

Review

Association Between *ERG/PTEN* Genes and Pathologic Parameters of Prostate Cancer With an Emphasis on Gleason Score: A Literature Review

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Abstract. *Background/Aim:* The purpose of this article was to review the association between the ETS-related gene (*ERG*) and the phosphatase and tensin homolog (*PTEN*) genes with pathologic parameters of prostate cancer, emphasizing on Gleason score. *Materials and Methods:* We performed a PubMed-based search of the literature emphasizing on articles that use pathological techniques, and especially on those that report the use immunohistochemical staining and FISH to investigate the association between *ERG* and *PTEN* mutations with the histopathologic parameters of prostate cancer. *Results:* *ERG* expression is frequently marked in patients with prostate cancer, usually due to the occurrence of the *TMPRSS2:ERG* gene fusion. Although some studies reported a potential link between the expression of *ERG* and Gleason score, there is no strong evidence supporting this finding. On the contrary, there is more solid evidence correlating loss of *PTEN* expression with worse prognosis and higher Gleason scores. Few studies

correlate the over-expression of *ERG* gene with the loss of *PTEN* expression. Finally, *PTEN* and *ERG* have been studied as potential therapeutic targets, and several promising results have been reported. *Conclusion:* Although, at some degree, *ERG* expression seems to be associated with the morphological features of prostate cancer, different studies reported controversial results. However, expression of *PTEN* is more clearly associated with the pathology and clinical course of the disease. More research is required to elucidate the role of these molecules in the molecular pathology of prostate cancer, as well as their potential use as therapeutic targets.

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Prostate cancer represents one of the most common forms of malignancy, with an estimated 1,4 million new diagnosed cases in 2020. The incidence of prostate cancer varies geographically, with a higher number of cases being reported in developed compared to developing countries; an observation residing in various modifiable and unmodifiable risk factors (1, 2). Despite being such a prominent health issue, the exact mechanism underlying the molecular pathology of prostate cancer has not been elucidated. Recent advances in the field of molecular biology and the wide use of sequencing techniques in medical research have transformed our understanding of this disease, showing the way for the era of precision medicine (3-5). The ETS-related gene (*ERG*) and the phosphatase and tensin homolog (*PTEN*) gene are two of the most widely studied molecular elements that have been correlated with the pathogenesis of prostate cancer. The purpose of this study is to investigate the association between *ERG/PTEN* expression and different pathologic parameters, with an emphasis on Gleason score, an important histopathological prognosticator of the disease.

Implications of ERG in the Molecular Pathology of Prostate Cancer

ERG is located at chromosome 21q22.2 and it is a member of the erythroblast transformation – specific (ETS) family of transcription factors, a group of highly conserved molecules with an important role in multiple cellular processes, including embryonic development, proliferation, and differentiation (6). It was originally introduced by Reddy *et al.*, in 1987, who determined its sequence in colon cancer cell-lines, as a member of the ETS oncogene family (7).

Under normal circumstances, *ERG* is not expressed in the epithelial cells of the prostate. However, increased expression is frequently present in patients with prostate cancer (8). The over-expression of *ERG* is highly attributed to the *TMPRSS2: ERG* gene fusion, a recurrent chromosomal rearrangement that represents the most common molecular alteration in prostate cancer, occurring approximately in one half of the cases (9, 10). *TMPRSS2:ERG* fusion can occur due to genomic translocations or to interstitial deletions of the intergenic region between the two genes (8, 11). This genomic event results to the fusion of the *ERG* proto-oncogene with the androgen – driven promoter of the *TMPRSS2*, setting the transcription of the former under hormonal control and resulting to its over-expression in cancerous cells (9, 11). The exact molecular mechanisms underlying the pathogenic role of *TMPRSS2:ERG* fusion in prostate cancer are yet to be fully uncovered, but there is evidence suggesting its association with the clinical course of the disease (12, 13).

