The role of PTEN and ERG networks in prostate cancer

Charalampos Fragkoulis¹, Athanasios Papatsoris²

¹General Hospital of Athens, G.N.A “G. Gennimatas”
²Ass. Professor of Urology, University Department of Urology, “Sismanoglio” General Hospital

Abstract

As prostate cancer represents the most common malignancy and one of the leading causes of cancer mortality among elder males in both Europe and the United States there is a wide interest of identifying new molecular pathways and markers which can be used in order to predict prognosis and thus differentiate indolent forms of PCa from aggressive ones. Several molecular pathways and oncogenes have been implicated in PCa development and progression with the PI3-Akt pathway and the ERG oncogene having a prominent role. There is a necessity of describing the exact molecular pathways and their influence in prostate carcinogenesis and their association with lethal prostate cancer, poorly differentiated tumors and higher stage disease.

Key words
prostate cancer; ERG; PTEN; PI3-Akt

Introduction

Prostate cancer represents the most common malignancy and one of the leading causes of cancer mortality among elder males in both Europe and the United States. As a disease, it may present with a variety of clinical behavior, including tumors of very low clinical significance but also highly aggressive tumors with increased risk of relapse after initial treatment. Well established risk factors for developing clinical PCa include increasing age, ethnic origin and heredity although it is highly possible that environmental factors also contribute for developing clinical disease. True hereditary PCa represents about 9% of PCa patients and is defined as three or more affected relatives, or at least two relatives who have developed early onset disease⁴.

Although currently used prognostic factors after include tumor type, PSA levels, tumor grade as defined by Gleason score, positive surgical margins after radical prostatectomy, tumor volume and tumor stage⁴ there is a wide interest of identifying new molecular pathways and markers which can be used in order to predict prognosis and thus differentiate indolent forms of PCa from aggressive ones.

Moreover, nowadays, tumors traditionally treated either by radical pros-
The role of PTEN and ERG networks in prostate cancer, p. 25-30

The role of PTEN and ERG networks in prostate cancer, p. 25-30

The Phosphatase and Tensin Homolog Gene - PTEN
The phosphatase and tensin homolog gene (PTEN) is a tumor suppressor gene located on chromosome 10q23.3 found to be mutated in a large number of cancers at a high frequency including prostate cancer (PCa)

The PI3K-Akt signaling pathway
The PI3K-Akt pathway is an important intracellular molecular pathway with an important role in regulating cell survival, proliferation, growth and apoptosis. It is estimated that the PI3K-Akt pathway is up-regulated in about 30-50% of prostate cancer patients [6]. Various growth factors including epidermal growth factor (EGF), platelet-derived growth factor receptor (PDGF) and insulin-like growth factor (IGF) initiate the PI3K-Akt pathway by activating receptors of tyrosine kinases leading to the phosphorylation of PI3K at the level of the cell membrane. As a result, the phosphorylated PI3K triggers the conversion of PIP2 to PIP3 with subsequently mediates the phosphorylation of Akt through PDK1. IGF signaling cascade is already known to be involved in prostate carcinogenesis. Circulating IGF-1 is associated with prostate cancer risk and it has been suggested that IGF-1 induces ligand-independent activation of the androgen receptor and enhances the expression of matrix metalloproteinase-2 and urokinase plasminogen activator. Furthermore, progression to androgen independence has been linked to deregulation of the IGF-1–IGF-1-receptor axis.

Activated Akt has a profound role in carcinogenesis by promoting cell growth and protein synthesis by regulating the mammalian target of rapamycin (mTOR) pathway. mTOR is a serine/threonine kinase with critical role in the regulation of cell growth, survival and division. Moreover, apart from interaction with the mTOR pathway Akt may also interact directly with the androgen receptor in an androgen independent manner leading to androgen receptor overactivation resulting in the development of castration resistant prostate cancer.

The purpose of this review article is to summarize the role of the deletion of the tumor suppressor gene PTEN and the expression of the oncogene ERG as prognostic markers in prostate cancer patients.

The Phosphatase and Tensin Homolog Gene - PTEN
The phosphatase and tensin homolog gene (PTEN) is a tumor suppressor gene located on chromosome 10q23.3 found to be mutated in a large number of cancers at a high frequency including prostate cancer (PCa). The protein product encoded by PTEN gene is a dual lipid phosphatase that acts as a negative regulator of the PIK3/Akt survival pathway which is found to be up-regulated in 30-50% of prostate cancer patients. More specifically, PTEN encoded protein negatively regulated the intracellular levels of PIP3 by removing the 3-phosphatase from PIP3 converting it back to PIP2. As a result, the phosphorylation of Akt mediated by PIP2 conversion to PIP3 is inhibited and a G1 cell cycle arrest is induced. Apart from interacting with the PIP3-Akt pathway, PTEN also presents PIP3 independent mecha-
The role of PTEN and ERG networks in prostate cancer, p. 25-30

