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ORIGINAL ARTICLE

C-MYC, *HIF-1α*, *ERG*, *TKT*, and *GSTP1*: an Axis in Prostate Cancer?

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Abstract

To analyze putative biomarkers for prostate cancer (PCA) characterization, the second leading cause of cancer-associated mortality in men. Quantification of the expression level of *c-myc* and *HIF-1α* was performed in 72 prostate cancer specimens. A cohort of 497 prostate cancer patients from The Cancer Genome Atlas (TCGA) database was further analyzed, in order to test our hypothesis. We found that high *c-myc* level was significantly associated with *HIF-1α* elevated expression ($p = 0.008$) in our 72 samples. Statistical analysis of 497 TCGA prostate cancer specimens confirmed the strong association ($p = 0.0005$) of *c-myc* and *HIF-1α* expression levels, as we found in our series. Moreover, we found high *c-myc* levels significantly associated with low Glutatione S-transferase P1 (GSTP1) expression ($p = 0.01$), with high Transketolase (TKT) expression ($p < 0.0001$). High TKT levels were found in TCGA samples with low GSTP1 mRNA ($p < 0.0001$), as shown for *c-myc*, and with ERG increased expression ($p = 0.02$). Finally, samples with low *GSTP1* expression displayed higher *ERG* mRNA levels than samples with high *GSTP1* score ($p < 0.0001$), as above shown for *c-myc*. Our study emphasizes the notion of a potential value of *HIF-1α* and *c-myc* as putative biomarkers in prostate cancer; moreover TCGA data analysis showed a putative crosstalk between c-myc, HIF-1α, ERG, TKT, and GSTP1, suggesting a potential use of this axis in prostate cancer.

Keywords Prostate cancer · *C-myc* · *HIF-1α* · *GSTP1, TKT, ERG*

Introduction

Prostate cancer (PCA) is the second leading cause of cancer-associated mortality in men. One of the greatest challenges in the management of prostate cancer patients is identifying biomarkers to predict clinical outcome. Gleason score, tumor stage, margin status and PSA levels represent classical prognostic factors, but they are insufficient for discriminating between patients with indolent tumors that are unlikely to progress and may be potentially over-treated and patients with aggressive, fatal disease.

The activation of the proto-oncogene *myc* is one of the earliest molecular alterations in prostate cancer [1], and it may be considered an important biomarker in the early detection and diagnosis of this disease. Myc protein expression has been described as detected by immunohistochemistry [2], as well as upregulation of *myc* at the mRNA level [3], but the mechanism responsible in prostate cancer remains unclear. Myc is able to directly and indirectly regulate the transcription of several genes and pathways.

HIF-1α overexpression has been associated with shorter time to biochemical recurrence, metastasis, and chemoresistance in prostate cancer patients [4–6]. Considering the role of HIF-1α in the activation of several cancer-related pathways, it should be an attractive target for cancer therapy [7], and a better knowledge of HIF-1α regulation in prostate cancer could provide better outcomes and therapeuthic chances for men with prostate cancer.

The occurence of prostate cancer has been associated with environmental factors, such as Glutathione S-transferase P1 (GSTP1), an enzyme of the glutathione S-transferases (GSTs) family modulating signaling pathways involved in cell

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proliferation, differentiation, and apoptosis. GSTP1 overexpression has been suggested to play a protective role in prostate cancer in vitro and in vivo through targeting c-myc [8].

Transketolase (TKT) is considered involved in so-called tumor metabolic reprogramming, and TKT activity is increased in rapidly growing breast cancer cells [9], but its role in prostate cancer and the putative crosstalk with c-myc has not yet been analysed.

In the last decade, the discovery of oncoproteins and gene rearrangements/fusion genes associated to the progression of prostate cancer has brought a great progress in identifying new modalities of treatment. One of the most common rearrangements in prostate cancer is the TMPRSS2-ERG fusion. *ERG* has been reported as an early event in prostate carcinogenesis, but its role in prostate cancer progression is still controversy [10–18].

From the perspective above, the aim of this study was to examine simultaneously expression of *c-myc* and *HIF-1α* in our 72 prostate cancer specimens, adding TCGA data concerning also other gene analysis (*GSTP1, TKT,* and *ERG*) in order to understand their potential use of this axis as biomarker in prostate cancer.