Correlation of ERG Expression With the Gleason Score

Since the discovery of the *TMPRSS2:ERG* chromosomal rearrangement, there has been a lot of discussion regarding the association of *ERG* expression with specific histopathologic features of prostate cancer and with the prognosis of the disease. However, the results from studies worldwide are controversial. For example, Fine *et al.*, investigated the association of *TMPRSS2: ERG* fusion with the Gleason score, using a cohort of patients with prostate cancer who underwent radical prostatectomy prior to any neoadjuvant therapeutic intervention. By applying FISH analysis, they assessed for any genetic aberration in the *TMPRSS2* and the *ERG* gene. They showed that genomic rearrangements in *TMPRSS2-ERG* genes were associated with a lower Gleason score, whereas copy number increase was correlated with a higher Gleason score (14).

In a different study by Peterson *et al.*, the expression of ERG protein, as an indicator of the presence of *TMPRSS2: ERG* gene fusion, was assessed by immunohistochemistry, in

a cohort of 1,180 male patients (15). The results were statistically analyzed to examine the correlation between *ERG* expression and the clinical outcome of the disease. In the same inquiry, the authors conducted a meta-analysis of 47 studies so as to further investigate the association between the rearrangement status and patient prognosis. This study indicated that, 49% of the cohort population demonstrated over-expression of ERG. However, although these patients were most likely to demonstrate a higher tumor stage, no important correlation was found between the ERG expression and the Gleason score or the clinical outcomes of the disease. These results were further supported by a simultaneously conducted meta-analysis, which showed that the presence of *TMPRSS2: ERG* fusion was associated with a higher risk for increased tumor stage at the time of diagnosis, but it was not correlated with the final outcome (15). Absence of any statistically significant correlation between ERG expression and the Gleason score was further documented in other studies that were performed on tissue samples retrieved from prostatectomy specimens or needle biopsies (16-18).

Implications of PTEN in the Molecular Pathology of Prostate Cancer

PTEN gene is located in chromosome 10 and encodes an enzymatically active molecule that acts as a phosphatase and impedes the activity of PI3K/Akt pathway. PTEN has been shown to represent the most frequently inactivated tumour suppressor gene in primary prostate cancer, and its loss has been associated with disease progression in both hormone naive and castration-resistant prostate cancer (19). Gray *et al.* observed in 1995 that the region q23-24 was often absent from chromosome 10 in patients with prostate cancer (20). The genetic localisation of *PTEN* gene was firstly described by two independent groups in 1997. They detected mutations of this tumour suppressor gene in samples originating from patients with different types of malignancies, including prostate cancer (21, 22). Various methods including immunohistochemistry, in situ and array comparative genomic hybridization have been used to highlight the loss of *PTEN* function in prostate cancer. Genomic deletion is the most commonly found *PTEN* alteration, while point mutations are rarer. Loss of PTEN expression in pathology specimens, as evidenced using immunohistochemistry staining, has been correlated with low *PTEN* molecular expression. Immunohistochemical staining showed the presence of *PTEN* protein in the nucleus and the cytoplasm of the basal and luminal prostatic cells, while loss of this staining pattern is frequently found in prostate cancer. Higher rates of *PTEN* loss have been associated with disease severity and progression along with poorer clinical outcomes (23).

Correlation of Loss of PTEN Expression With the Gleason Score

Without any doubt, Gleason score represents one of the most useful histopathologic variables for defining prostate cancer course and prognosis (24). Many studies indicated the association between Gleason score and *PTEN* expression. Yoshimoto *et al.*, by applying tissue micro-arrays (TMAs) in 142 radical prostatectomy specimens, reported deletions of *PTEN* that occurred more frequently in specimens with a modified Gleason pattern of 4 and 5, compared to those of Gleason pattern 3. The authors documented, in the discussion part of their article, that deletion of *PTEN* in prostate biopsies could potentially represent more aggressive tumors, questioning whether patients with these alterations should be set under surveillance (25). Likewise, Lotan *et al.*, studied *PTEN* expression by immunohistochemistry in specimens from 376 patients and reported that loss of *PTEN* was highly correlated with the pathologic stage and the Gleason score of the disease. *PTEN* deletion was found in 45% of patients with a Gleason score of 8-10 and 39% of patients with a Gleason score of 7, while only 20% of patients with a Gleason score of 5-6 showed loss of expression of *PTEN* protein. Regarding the pathologic stage of the disease, *PTEN* loss was more frequently reported in patients with pT3bN0 over pT3aN0 and pT2N0. Moreover, lymph node and distant metastases were associated with loss of *PTEN*, while *PTEN* deletion was an infrequent event in patients in patients with high grade prostatic intraepithelial neoplasia (HGPIN) (26). Strong evidence for the association of *PTEN* with the Gleason score arrives from a meta-analysis performed by Wang *et al.* in 2015, which included 7 studies, published from 1999 to 2004. Only studies involving patients with localized and operable prostate cancer were included. This study demonstrated that loss of *PTEN* expression was associated with a higher Gleason score, increased probability for capsular penetration and worse overall outcome (27).

