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Inflammatory Pathways from Benign Prostatic Hyperplasia to Prostate Cancer - in Search of New Therapeutic Options

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Abstract

Introduction: The inflammatory process has impact on tumor cells development or anti-tumor responses. Inadequate innate or acquired stimulation of the immune system can cause chronic inflammation that can lead to oncogenesis. Benign Prostatic Hyperplasia (BPH) and Prostate Cancer (PCa) can be combined at the cellular and molecular level on hormonal, genetic and inflammatory platforms, suggesting that these prostate diseases share common pathophysiological factors.

Aim: The aim of the study is to retrospectively assess the histological material of BPH and PCa with divided into few groups using the Gleason score and correlation with inflammatory factors. The evaluation of the expression of pro-inflammatory factors such as IL-17A, IL-17F, IL-17RA, IL-17RC, AKT1, C/EBPbeta, TRAF-6 and NF-kB made it possible to assess the influence of the inflammatory process on the development of BPH with regards to their PCa risk.

Material and Method: Studies were carried out on archival tissue material in the form of paraffin blocks of 40 men with PCa after radical prostatectomy. The control group was 10 men with Benign Prostatic Hyperplasia (BPH). The material was obtained by the Transurethral Resection of the Prostate (TURP). The immunohistochemistry was performed on the material using specific primary antibodies against IL-17A, IL-17F, IL-17RA, IL-17RC, ACT1, TRAF-6, C/EBPbeta and NF- kB. The expression of the antibody was examined using the light microscopy and the Remmele Stegner score (IRS). Statistical analysis was performed using the non-parametric Kruskal-Walli's test.

Results: In statistical analysis, it was shown that the inflammatory pathway IL17A/IL-17RC/TRAF6/NF-kB and IL17A/IL-17RC/AKT1/NF-kB occurs in both BPH and PCa. IL-17RA did not show expression in any group of patients and in the control group. In addition, along with the increase in the grading of Gleason score, a decrease in the expression of the tested inflammatory parameters was demonstrated.

Summary and Conclusion: The inflammatory process has an impact on the BPH and PCa. The presence of the inflammatory pathways IL17A/IL-17RC/TRAF6/NF-kB and IL17A/IL-17RC/AKT1/NF-kB in BPH with increased risk to development of PCa. The inflammatory process correlated with increased risk to development of PCa with a lower histological grade according to Gleason score.

Keywords: Prostate cancer; Benign prostatic hyperplasia; Cytokines; Pathogenesis; Cancer immunology

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Introduction

The inflammatory immune response may affect cancer cells development or antitumor response. Immune system can be divided into innate and acquired. A properly regulated acquired immune response is considered anti-cancer. And inadequate innate or acquired stimulation of the immune system can cause chronic inflammation that can lead to oncogenesis [1]. Inflammation