Materials and Methods

Patients

A total of 72 prostate cancer patients who underwent surgical resection in Division of Urology, Department of Translational Research, at Pisa University between 2010 and 2015 were retrospectively selected. Histological diagnoses were independently formulated by PF, according to the World Health Organization classification. Clinic-pathological characteristics were collected whenever available for all the patients. Our study was conducted in accordance with the ethical standards of our institutional research committee and with the 1964 Helsinki declaration; all the patients gave their informed consent to the molecular analyses.

The Cancer Genome Atlas (TCGA) Database From the TCGA data portal (http://tcga.cancer.gov/; accessed December 2017), we extracted *c-myc; HIF-1α; GSTP1, TKT,* and *ERG* expression together with the corresponding clinical-pathological characteristics and survival data for 497 prostate cancer patients.

RNA Isolation

Total RNA were isolated from a representative area selected and marked on the surface of 5 μm sections of formalin-fixed, paraffin-embedded (FFPE) tissues using the miRNeasy FFPE Kit (Qiagen Inc., Hilden, Germany) according to the manufacturer's instructions. The quality and concentration of RNA was assessed using a NanoDrop spectrophotometer (Thermo-Scientific, Wilmington, Del).

c-myc and *HIF-1α* mRNA Expression

A total of 600 ng of total RNA was used to synthesize cDNA using the RevertAid First Strand cDNA Synthesis Kit (Thermo Scientific, Waltham, MA, USA) in a reaction volume of 20 μl. Simultaneous quantification of the expression level of *c-myc* and *HIF-1α* with real-time PCR technology (qPCR) was performed in 72 prostate cancer specimens. Quantification was carried out in triplicate using the Rotor Gene Sybr Green PCR Kit (Qiagen) on a Rotor Gene 6000 (Qiagen) instrument. The following primers were used for qPCR: for *c-myc*, forward primer: 5′-CCTCAACGTTAGCT TCACCAAC-3′ and reverse primer: 5′-CTGC TGGTAGAAGTTCTCCTC-3′); for *HIF-1α*, forward primer: 5′-TTTAGGCCGCTCAATTTATGA-3′ and reverse primer: 5′-TCCTGTGGTGACTTGTCCTT-3′); and for *beta-Actin,* forward primer: 5′-CCAACCGCGAGAAGATGA-3′ and reverse primer: 5′-CCAGAGGCGTACAGGGATAG-3′. The threshold cycle (Ct) and baselines were determined by the manual settings. Expression was calculated by relative quantification using *beta-Actin* as reference control for *c-myc* and *HIF-1α*. Fold expression changes were determined by the $2^{-\Delta\Delta Ct}$ method, using a pool of 12 non-cancerous tissues as a calibrator group; the analysis was performed by the DataAssist™ software (Applied Biosystems, Foster City, California, USA).

Statistical Analysis

Differential expression was determined by applying the non-parametric Wilcoxon test in order to determine the association between mRNAs expression and the clinic-pathological parameters. Survival analyses were performed using the Kaplan-Meier method with log-rank test and the Cox proportional hazard model. Statistical analyses were performed using JMP10 software (SAS, Milan, Italy), and a two-tailed p value <0.05 was considered significant.

Results

Patient Characteristics

This study was conducted in 72 patients with prostate cancer, with a median age at diagnosis of 67 years (range: 51–78, mean: 66.4 years). Most of the tumors were pT2c (48 cases), 12 tumors were pT3a, 3 cases were pT2b, and there were 4 cases for pT2a and 5 for pT3b. Regarding the Gleason score there was only 1 case with score 9, there were 8 cases with score 8 (4 + 4 in 7

cases, and 5 + 3 in 1 case), 36 tumors with Gleason score 7 (3 + 4 in 28 cases, and 4 + 3 in 8 cases), and 27 cases with score 6.

c-myc and *HIF-1α* mRNA Expression in our Prostate Cancer Samples

We quantified *c-myc* and *HIF-1α* mRNA expression, normalized to the *β-actin* housekeeping gene, using real-time qPCR. The samples were divided into high and low expression groups based on the median fold-change value (265.87 for *c-myc* and 2.24 for *HIF-1α*). *C-myc* mRNA expression was low in 36/72 (50%) cases, as well as *HIF-1α* in 36/72 (50%) cases. We determined whether *c-myc* and *HIF-1α* expression were correlated with the main clinic-pathological characteristics, but no statistically significant associations were observed (Table 1).

