP) a histone acetyltransferase [51]. These data indicate the diversity of WT1 functions that enhance the understanding of complex WT1-mediated carcinogenesis pathway.

Role of WT1 in Human Cancer

The survey of WT1 gene expression in human cancer specimens further supports the contribution of WT1 in human malignancies. Whereas WT1 mutations were detected in a small subset of human malignancies, aberrant expression of WT1 has been detected in the majority of several types of tumors. In Wilms tumors, overexpression of WT1 was detected in a large proportion of the tumors. WT1 overexpression was detected in 75% of ovarian tumors [52] and about 80% of acute leukemias [53,54]. In contrast, WT1 expression was undetectable in normal peripheral blood and bone marrow cells. The prognostic value WT1 expression in acute leukemias was clearly shown, in that lower WT1 expression was correlated with a favorable clinical course [53]. WT1 overexpression was also shown in breast cancer [55,56]. By RT-PCR, WT1 mRNA was detected in most breast malignant samples but not in benign counterparts. On the other hand, downregulation of WT1 has been shown by immunohistochemical technique in in situ cancers of both ductal and lobular carcinoma types [56]. This pattern of expression is maintained during tumor progression. However, WT1 was more frequently detected in the ER-positive cancers as compared with ER-negative cancers.

Role of WT1 in Prostate Cancer

The role of WT1 in carcinogenesis of prostate cancer was supported by both *In vitro* and *In vivo* data. WT1 has been shown to be a key transcriptional regulator of several genes involved in prostate tumorigenesis, especially the genes encoding growth factors and growth factor receptors such as IGF1-R, EGFR, IGFII. By using *in vitro* cell culture model to measure the level of WT1 expression, WT1 mRNA was detected at a high level in some human prostate cancer cell lines [57-61]. Moreover, the results of functional *in vitro* studies also supported the role of WT1 in prostate carcinogenesis. WT1 has been shown to repress IGF1-R promoter activity in the P69SV40TAg human prostate epithelial cell line [62]. Another study showed that WT1 can repress AR promoter activity in transient transfection assays [63]. Moreover, WT1 expression level was shown to be higher in androgen-insensitive

cell lines (PC3 and DU145) when compared with androgen-sensitive cell lines (LNCaP and MDAPCa2b). The inverse correlation between WT1 and AR expression suggested that WT1 likely contributed to the development of castration-resistant phenotype. The study for WT1 expression in clinical prostate cancer specimen showed intriguing results. By using RNA microarray and validated quantitative RT-PCR on tumor cells obtained by laser captured microdissection tissue to separately detection of WT1 in epithelial and stromal cell components, higher level of WT1 expression at mRNA level in cancer epithelial cells was demonstrated [59].

The confirmation study in frozen cancer tissue and tissue microarray also provided a similar differential expression profile [59]. This data indicated that WT1 expression in prostate cancer cells contributes to the metastatic characteristic in this cancer. To address the role of WT1 in providing the more aggressive and metastatic property of prostate cancer, studies to test this hypothesis were reported. By using TMA WT1 gene expression analysis on tissue samples, WT1 protein was shown to be higher in high Gleason grade as compared with low Gleason grade tumors [59]. Moreover, no WT1 is detected in non-tumor tissue. The microarray study for WT1 expression in a hormone refractory LuCaP xenograft prostate cancer model also showed higher level of WT1 in cancer cells. The study for WT1 expression by quantitative RT-PCR on 40 paired tumor and adjacent non-tumor cells of biopsied tissue showed that WT1 mRNA levels were higher in invasive stage T3 tumors when compared to adjacent benign tissue. Moreover, the study for WT1 detection by immunohistochemical study on formalin-fixed, paraffin embedded TMAs, showed that WT1 was detected in 65% of tumor samples whereas no WT1 detectable in non-cancerous tissue including benign prostatic hyperplasia tissue. As WT1 was likely expressed in high-grade prostate cancer, the possible mechanism underlying the involvement of WT1 in metastatic process was elucidated. WT1 was shown to play a critical role in epithelial to mesenchymal transition (EMT) of epicardial cells of the heart [64].