can be divided into acute and chronic. Chronic inflammation take part in the development of many cancers. Numerous reports have revealed a relationship between chronic prostatitis and PCa [2]. The inflammatory infiltration in the histological examination of the PCa is most often composed of chronic inflammation cells, mainly composed of lymphocytes, macrophages, and less frequently of plasma cells and eosinophils. Chronic inflammatory microenvironment develops through the action of various inflammatory mediators such as a Nitric Oxide (NO), cytokines including IL-6, IL-17, growth factor and chemokines. Acute inflammation is found in a smaller percentage of PCa cases and consists mainly of neutrophils. Long-term inflammation can also cause altered expression of oncogenes and tumor suppressor genes [1]. Despite the numerous available dates on the occurrence of prostatitis, there are still many unanswered questions about the role of the inflammatory process in the development of PCa [3]. Cytokines secreted by tumor cells may either stimulate tumor growth, the survival of cancer cells or exert anti-tumor effects. An important element in response to the inflammatory process are Th17 lymphocytes characterized by the production of IL-17 [4]. IL-17 induces the recruitment of immune cells to peripheral tissues, which requires the activation of NF-kB by the IL-17 receptor [5]. Studies have been published that highlight the role of IL-17 in chronic inflammation and the development of malignancies [6]. In recent years, the huge breakthrough in oncology was the introduction of immunological treatment. Immunotherapy of the cancer is designed, among others, to modify the patient's immune system in such a way as to lead to the activation of own anti-tumor defense pathways with the participation of cytokines [7]. Immunotherapy can be divided into three categories, such as immune checkpoints inhibitors, cytokines and therapeutic vaccines [8]. Currently, research reports on numerous satisfactory results of cancer treatment, including PCa using particular types of immunotherapies [9]. PCa was first cancer in which a specific vaccine significantly improved survival. However, the goal has still not been achieved due to certain limitations of individual therapies. For example, vaccines based on neoantigens may bypass central tolerance, still must act against peripheral tolerance and immune escape mechanisms. Therefore, it is very likely that even when neoantigens are produced, cancer vaccines will not be able to achieve large clinical results on their own. Strategies that inactivate the most important immunosuppressive mechanisms and/or stimulate the cytotoxic response can be optimally combined with cancer vaccines [10]. Tumor-targeted therapies mostly improve PFS, and immune-targeted therapies seem to provide greater OS benefits (at least in metastatic disease), a combination of two categories of immunotherapy can significantly improve both survival and clinical response in many types of cancer. Of course, the results of preliminary studies indicate that immunotherapy also involves side effects, often described as less significant than in chemotherapy. However, at the moment we can only state that these are other side effects, without unambiguous claims regarding comparisons with other therapeutic options [11]. New immunomodulatory targets and rational combination strategies aim to achieve more favorable results. Recent progress has been made in determining biological prognostic factors for response and toxicity in the immunotherapy of prostate cancer to improve patient selection and treatment safety. In the USA, the FDA has currently approved two types of immunotherapies in PCa, i.e., cancer vaccines - Sipuleucel-T. It is a vaccine composed of patients' immune cells, which have been stimulated to target the PAP (Prostatic Acid Phosphatase) protein. It is approved for subsets of patients with advanced PCa [12]. And the second immunomodulators i.e., pembrolizumab. It is a checkpoint inhibitor that targets the PD-1/PD-L1 pathway. It is also approved for subsets of patients with advanced, MSI-high PCa [13]. Steady progress is expected in the field of prostate cancer immunotherapy, including the continuous development of new cancer vaccines, immune checkpoint therapy, and combinatorial strategies. Inflammation may be also a component of BPH pathogenesis. Prostatic stromal cells exert a critical role in the induction of inflammatory responses by activating CD4+ lymphocytes. Thus, BPH may be viewed as a form of asymptomatic inflammatory prostatitis, whose pathogenesis may be triggered by a multitude of factors and inflammatory pathways. Moreover, the release of prostatic self-antigens following tissue damage may sensitize the immune system and start autoimmune responses [2]. BPH and PCa can be combined at the cellular and molecular level on hormonal, genetic and inflammatory platforms, suggesting that these prostate diseases share common pathophysiological factors [14-16]. However, to the best of our knowledge, there is no systematic review and research that studied the association between BPH and PCa based on inflammatory pathways. Therefore, we would like to present in our current research the impact of IL-17 pathways in the development of BPH and PCa and their correlations.

Moreover, the patients with PCa were divided into histological the grading of Gleason score. In our studies, we examined the presence of IL-17A, IL-17F, IL-17RA, IL17RC, AKT1, TRAF6, C/EBPbeta, and NF-kB in PCa with grading of Gleason score and BPH. We presented some of the results in our previous publication [17,18]. In this article, we focused on the entire inflammatory pathway. Our results can be useful in better understanding the pathogenesis of BPH and PCa and in predicting its clinical course.

Material and Method

Studies were carried out on archival tissue material in the form of paraffin blocks. Studied group consists of 40 men with PCa. Tissue material was selected from a group consisted of 116 patients from years 2010-2017 who underwent complete prostatectomy. Patients' age ranged from 50 to 76 years, and the mean age of patients was 67 years. The control group of 10 men with BPH. The material was obtained using the Transurethral electro-Resection of the Prostate (TURP). The whole material was fixed in 10% buffered formalin and processed according to a standard protocol. Finally, paraffin blocks were prepared. The TMA Master obtained tissue microarrays from paraffin blocks. After preliminary evaluation of hematoxylin and eosin slides, the material was selected for immunohistochemical studies. We used primary antibodies against IL-17A (Sigma Aldrich, HPA 052258, 1:175), IL-17F (Abcam, Ab 190340, 1:100), IL-17RA (Abcam, Ab 180904, 1:100), IL-17RC (Abcam, Ab 69673, 1:100), AKT1 (Abcam, Ab 81283, 1:50), TRAF6 (Abcam, Ab 33915, 1:100), C/EBPbeta (Abcam, Ab 52194, 1:100), NF-kB (Abcam, Ab 31481, 1:100) and for detection - EnVision system (DAKO). Tonsil tissue was used as a positive control for IL-17A, IL-17RC, and IL-17RA. The large intestine was used as a positive control for IL-17F, TRAF-6 and NF-kB. Cervical carcinoma was used as a positive control for AKT-1. Breast carcinoma was used as a positive control for C/EBP beta. Antigen expression evaluation in inflammatory infiltration of selected lesions was carried out using modified Remmele-Stegner scale according to the intensity of expression and the number of positively expressed cells/tissue area (ranging from 1 - lowest expression to 12 - highest expression). The analysis was performed at 20× original objective magnification for each of the studied antibodies

on 3 representative and randomly selected areas. The results were analyzed statistically using the nonparametric Kruskal-Wallis test at a fixed level of significance of 0.05.