Focusing on the relationship between *c-myc* and *HIF-1α* expression, we found that high *c-myc* level was significantly associated with *HIF-1α* elevated expression (chi-square test, $p = 0.0008$). Figure 1 showed that samples with a low *HIF-1α* level expression displayed lower *c-myc* mRNA levels (270.17 fold change value ±76.99) than samples with high *HIF-1α* score (650.9 ± 77) (t-test, p = 0.0008).

TCGA Data Analysis

A cohort of 497 prostate cancer patients from TCGA database was further analyzed, in order to validate our findings and to add more data on a larger population. The samples were divided into high and low expression groups based on the median value of *c-myc* and *HIF-1α* in a first step, then of *GSTP1, TKT*, and *ERG* expression.

Statistical analysis of 497 TCGA prostate cancer specimens confirmed the strong association (chi square test, $p = 0.0005$) of *c-myc* and *HIF-1α* expression levels, as we found in our series.

To find the potential link between *c-myc* and others prostate cancer markers, we analyzed the relationship with *GSTP1, TKT*, and *ERG* expression. As first result, we found that high *c-myc* levels were significantly associated with low GSTP1 expression (chi square test, $p = 0.01$). Figure 2 showed that samples with low *GSTP1* expression displayed higher *c-myc* mRNA levels (28.379.475 mean value ±1.063.536) than samples with high *GSTP1* score (22.089.901 mean value ±1.061.399) (t-test, $p < 0.0001$).

Then, increased *c-myc* expression was found to be associated with high TKT expression (chi square test, $p < 0.0001$); moreover, high TKT levels were found in TCGA samples with low mean of GSTP1 mRNA (chi square test, $p < 0.0001$), as shown for *c-myc*, and with ERG increased expression (chi square test, $p = 0.02$). Finally, samples with low *GSTP1* expression displayed higher *ERG* mRNA levels (35.935.827 mean value ±2.240.848) than samples with high *GSTP1* score (18.811.341 mean value ±2.236.344), as above shown for *c-myc* (t-test, $p < 0.0001$).

Discussion

Prostate cancer is extremely heterogeneous, with a wide range of prognosis, and a consequent difficulty in discriminating between indolent and aggressive tumors. PSA serum level and Gleason grading on histological specimens are currently the classical prognostic factor, but they are often unable to predict a correct disease progression. Advances in molecular technologies analysed multiple pathways involved in prostate cancer, helping to identify new markers and modalities of treatment; however, simultaneous multiple markers analysis rather than the study of a single factor may have high robustness and the discovery of an hypothetic targetable axis may be of great use in clinical practice of prostate cancer.

Table 1 Correlations between *c-myc* and *HIF-1α* expression level and the main clinicopathological characteristics of our 72 prostate cancer patients

Characteristic	*c-myc* expression[a]		p-value[b]	*HIF-1α* expression[a]		p-value[b]
	Low	High		Low	High	
Age						
≤67 years	17	24	0.09	21	20	0.81
>67 years	19	12		15	16	
TNM						
T2 (T2a-T2b-T2c)	27	28	0.78	28	27	0.78
T3 (T3a-T3b)	9	8		8	9	
Gleason score						
6	16	11	0.47	14	13	0.92
7 (3 + 4–4 + 3)	16	20		18	18	
8,9 (4 + 4–5 + 3, 4 + 5)	4	5		4	5	

[a] Values are shown as n

[b] p-values are assessed by χ^2 test

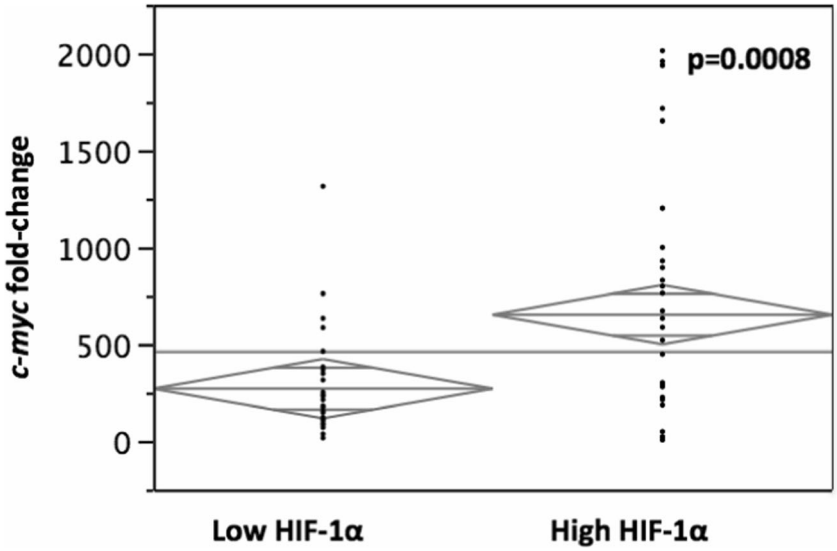

Fig. 1 Relationship between *c-myc* and *HIF-1α* mRNA expression (t-test, $p = 0.0008$)