In a different study, loss of *PTEN* expression, as evidenced by immunohistochemistry and FISH, was found as a potential indicator in a subgroup of prostate cancer patients with Gleason score 6 in needle biopsy specimens, who were later found to have progressed to 7 or higher Gleason scores, in their radical prostatectomy specimens. The study compared 71 patients with different Gleason scores in biopsy with 103 patients with the same Gleason scores in and prostatectomy specimens and concluded that *PTEN* loss could predict pathologic upgrading in a statistically significant manner. This study once again outlines the potential role of molecular markers in identifying patients with more aggressive prostatic tumors (28).

Similarly, Picanço-Albuquerque *et al.* reported that loss of *PTEN* in patients with a Gleason Grade 7 prostate cancer could predict unfavourable pathological parameters, such as

positive surgical margins and higher Gleason score (29). Cuzick *et al.*, noted that loss of *PTEN*, documented with immunohistochemistry staining, in patients with localised prostate cancer and low Gleason scores, could add prognostic value and predict prostate cancer associated death, along with already documented parameters, such as the Gleason score, Ki-67 expression and extent of the disease. *PTEN* immunohistochemistry pattern was available for 675 men from 6 different cancer registries in Great Britain and was found to predict prostate cancer death reliably but only in low-risk patients (30).

Relationship Between ERG Expression and PTEN Loss

There is a lot of discussion regarding the molecular interconnection between *ERG* and *PTEN*, as two of the most important molecular elements underlying the pathogenesis and the progression of prostate cancer. Deletion of *PTEN* has been found to be two to five times more frequent in patients with *ERG* rearrangements in comparison with patients with intact *ERG* (19). Moreover, it has been reported that over-expression of *ERG* potentially cooperates with loss of *PTEN* expression in promoting progression of HGPIN to invasive prostatic adenocarcinoma (31). In a Brazilian cohort of 116 patients with prostate cancer, immunohistochemical staining for *ERG* and *PTEN* was examined and correlated with various parameters. All different combinations of *ERG* and *PTEN* expression patterns were observed. Only 32% of patients who did not express *ERG* also showed loss of expression of *PTEN*, while *PTEN* deletion was evidenced in 46% of patients with preserved *ERG* expression. However, this difference was not statistically significant. Positive expression of both *ERG* and *PTEN* was associated with lower Gleason scores, lower grading, and lower prostate weight. Although this study included only a small group of patients, it underlined the importance of molecular profiling and personalized treatment approach in prostate cancer (32). Similarly, Bismar *et al.* performed immunohistochemical staining for both *ERG* and *PTEN* in 463 prostate cancer samples and correlated their expression with different pathological features, including Gleason score. In their study, 21.8% of patients with loss of *PTEN* expression were *ERG* positive, while only 16.1% of them were *ERG* negative. This difference was statistically significant. According to the results of their study, Gleason score was positively and negatively associated with *ERG* and *PTEN* expression, respectively. Patients with combined loss of *PTEN* and *ERG* showed the worst prognosis, and not these with *ERG* rearrangements and *PTEN* deletion as it was reported in other studies, including that by Morais *et al.* described before (33).