Results

BPH and PCa

IL-17F the lowest expression was demonstrated in the control group in comparison on study group ($p<0.05$). There were no differences between expression of IL-17RA in BPH and the study group. IL 17A, IL-17RC, AKT1, TRAF6, NF-kB were found to be more highly expressed in the control group compared to the study group ($p<0.05$). The expression of C/EBPbeta was no statistical significance in the study group compared to the control group ($p>0.05$) (Table 1).

BPH and PCa with Gleason score

The expression of IL-17A, IL-17F, IL-17RC, AKT-1, TRAF6, C/EBPbeta and NF-kB was demonstrated in the control group of patients with BPH and in the PCa. The level of expression IL-17A, IL-17F, AKT-1 and C/EBPbeta in PCa was the highest in Gleason score 6. The level of expression IL-17RC, TRAF-6 and NF-kB in PCa was the highest in Gleason score 6 and 7. The lowest expression of IL-17A was demonstrated in the group of patients with Gleason score 8 and 9 PCa. The lowest expression of IL-17F and IL-17RC was demonstrated in the group of patients with Gleason score 8 and 9 PCa. The lowest expression of AKT-1, TRAF-6, NF-kB and C/EBPbeta was demonstrated in the group of patients with Gleason score 9 PCa (Figure 1 and Table 2).

Discussion

Numerous studies have reported that some PCa develop based on BPH but has not been shown to this day pathogenesis of this phenomenon. Besides, studies are showing a link between the occurrence of inflammation in the prostate gland and the development of BPH and/or PCa. However, there is currently no unambiguous data on the specific relationship between prostatitis, BPH and PCa. In this connection in our study, we want found the answer to question: Does presence of inflammation in BPH can increase risk to development of PCa? Zhang et al. [19] carried out a meta-analysis to answer these questions. They investigated online databases PubMed, PMC, EMBASE and Web of Science was performed to acquire eligible studies, up to April 1st, 2019. Pooled Odds Ratios (ORs) with 95% Confidence Intervals (CIs) were calculated to clarify their correlations. 35 studies were included in the meta-analyses. Meta-analysis showed correlations among prostatitis, BPH and PCa. A case-control study and a cohort study supported that prostatitis could enhance the risk of BPH. Moreover, prostatitis or BPH could lead to escalating risks of PCa. However, it should be considered, that this meta-analysis has several limitations i.e., results were based on unadjusted estimates without modifying the influences of some other covariates like age and race. Moreover, it was huge the heterogeneity among enrolled studies and many factors were left out like age, environment, lifestyle, and inheritance [19]. Nunzio et al. [20] found common inflammatory infiltrates in BPH. The cytokines and growth factors released by inflammatory cells could stimulate the stroma and epithelial cells to hyperproliferation [20]. Many studies have suggested that prostatitis and BPH are closely related [21].

We show in our research, that the inflammatory process has an influence on BPH and PCa by various inflammatory pathways. IL-17A and IL-17F initiate some of these pathways (Figure 2, 3). These pathways have a common receptor, which is IL-17RC. There was no expression of IL-17RA in BPH and PCa, which we showed in an earlier publication [17,18].

Having obtained all the results, we would like to draw attention to the role of IL-17A and IL- 17F, not as a single element of the inflammatory process, but as one of many elements involved in the inflammatory process and acting on subsequent elements. The individual elements, interacting with each other, form a whole that affects the development of BPH and PCa. In our research we show two cascades that are present in both lesions BPH and PCa. There is IL17A/IL-17RC/TRAF6/NF-kB and IL17A/IL-17RC/AKT1/NF-kB. Liu et al. [22] showed increased expression of IL-17A, IL-17RA, IL-17E and IL-17F in the prostate in both BPH and PCa compared to expression in the control group. However, the histological grade of PCa was not included in these studies. One study shows a relationship between high C/EBPbeta expression in tumor epithelial cells with high Gleason scores, high tumor cell proliferation, metastasis, and poor outcome [23]. In our studies, the inflammatory process was more associated with low- grade histological Gleason score (Gleason scale below 7). Similar observations were made as part of a very large research project at the Society of Urologic Oncology meeting in 2015 by Dr. Daniel Moreira from the Mayo Clinic. The study included 889 men (aged 50-75 years) with negative first biopsies, but whose second biopsies 2 years later were positive for PC. About 10% of the biopsy showed inflammation in addition to PCa. The study