Myc was one of the top genes overexpressed in human prostate cancer tissues [19–26], and the activation of this proto-oncogene seems to be one of the earliest somatic molecular alterations in prostate cancer [1]. However, several data in literature showed that c-myc is essential not only for tumor initiation but also for progression and tumor maintenance [27–33].

Even if c-myc expression is alterated in ~70% of human tumors, the mechanism responsible for it is still largely unclear in each cancer type [34], as well as the c-myc target genes in prostate tumors are also unknown. In this work we focused on several genes in order to have a better identification of c-myc target genes and a comprehensive knowledge of the c-myc-related tumorigenesis for the development of new therapeutic strategies.

Overexpression of c-myc enhances and synergizes with HIF-1 α stabilization and accumulation in hypoxic microenvironment in order to promote cell proliferation [35]. Hypoxia and the adaptive changes low oxygen-induced have been involved in genetic instability [36, 37] and increase of mutations frequency [38].

The present study started with the investigation of *c-myc* and *HIF-1α* expression level in our 72 prostate cancer samples, confirming their strong associations in oncogenic conditions. Moreover, further analysis on a cohort of 497 prostate cancer patients from the TCGA database confirmed our findings on a larger population and also using a different transcriptome-based technology, such as Illumina HiSeq quantification.

Myc is known to directly and indirectly regulate the transcription of numerous genes and pathways; *GSTP1, TKT,* and *ERG* are important players in prostate cancer, but the way of their interactions is not yet clear as well as their relationship with c-myc. Our study suggested the notion of a putative axis, involving *c-myc; HIF-1α; GSTP1, TKT, ERG*, which should represent a target in prostate cancer.

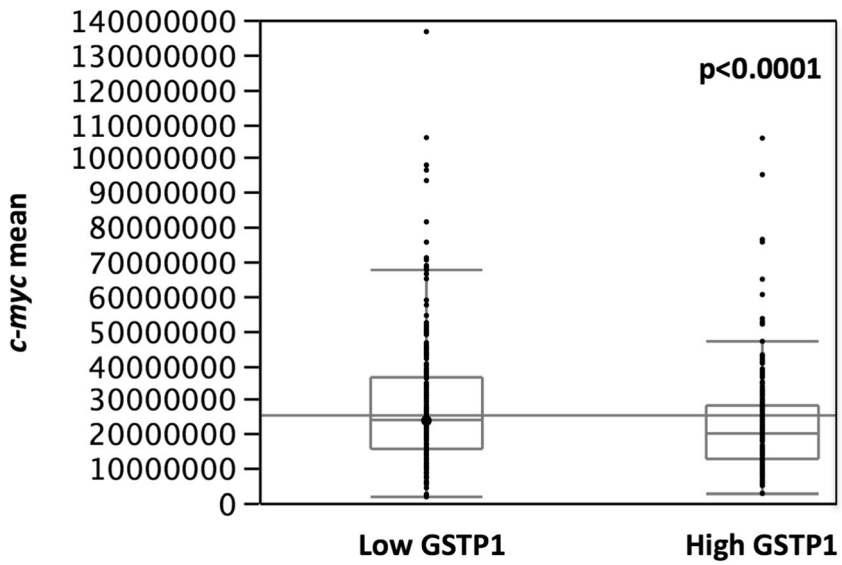

Fig. 2 Relationship between *c-myc* and *GSTP1* mRNA expression (t-test, $p < 0.0001$)