Brady *et al.* studied 132 patients with prostate cancer and divided them in 3 groups. Group 1 consisted of patients with

biochemical recurrence, Group 2 included patients without biochemical recurrence and Group 3 consisted of patients who progressed shortly after surgery. Immunohistochemical staining for *ERG* and *PTEN* was performed and the combination of their expression was studied in all three patient groups. Most patients with *PTEN* deletion (74.2%) were also *ERG* negative, while 47% of patients without *PTEN* loss were *ERG* negative. Immediate progression after prostatectomy was more frequently observed in patients without *ERG* expression, while loss of *PTEN* expression was also correlated with rapid disease progression but not in statistically significant manner. Although the combination of negative expression of *ERG* and *PTEN* tended to be associated with immediate disease progression, this trend was not statistically significant (34). Shah *et al.* reported heterogeneity regarding *ERG* and *PTEN* expression on core needle biopsies from patients with prostate cancer. In their study, aberrant expression of *ERG* was significantly correlated with loss of *PTEN* expression. Moreover, the association between *ERG* over-expression and *PTEN* loss with different Gleason scores was investigated. Researchers noted that despite the absence of a strong connection between *PTEN* and higher Gleason scores, a significant correlation of *ERG* with Gleason score was not documented. In their conclusion the authors emphasized the importance of recognizing *ERG* and *PTEN* heterogeneity. Finally, *ERG* and *PTEN* expression was studied in combination in a systematic review and meta-analysis, which correlated these parameters with disease recurrence. A total of 17 eligible studies involving 6744 patients with prostate cancer were included in the final qualitative and quantitative synthesis. The authors observed significant correlation between the loss of *PTEN* expression and poorer biochemical recurrence free (BRF) and shorter recurrence-free survival (RFS) rates, but failed to document a suchlike trend for *ERG* over-expression. BRF and RFS were also conversely related with Gleason score (35).

ERG and PTEN as Therapeutic Targets

Shao *et al.* targeted the *TMPRSS2/ERG* fusion gene with liposomal nanovectors and studied the efficacy of this strategy in docetaxel therapy response. The authors reported increased docetaxel effectiveness in patients with advanced disease. Moreover, they concluded that this approach could potentially be used as a monotherapy (36). Tanaka *et al.* investigated the efficacy of *PTEN* gene therapy in enhancing response to chemotherapy. Using human prostate cancer cell lines and recombinant *PTEN* adenoviruses, they showed that this therapeutic strategy increased doxorubicin chemotherapy efficacy (37). *PTEN* pathway targeting was also reported by Qi *et al.* In their study, they demonstrated that intermittent P13K blockage could represent a solution to immune checkpoint therapy (ICT) resistance (38). In a review article, Turnham *et al.*, summarized all the reported therapeutic

strategies for targeting the *PTEN* gene and restoring its function (39). Lahdensuo *et al.* proposed that patients with *ERG*-negative prostate cancer with loss of *PTEN* could benefit from adjuvant therapies (40). Finally, Rescigno *et al.* studied the response of patients with prostate cancer and abnormal *ERG* and *PTEN* expression to docetaxel therapy. They concluded that in patients with loss of *PTEN* and castration-resistant prostate cancer, docetaxel chemotherapy was more effective than hormonal treatment, while no correlation was found between *ERG* expression and docetaxel response (41).

Conclusion

Although some articles report a correlation between *ERG* protein and Gleason score, there is no strong evidence supporting this finding. Furthermore, a meta-analysis of 47 studies failed to show any association between these two parameters (15). On the contrary, loss of *PTEN* expression has been clearly connected with worse prognosis and higher Gleason scores. A meta-analysis demonstrated a statistically significant correlation of these two parameters (27). Few studies relate over-expression of *ERG* gene with loss of *PTEN* expression. Regarding the combined expression of *ERG* and *PTEN*, all studies correlated negative *PTEN* expressions with higher Gleason scores, while both positive and negative *ERG* expression were reported in different studies. Some articles report the combined negative *PTEN* and *ERG* expression is associated with the highest Gleason score, while others conclude the over-expression of *ERG* combined with the deletion of *PTEN* is the least favorable combination. Finally, *PTEN* and *ERG* have been studied as potential therapeutic target and several promising results have been reported. An important limitation of this review is that not all articles studied exclusively the expression of *PTEN* and *ERG* in pathologic specimens using immunohistochemistry. Thus, some studies were based in molecular biology assays or were *in vitro* experiments. Additional studies on the association between *PTEN* and *ERG* immunohistochemical expression and pathologic parameters, such as the Gleason score, are of utmost importance.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

All Authors contributed to the conception and design of the manuscript. The authors T. Spinos and A. Georgiou have equally participated in the writing process of the text. Dr. Andreas C. Lazaris and Dr. Georgia Eleni Thomopoulou supervised the writing of this review.

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