Table 1: The differences in the values of IL-17A, IL-17F, IL-17RA, IL17RC, AKT1, TRAF6, C/EBPbeta, and NF-kB among the Benign Prostatic Hyperplasia (BPH) group were analyzed by Kruskal-Wallis, significance of difference relative to Prostate Cancer (PCa). P-value <0.05.

Variable- Factor tested	p-value
IL-17A	0.000000
IL-17F	0.000064
Il-17RA	0.000000
IL-17RC	0.000000
AKT-1	0.004893
TRAF-6	0.005986
NF-kB	0.001813
C/EBPbeta	0.476908

Table 2: Correlation of expression levels of IL-17A, IL-17F, IL-17RA, IL17RC, AKT1, TRAF6, C/EBPbeta, and NF-kB in Benign Prostatic Hyperplasia (BPH) and Gleason score in Prostate Cancer (PCa) (G-6- Gleason score 6, G-7-Gleason score 7, G-8- Gleason score 8, G- 9-Gleason score 9). P-value <0.05.

Variables	BPH							
	IL-17A	IL-17F	IL-17RA	IL-17RC	AKT-1	TRAF6	NF-kB	C/EBPbeta
G-6	0.012932	0.000000	0.000000	0.000000	0.215938	10.00.000	10.00.000	10.00.000
G-7	0.000000	0.053280	0.000000	0.000000	0.917285	10.00.000	10.00.000	10.00.000
G-8	0.000000	0.677119	0.000000	0.020575	0.002525	0.042077	0.002628	10.00.000
G-9	0.000000	0.652600	0.000000	0.616921	0.000000	0.000000	0.000000	0.053771

