The role of inflammation and infection in the pathogenesis of prostate carcinoma

Florian M.E. Wagenlehner, Johny E. Elkahwaji*, Ferran Algbaba†, Truls Bjerklund-Johansen‡, Kurt G. Naber¶, Rudolf Hartung§ and Wolfgang Weidner

Department of Urology, Justus-Liebig-University Giessen, Germany, *Department of Surgery, Division of Urological Surgery, University of Nebraska Medical Center, Omaha, USA, †Department of Pathology, Fundacio Puigvert, Barcelona, Spain, ‡Department of Urology, Telemark Hospital, Porsgrunn, Norway, ¶Technische Universität, München, and §Department of Urology, der Technischen Universität Munich, Klinikum rechts der Isar, Munich, Germany

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Prostatitis and prostate carcinoma are both frequent entities of prostatic diseases. Epidemiological studies show significant associations between infection and inflammation and prostate carcinoma. However, because of various confounding factors the results of these studies are inconclusive. Further findings are therefore needed to confirm the hypothesis that prostatic infection and inflammation might be a cause of prostatic carcinoma. We reviewed selected reports on the role of inflammation and infection in the pathogenesis of prostate carcinoma.

Extensive genetic analyses show that several gene products, e.g. 2′-5′-oligoadenylate (2–5 A)-dependent Rnase, macrophage scavenger receptor 1 and Toll-like receptor-4, influence the susceptibility of prostate cells to infectious agents. Proliferative inflammatory atrophy (PIA) could be a connection between prostatitis and prostatic carcinoma. In the transition from PIA to prostatic intraepithelial neoplasia, the function of cellular detoxification is gradually lost by silencing of glutathione-S transferase, a detoxifying enzyme. This cellular feature leads to an increased susceptibility of the prostatic epithelial cells to genomic damage by inflammatory oxidants or nutritional carcinogens. Consecutive somatic genome damage might then arise which modulates the further pathogenesis of prostate carcinoma. Summarising these epidemiological, genetic and cell biological aspects, infectious prostatitis might have a causative role in the complex and multifactorial process of prostate carcinogenesis.

KEYWORDS
prostatic carcinoma, prostatitis, genetic susceptibility, proliferative inflammatory atrophy

INTRODUCTION

Chronic inflammation and chronic infection influences the emergence of various human neoplasms; the inflammatory process causes repeated cell and genome damage which leads to increased cell proliferation. If an
infection is the cause of the inflammation, the inflammatory cells, e.g. macrophages and neutrophils, frequently produce reactive oxygen and nitrogen species in response, to eliminate the micro-organisms. These free radicals can be toxic and because of their hyperactive state are then able to cause protein and tissue damage (peroxynitrite) and permanent lesions on DNA (8-hydroxy-2-deoxyguanosine). Another feature of these oxidative stress reactions is the production of arachidonic acid from lipid membranes, a process which also generates reactive oxygen radicals and induces oxidative damage to vascular tissue [1]. The sequelae of chronic inflammation and infection could potentially link prostatitis with the carcinoma of the prostate.

Carcinoma of the prostate is the most frequently diagnosed malignancy of men in western countries. In an autopsy series the presence of histological prostate carcinomas was up to 29% in men aged 30–40 years, and 64% of men aged 60–70 years [2]. Prostatitis is diagnosed at least as often; the prevalence of symptoms indicative of chronic prostatitis in the population varies in different studies and study designs, at 5–11% [3]. However, a routinely cultured, causative pathogen is detected in only 5–10% of cases [4]; in most the cause remains unknown. Asymptomatic prostatitis is common in histological specimens of resected or biopsied prostatic tissue, but has not gained much scientific interest to date [5].

ASPECTS CORRELATING PROSTATITIS AND PROSTATE CARCINOMA

EPIDEMIOLOGY

Various epidemiological studies have shown a significant association of prostatitis and prostate carcinoma. The ‘osteoporotic fracture in men’ study [6], a cross-sectional analysis from a prospective cohort study of 5821 men aged 265 years, found positive associations for a self-reported history of prostatitis with a history of prostate cancer, with an odds ratio of 5.4.

The Olmsted County study, a case-control study, investigated 409 cases at diagnosis of prostate cancer and 803 control subjects from 1980 to 1996 [7]. The odds ratio of prostate cancer in men with any type of prostatitis was 1.7. The relative risk estimates for acute bacterial prostatitis was 2.5, for chronic bacterial prostatitis 1.6 and for chronic pelvic pain syndrome (CPPS) 0.9. Therefore, infectious prostatitis might be associated with prostate cancer.

A meta-analysis of case-control studies that investigated the association between prostate cancer and prostatitis evaluated 11 studies from 1971 to 1996. There was a greater risk, especially with population-based case-control studies, with an odds ratio of 1.8. Relative risk estimates were also greater among men with a history of syphilis (odds ratio 2.3) and gonorrhoea (odds ratio 1.3) [8].

However, the causality in these epidemiological studies is unclear, because potential confounders, e.g. recall bias or detection bias, cannot be excluded. Also, asymptomatic prostatitis (National Institutes of Health category IV) has not been assessed in such an epidemiological study.

CELL BIOLOGY

Histologically multifocal areas of epithelial carcinomas are frequently found in radical prostatectomy (RP) specimens. Many of these areas are associated with chronic inflammation, consisting of CD3-positive T-lymphocytic infiltrates with varying numbers of macrophages involving epithelium and stroma [9]. These areas also comprise epithelial cells with a high proliferative index [10] in the secretory layer, and decreased expression of p27 (Kip1), a finding reminiscent of high-grade prostatic intraepithelial neoplasia (PIN) [9]. Because these lesions are hyperproliferative, associated with inflammation, and have a distinct morphological appearance recognized as prostatic atrophy, the term ‘proliferative inflammatory atrophy’ (PIA) was suggested [9]. Elevated Bcl-2 expression might be responsible for the very low apoptotic rate found in PIA, and is consistent with the conclusion that PIA is a regenerative lesion [9].