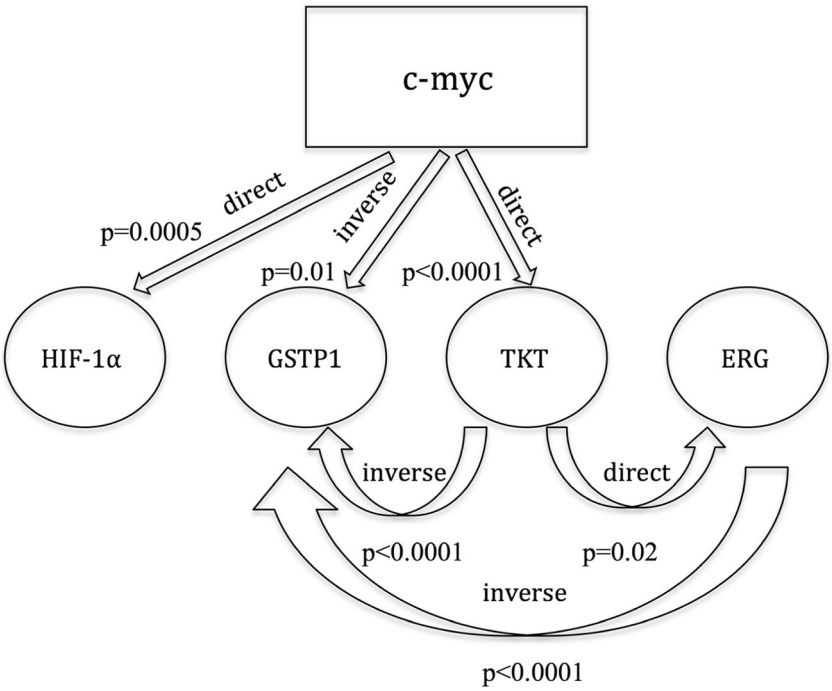

Fig. 3 Balance among dysregulated expression of *c-myc* and other genes, such as *HIF-1α; GSTP1, TKT, ERG*: a potential axis as diagnostic marker and therapeutic target in prostate cancer

GSTP1, an important member of glutathione S-transferase (GST)s family, contributes to the regulation of cell proliferation and so is one of the most largely investigated tissue biomarker in several malignancies, including prostate cancer. The regulation of the GSTP1 expression level may help control the progress of prostate cancer, but it is not yet clear how GSTP1 plays its protective role. Wang et al. [8] recently reported that GSTP1 overexpression inhibits the viability and motility of prostate cancer in vitro and in vivo through targeting myc. TCGA data analysis in this study showed an activation of c-myc associated with GSTP1 downregulation; oncogenic myc deregulation may promote neoplastic transformation by distrupting GSTP1 tumor suppressor gene function.

C-myc is a transcription factor able to regulate several genes [39–41] and its deregulation in cancer commonly involves different signaling pathways [42]. Metabolic reprogramming has recently been recognized as a hallmark of cancer [43], and deregulated in several tumours [44]. Silencing of TKT induced cell cycle arrest as well as overexpression correlated with poor prognosis in breast cancer patients [9], suggesting that TKT could be coordinately modulated as part of a central metabolic reprogramming.

In this view, we focused our attention on TKT in order to investigate for the first time its role to achieve a fully malignant prostate phenotype and the putative regulation by c-myc. Our analysis of TCGA samples showed an association between TKT expression and c-myc, suggesting that myc deregulation in prostate cancer may increase TKT levels while distrupting GSTP1 protective function, as demonstrated by high TKT levels in TCGA samples with low GSTP1 expression.

The *ERG* oncogene is activated in more than 50% of prostate cancer cases, generally through a gene fusion [45], and much attention has been recently focused on it [46, 47]. In the current study we looked into the possibility that ERG could be involved in metabolic reprogramming in prostate cancer along with *GSTP1* downregulation and TKT activation, as suggested by the association we found between low *GSTP1* expression and high *ERG* and *TKT* mRNA levels.

In conclusion, our findings suggested that the dysregulated expression of *c-myc* in prostate cancer could also synergize with other genes, such as *HIF-1α; GSTP1, TKT, ERG* (Fig. 3) and the balance among these factors in turn would induce cellular proliferation and tumorigenesis; the potential of this axis as diagnostic marker and therapeutic target may have a clinical role in the pathogenesis, development and progression of prostate cancer.

Authors' Contributions Boldrini Laura, and Faviana Pinuccia: project development, data analysis and manuscript writing. Giordano Mirella: data collection. Farci Fabiola: other (prostate cancer diagnosis with Faviana Pinuccia supervision). Bartoletti, Manassero and Selli: other (prostate surgery). Panichi Marco and Galli Luca: other (follow-up).

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Research Involving Human Participants For this retrospective study formal consent is not required.

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