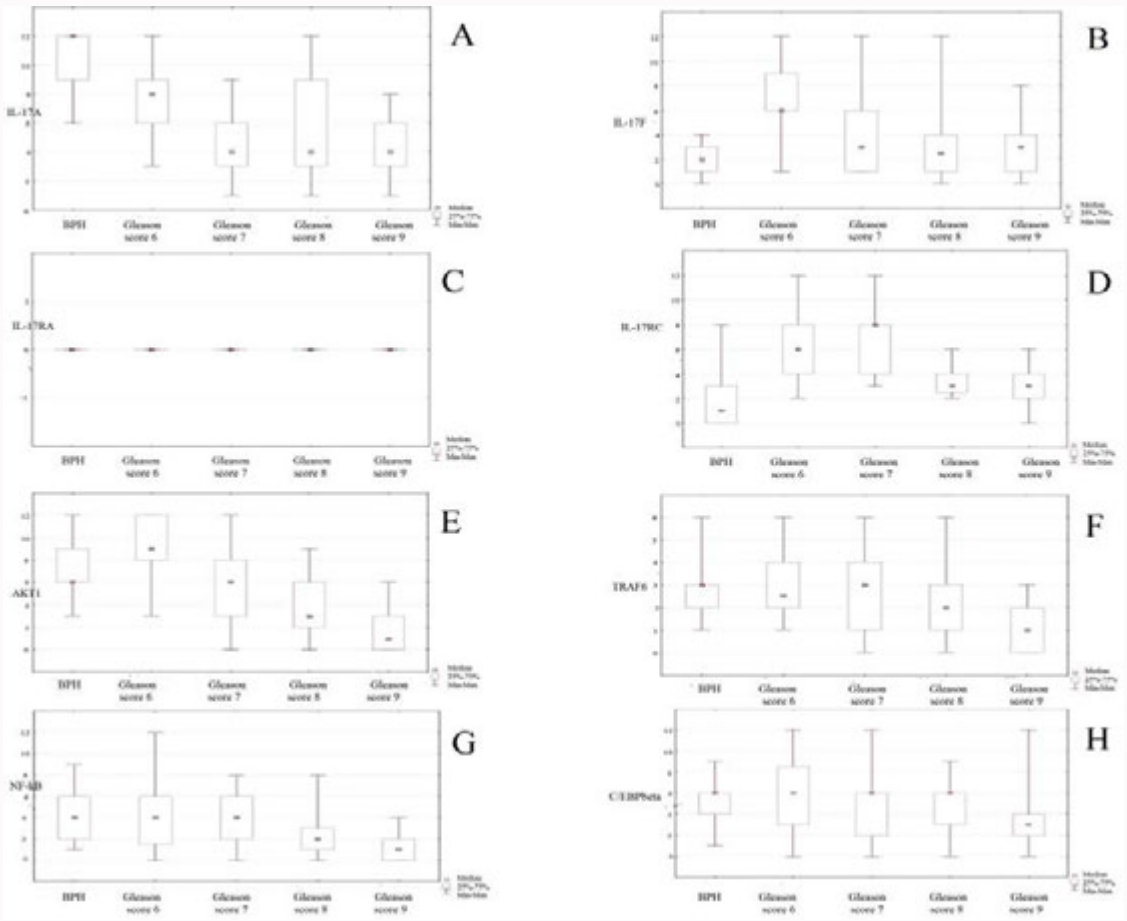

Figure 1: The expression of IL-17A (A), IL-17F (B), IL-17RA (C), IL-17RC (D), AKT1 (E), C/EBPbeta (F), TRAF 6 (G) and NF-kB (H) in Benign Prostate Hyperplasia (BPH) and in Prostate Cancer (PCa) divided on histological grading of Gleason score.

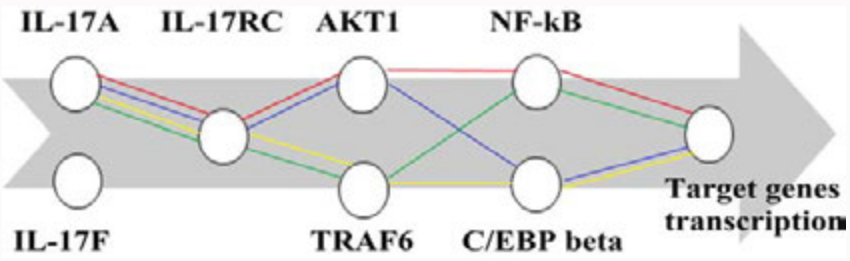

Figure 2: The potentially inflammatory pathway in benign prostate hyperplasia and in prostate cancer initiated by IL-17A.

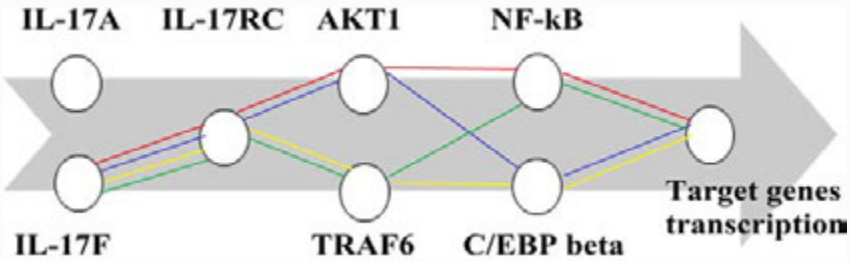

Figure 3: The potentially inflammatory pathway in benign prostate hyperplasia and in prostate cancer initiated by IL-17F.

found that chronic inflammation was more associated with benign prostatic hyperplasia. Perhaps the most important fact was that 70% of tumors had a low level of histological malignancy (Gleason score below 6), and only 30% were with a higher degree of malignancy. Interestingly, men with chronic inflammation and PCs had a lower risk of developing a high-grade disease compared to men who did not

have an inflammatory [24]. The above data show that the relationship between inflammation, BPH, and PCa is not yet fully understood. The key question is why there are such huge discrepancies in the presented reports. Probably the problem is a different way of assessing the inflammatory process. Further research and analysis are needed to determine the key factor of inflammation in tumorigenesis.

Conclusion

The inflammatory process has an impact on BPH and PCa. Moreover, there is a correlation between the grades according to the Gleason score in PCa and the level of expression of inflammation parameters. Activation of the inflammatory pathway through IL17A/IL- 17RC/TRAF6/NF-kB and IL17A/IL-17RC/AKT1/NF-kB cascade in BPH could increase risk development on PCa. This correlation is detected probably in patients with PCa with Gleason score 6 and 7, because the inflammatory process was more associated with low-grade histological Gleason score (Gleason scale below 7). Evaluation of the inflammatory pathway in PCa and BPH, initiated by IL-17, may become a starting point for further research on an attempt to use immunotherapy in PCa or for early diagnosis PCa in patients with BPH.

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