mechanisms of genomic stability regulation with involvement also in the MAPK signaling pathway. Activation of MAPK signaling network is known to affect directly and/or indirectly androgen receptor (AR) activity. This multi-partite network propagates chemical stimuli from the cell surface to the nucleus via sequential kinase signaling and intensive cross-talk. During prostate carcinogenesis, crucial components of this network are deregulated, thus affecting cellular proliferation, apoptosis, and metastasis with various molecules of the MAPK network represent appealing selective targets for prostate cancer therapeutics.

Nowadays, as PCA is the leading cause of cancer mortality among elder males the understanding of PTEN genomic status and alterations and its cooperation with other genetic markers and their clinical significance becomes quite compelling. Immunohistochemical staining of PTEN loss is associated with a 64% risk of definite PCA on subsequent biopsy in patients with borderline lesions in the primary biopsy and may also be utilized in intraductal prostate cancer differential diagnosis from high grade pin13. In addition, in a retrospective analysis of 77 patients treated with radical prostatectomy PTEN loss at the time of the initial biopsy seems to predict time to development of metastasis, prostate cancer-specific mortality and, for the first time, castration-resistant prostate cancer and response to androgen deprivation therapy after radical prostatectomy. Moreover, in a study comparing 451 patients who presented with clinical or biochemical recurrence after radical prostatectomy for clinically localized prostate cancer with a control group of 451 with no recurrence, PTEN loss as a prognostic marker was associated with a higher risk of recurrence. The complete PTEN loss in paraffin embedded PCA specimens in patients with primary PCA was also found to correlate significantly with the presence of high stage disease (T3b-T4) as well as with a Gleason score ≥7. Moreover as far as it concerns oncologic results after radical prostatectomy, in a multicenter study by Troyer et al. published in 2015, PTEN deletion status showed a highly significant correlation with pathologic stage (19% homozygous deletion for stage pT3/pT4 tumors versus 6% for stage pT1/pT2). This effect was less pronounced for the hemizygous deletions with 12% (17/146) stage pT3/pT4 tumors showing deletions and 8% (26/331) of stage pT1/pT2. The presence of PTEN deletion was also correlated strongly with seminal vesicle invasion, extracapsular extension and higher Gleason scores.

In a study by Cuzick et al., the prognostic value of PTEN loss was evaluated in a cohort of 675 men with conservatively managed prostate cancer diagnosed by transurethral resection of the prostate with primary endpoint being death from PCa. An overall PTEN loss as evaluated by immunohistochemical staining was present in 18% of patients. In a univariate analysis it was significantly associated with prostate cancer death and was found to be highly predictive in the group of patients characterized as low risk in terms of Gleason score and PSA but had no prognostic value in higher risk patients. In a study by Zu et al. involving 805 patients diagnosed with PCA and underwent radical prostatectomy, PTEN expression was assessed along with its interaction with IGF1R and their relation with lethal prostate cancer. Low PTEN expression was associated with an increase risk of lethal prostate cancer and a significant negative interaction between PTEN and IGF1R was found.

As patients with PCA characterized as clinical insignificant represent an over-treated population, the role of PTEN in the separation of insignificant from significant PCA was examined in a recent study published in 2016 involving 48 patients with clinically insignificant disease and 76 with significant all treated by radical prostatectomy. As a result, PTEN loss was present in only 2% of clinically insignificant PCA patients and on the contrary it was present in 13% of large volume Gleason score 6 patients and in 46% of Gleason score 7 or higher patients. In terms of castration resistant prostate cancer, the role of PTEN is also quite important as alteration in the PTEN/PI3K pathway are nowadays associated with late stage and castrate resistant prostate cancer (CRPC). PTEN loss suppresses androgen-responsive gene expressions by modulating androgen receptor transcription factor activity. These data support the hypothesis that PI3K-Akt pathway and androgen receptor cross-talk form a possible mechanism of CRPC development, with potentially important implications such patients’ treatment. As both clinical and preclinical evidence suggests that activation of PI3K/AKT signaling through loss of PTEN can result in resistance to hormonal treatment in prostate cancer, the antitumor activity of abin
Ratertone acetate in CRPC patients with and without loss of PTEN protein expression was evaluated. In a retrospective study of 144 patients an were overall, loss of PTEN expression was observed in 40% of patients. Loss of PTEN expression was associated with shorter median overall survival and shorter median duration of abiraterone treatment 24.