This process was likely involved in the modulation of E-cadherin by WT1. According to this scenario, the possible role of WT1 in promoting the epithelial to mesenchymal transition that occurs during prostate cancer metastasis was tested. Additionally, the role of WT1 in modulation of important angiogenic regulatory gene (VEGF) was also investigated. By using the *In vitro* cell culture model (NIH-3T3), WT1 was shown to be the transcriptional regulator of E-cadherin gene [65]. Moreover, experimentally induced overexpression of WT1 gene in Prostate cancer cell line (LNCaP) induced downregulation of E-cadherin and promoted migration ability of the cancer cells [66]. According to this WT1 function, the role of WT1 in driving the epithelial to mesenchymal transition during prostate cancer progression is strongly supported. According to study in cardiac model, WT1 was shown to be able to transcriptionally repress E-cadherin expression [64]. Upregulation of Snail by WT1 also involved in this process [64]. WT1-induced E-cadherin expression was also demonstrated in non-small cell carcinoma model [67] In the context of prostate cancer, the inverse relationship between WT1 and E-cadherin expression was shown in some prostate cancer cell lines and WT1 expression was associated with tumor cell motility [58]. In functional study, forced WT1 expression in LVCaP cells resulted in 2-folded downregulation of E-cadherin mRNA along with increased migration property [58].

Moreover, silencing of WT1 gene in PC, a metastatic cell line resulted in decreased cell motility. Subsequently, would healing assay of PC3 also showed a similar result [58]. According to this evidence, WT1 is likely involved in epithelial to mesenchymal transition (EMT) via the modulation of E-cadherin expression in prostate cancer. WT1 was shown to play critical role in neovascularization during ischemia of cardiac muscles likely via upregulation of VEGF gene expression in vascular cells [68,69]. Moreover, co expression of WT1 and VEGF was demonstrated in both podocytes and some Wilms tumor cells [70-72]. Additionally, WT1 gene silencing in Ewing sarcoma cells led to downregulation of VEGF. As expected, WT1 induced expression in this cell resulted in upregulation of VEGF. According to this finding, the role WT1 as a transcriptional regulator of VEGF in this cell is strongly supported. To further elucidate the role of WT1 in VEGF regulation in prostate cancer cells, research works to address this issue were pursued. The functional study by reporter assay, WT1 was shown to upregulate VEGF promoter activity in LNCaP cell [73]. Moreover, the electrophoretic mobility shift assay and chromatin immunoprecipitation also support the binding of WT1 to the VEGF promoter region in prostate cancer cells [74]. The site directed mutagenesis indicated that the proximal promoter of VEGF is the binding site for WT1 [75]. The additional study in hormone responsive prostate cancer cell lines, C4-2 and CWR22Rv1 also showed a similar result.

Further functional study to induce expression in LNCaP cells showed that WT1 was able to upregulate VEGF expression. However, the silencing of WT in this cell line did not significantly downregulate the VEGF expression. This finding implied that WT1 is sufficient for transcriptional activate the VEGF but is not necessary. The other transcription factor like SP1 may contribute to modulate VEGF promoter activity. In contrast, WT1 was not able to activate the VEGF promoter activity in PC3, a hormone-insensitive cell line and WT1 was shown to repress VEGF promoter activity in embryonic kidney cells, HEK293 [73]. AR was shown to be a potential transcriptional regulator of VEGF in hormone-responsive prostate cancer cells. However, the mechanism of regulation was not fully elucidated. Site-directed mutagenesis of three AR half-sites did not abrogate the activation of VEGF promoter by hormone activation of VEGF promoter [76]. This finding led to the assumption that AR-WT1 interaction can activate the VEGF promoter activity via binding to other sites on the promoter region. Intriguingly, non-classical AR half-sites were detected adjacent to WT1/EGR1/Sp1 sites in VEGF promoter [77]. Based on the data aforementioned, the multiple pathways for activation of the AR responsive VEGF promoter were postulated besides the classical pathway. One possibility is that AR dimers bind to the half-site ARE

and bridge to WT1 binding site. Another model proposed that AR is tethered via WT1 or other ZFTF and then bind to the G-rich VEGF promoter.

The function study using reporter assay showed that VEGF promoter was activated by hormone treatment at the similar level to induced WT1 expression (3- to 4-fold increased promoter activity). However, in the presence of both factors, the activity of the VEGF promoter was more than 12-fold upregulation. This finding supported the hypothesis that WT1-AR complex bind to G-rich and AR half site on the VEGF promoter and resulted in strong enhancement of VEGF promoter activity.

Conclusion

The role of WT1 in prostate cancer is strongly supported by evidence in literature. The WT1-mediated carcinogenesis process is attributable to complex molecular mechanisms including genetic and epigenetic gene regulatory function of WT1. WT1 was shown to be transcriptional regulator of key growth factors and growth factor receptors critically involved in prostate cancer proliferation, differentiation, survival and apoptosis. Moreover, WT1 was shown to be able to transcriptionally regulate E-cadherin and VEGF, the key proteins involved in cancer progression and metastasis. These data support the role of WT1 in prostate cancer and the analysis of WT1 alteration in clinical samples would verify the potential application of this knowledge for management of the patients.

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