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PTEN and ERG Molecular Networks in Prostate Cancer

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Editorial

Prostate cancer (PCa) represents a common malignancy among elder males and one of the leading causes of cancer mortality [1]. 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. Nowadays, many tumors traditionally treated either by radical prostatectomy or by external beam radiation therapy are considered of low clinical significance and such patients are placed under active surveillance protocols with purpose to reduce overtreatment. As a result, in the "active surveillance" era, there is a need of establishing strong prognostic markers identifying aggressive tumors as well as clinical significant tumors even among these initially characterized of low or intermediate risk.

Several molecular pathways and oncogenes have been implicated in PCa development and progression. Progression of PCa to castrate resistant metastatic form is associated with the expression of cellular adhesion molecules, which mediate aberrant interactions between glandular epithelial cells and the extracellular matrix. There is an association between the expression of the E-cadherin/catenin complex and high grade PCa with ongoing clinical trials evaluating the efficacy of integrin antagonists showing promising results [2]. Moreover, autocrine and paracrine events regulated by nerve growth factor (NGF) and relevant receptors seem to play a significant role in prostate carcinogenesis. Studies reveal that p75NTR is both a tumor suppressor of growth and a metastasis suppressor of human prostate cancer cells. Furthermore, p75NTR is progressively lost during prostate carcinogenesis with an imbalance between p75NTR and tropomyosin receptor kinase A (TrkA)-mediated signals being involved in the progression of PCa through increased proliferation and reduced apoptosis [3].

The PI3K-Akt pathway is an important intracellular molecular pathway with a crucial role in regulating cell survival, proliferation, growth, and apoptosis, found to be upregulated in about 30-50% of PCa patients [4]. Various growth factors (epidermal growth factor EGF, platelet-derived growth factor receptor PDGF, insulin-like growth factor (IGF) may initiate the PIP3-Akt pathway by activating receptors of tyrosine kinases leading to the phosphoryliation of PI3K at the level of the cell membrane. The phosphorylated PI3K triggers the conversion of PIP2 to PIP3 and mediates the phosphorylation of Akt through PDK1 [5]. Activated Akt has a profound role in carcinogenesis by promoting cell growth and protein synthesis by regulating the mammalian target of rapamycin (mTOR) pathway. Moreover, apart from interaction with the mTOR pathway Akt may also directly interact with the androgen receptor in an androgen independent manner leading to androgen receptor overactivation resulting to the development of castration resistant prostate cancer [5,6]. 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 [7].

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 PCa [8]. The protein product is a dual lipid phosphatase acting as a negative regulator of the PIK3/Akt survival pathway by negatively regulating 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 [5,8]. Apart from interacting with the PIP3-Akt pathway, PTEN also presents PIP3 independent mechanisms of genomic stability regulation with involvement also in the MAPK signaling pathway [9]. Activation of MAPK signaling network is known to affect directly and/or indirectly androgen receptor (AR) activity. 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 [10].

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 PCa differential diagnosis from high grade pin [11]. 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 metastasis development, prostate cancer-specific mortality and, for the first time, castration-resistant prostate cancer, and response to androgen deprivation therapy after radical prostatectomy [12]. 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 [13]. 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 [14]. Moreover, as far as it concerns oncologic results after radical prostatectomy, in a multicenter study by Troyer et al. PTEN deletion status showed a highly significant correlation with pathologic stage and was also correlated strongly with seminal vesicle invasion, extracapsular extension and higher Gleason scores [15]. 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 [16]. Moreover, the role of PTEN in separating clinically insignificant from significant PCa was examined in a study involving 48 patients with clinically insignificant disease and 76 with significant all treated by radical prostatectomy. 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 [17].

In terms of castration resistant prostate cancer, the role of PTEN is also quite important as alteration in the PTEN/PI3K pathway is nowadays associated with late stage and castrate resistant prostate cancer. 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 crosstalk form a possible mechanism of CRPC development, with potentially important implications such patients' treatment [18].

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 megakaryotic cells differentiation [19]. In PCa, ERG is most frequently been involved as a fusion protein with transmembrane protease, serine 2 (TMPRSS2), a protein encoded by TMPRSS2 gene located in 21q22.3 [20]. Recurrent translocations resulting in TMPRSS2: ERG fusion is involved in about 40% of prostate cancer cases. In terms of predictive value, expression of TMPRSS2: ERG oncoprotein is associated with a greated likehood of lethal prostate cancer, poorly differentiated tumors and higher stage diseases with pelvic lymph node involvement [21]. As far as it concerns the combination of PTEN loss with the expression of TMPRSS2: ERG protein it is associated with poor prognosis, suggesting these molecular pathways may be the target of preclinical therapeutic research [22]. In a study by Ahearn et al. PTEN loss was independently associated with greater risk of lethal prostate cancer especially among ERG fusion negative subgroup [23].

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 PCa from aggressive ones. As PTEN loss and TMPRSS2: ERG fusion protein expression is 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.

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