**ERG - ETS Related Gene**

ERG (ETS Related Gene) is an oncogene located in 21q22.2, member of the ETS family. It encodes a protein named also ERG which acts as a regulator of vascular cell remodeling and megakaryocytes differentiation 25. In prostate cancer, ERG has most frequently been involved as a fusion protein with transmembrane protease, serine 2 (TMPRSS2), a protein encoded by TMPRSS2 gene located in 21q22.3 26. Recurrent translocations resulting in TMPRSS2:ERG fusion are involved in about 40% of prostate cancer cases. In terms of predictive value, expression of TMPRSS2: ERG oncoprotein is associated with a greater likelihood of lethal prostate cancer, poorly differentiated tumors and higher stage diseases with pelvic lymph node involvement 27.

As far as it concerns the combination of PTEN loss with the expression of TMPRSS2: ERG protein is associated with poor prognosis, suggesting these molecular pathways may be the target of preclinical therapeutic research 28. In a study by Ahearn et al. 1,044 incidental prostate cancer cases were followed up for an average of 11.7 years and correlation of cancer specific mortality and all cause mortality with PTEN loss and TMPRSS-2 ERG expression was examined. As a result, PTEN loss was independently associated with greater risk of lethal prostate cancer especially among ERG fusion negative subgroup 29. In addition, Leinonen et al. investigated the association of ERG overexpression combined with PTEN loss with prostate cancer clinical behavior. The study included 326 prostatectomies, 166 needle biopsies from men treated primarily with endocrine therapy, 177 transurethral resections of castration-resistant prostate cancers (CRPC), and 114 CRPC metastases obtained from 32 men. Immunohistochemistry, FISH, and sequencing was used for the measurements. ERG expression was found in about 45% of all patient cohorts. ERG positivity was significantly associated with loss of PTEN expression in prostatectomy and locally recurrent CRPCs. Moreover PTEN loss was associated with shorter progression-free survival in ERG-positive, but not in negative cases 30.

Moreover, in a recent study analyzing data from 68 patients who underwent radical prostatectomy for localized prostate cancer PTEN and TMPRSS-2 ERG expression was assessed by immunohistochemistry methods. Patients were divided into four groups according to PTEN and TMPRSS-2 combined expression and oncologic results were compared accordingly. PTEN loss was proved to be an unfavourable prognostic marker with the worst oncologic results following radical prostatectomy being present in the group of patients who had PTEN deletion without expression of TMPRSS-2 ERG fusion protein. Loss of PTEN expression combined with non expression of TMPRSS-2 ERG fusion was associated with higher rates of positive surgical margins, higher rates of Gleason Score 8 or 9 and more frequent rates of seminal vesicles invasion 31.

**Epilogue**

Nowadays there is a wide interest of identifying new molecular pathways and markers which can be used in order to predict prognosis and thus differentiate indolent forms of PCs from aggressive ones. As PTEN loss and TMPRSS2: ERG fusion protein expression are common in prostate cancer patients, there is a necessity of describing the exact molecular pathways and their influence in prostate carcinogenesis. In addition, more studies are mandatory in order to clarify the clinical significance of PTEN loss and TMPRSS2: ERG fusion as well as their role as molecular prognostic markers in prostate cancer patients.

**Conflicts of interest**

The authors declared no conflicts of interest.
Ο καρκίνος του προστάτη αποτελεί την πιο συχνή κακοήθεια και μία από τις κύριες αιτίες θανάτου από καρκίνο μεταξύ των ανδρών τόσο στην Ευρώπη όσο και στις Ηνωμένες Πολιτείες. Συνεπώς υπάρχει ευρύ ενδιαφέρον για τον εντοπισμό νέων μοριακών μονοπατιών και προγνωστικών δεικτών που μπορούν να χρησιμοποιηθούν για να διαχωρίσουν τις πιο επιθετικές μορφές της νόσου. Αρκετά μοριακά μονοπάτια και ογκογονίδια έχουν εμπλακεί στην ανάπτυξη του καρκίνου του προστάτη και την εξέλιξη του με το PI3-Akt μονοπάτι και το ογκογονίδιο ERG να διαδραματίζουν εξέχοντα ρόλο. Ως αποτέλεσμα υπάρχει αναγκαιότητα να περιγραφούν οι ακριβείς μοριακές οδοί καθώς και την επιρροή τους στην καρκινογένεση του προστάτη και η συσχέτισή τους με θανατηφόρες μορφές της νόσου, ελάχιστα διαφοροποιημένους όγκους και υψηλότερα στάδια αυτής.

**Περίληπτη**

19. Troyer DA, Jamaspishvili T, Wei W. A multicenter study shows PTEN
deletion is strongly associated with seminal vesicle involvement and extracapsular extension in localized prostate cancer. *Prostate* 2015;75(11): 1206-1215.