PIA lesions morphologically show transitions to high-grade PIN, which is considered to be a direct neoplastic precursor lesion of prostate carcinoma. In a study assessing 5510 sample areas of RP specimens because of prostate carcinoma, PIA lesions were significantly more common in the peripheral zone of the prostate and adjacent to areas of prostatic carcinomas than were simple atrophic lesions [10]. The number of proliferating nuclei increased significantly from benign (1.2%), simple atrophic (2.7%), PIA (3.6%), high-grade PIN (6.1%), to prostatic carcinoma (12%).

GENETIC ASPECTS

The contribution of hereditary factors to the cause of sporadic cancer was evaluated in a study of twins, combining data on 44 788 pairs of twins to assess the risks of cancer at 28 anatomical sites for the twins of people with cancer. Statistically significant effects of heritable factors were highest for prostate cancer (42%), followed by colorectal cancer (35%) and breast cancer (27%). Thus prostate cancer had the highest heritable component amongst all cancers studied [11].

To define the nature of this familial aggregation and to assess whether Mendelian inheritance can explain prostate cancer clustering, proportional-hazards, segregation analyses and linkage studies were performed. These analyses of familial prostate carcinoma revealed candidate genes whose products are frequently involved in infectious and inflammatory processes.

A study of 691 families provided evidence that prostate cancer is inherited in a Mendelian fashion in a subset of families [12]. Subsequent studies, conducted as a genome-wide scan in 66 high-risk prostate cancer families, provided evidence of linkage to the long arm of chromosome 1 (1q24–25) [13]. Further analysis of this region provided strong evidence of a major prostate cancer susceptibility locus on chromosome 1 [13]. The gene at this region was termed ‘hereditary prostate cancer 1’. Subsequent investigations showed that the gene encodes a 2′-5′-oligoadenylate (2–5 A)-dependent RNaseL (RNaseL), which regulates cell proliferation and apoptosis through an interferon-regulated 2–5 A pathway, and thus is implicated in viral defence.

Microdissected tumours with a germline mutation showed loss of heterozygosity and loss of RNaseL protein. RNaseL activity was reduced in lymphoblasts from heterozygous individuals compared with family members who were homozygous for the wild-type allele. RNaseL has therefore been suggested to be a candidate tumour suppressor gene product [14].
Subsequent investigations assessed RNaseL variants. A single variant, Arg462Gln, was found, having significantly less enzymatic activity than the wild-type and was thus significantly associated with prostate cancer risk ($P = 0.007$). At least one copy of the mutated allele that caused this substitution was carried by nearly 60% of the men in that study. Men who were heterozygous for the mutated allele had a 50% greater risk of prostate cancer than non-carriers, and homozygotes had more than double the risk [15].

Another study assessed deletions on chromosome 8p22-23 in prostate cancer cells, and linkage studies in families affected with hereditary prostate cancer. The macrophage scavenger receptor 1 gene (MSR1, also known as SR-A) is located at 8p22. MSR1 is a heterogenous receptor binding a variety of antigens, amongst others lipopolysaccharides of Gram-negative bacteria. The results of that study showed that MSR1 might be important in susceptibility to prostate cancer in men of both African, American and European descent [16]. To further evaluate the role of MSR1 in prostate cancer susceptibility, five common variants of MSR1 were studied in 301 patients with nonhereditary prostate cancer who had treatment, and in 250 control subjects who participated in prostate cancer screening programmes. There were significantly different allele and haplotype frequencies between cases and control for each of the five variants [17]. These results consistently suggested that MSR1 might be important in prostate carcinogenesis.

The lipopolysaccharide receptor Toll-like receptor 4 (TLR4) is central in the signalling pathways of the innate immune response to infection by Gram-negative bacteria, and is an important candidate inflammatory gene. A systematic genetic analysis of TLR4 sequence variants was done among 1383 patients with newly diagnosed prostate cancer and 780 age- and residence-matched controls in newly diagnosed prostate cancer and 780 age- and residence-matched controls in Sweden [18]. There was an association between a sequence variant (11,381G/C) in the coding region of the TLR4 gene and prostate cancer risk. The frequency of the variant genotypes (CG or CC) was significantly higher in the patients (24.1%) than in the controls (19.7%; $P = 0.02$). The frequency of risk genotypes among patients diagnosed when aged <65 years was even higher (26.3%). Compared with men who had the wild-type genotype of this single-nucleotide polymorphism (GG), those with GC or CC genotypes had a 26% greater risk of prostate cancer and a 39% greater risk of early-onset prostate cancer (before age 65 years).

ALTERATIONS AT THE MOLECULAR BIOLOGICAL LEVEL

GSTM1 encodes a glutathione-S-transferase and is responsible for detoxifying carcinogens and inflammatory oxidants in prostate cells. GSTM1 normally is only expressed in the basal cells of the prostate epithelium. GSTM1 expression is markedly increased in inflammation in the prostate and is a true sign of cellular stress. PIA lesions have significantly increased expression of GSTM1, whereas PIN and prostatic carcinoma lesions show markedly decreased expression of GSTM1, caused by inactivation of transcription due to GSTP1 CpG island hypermethylation. The latter is the most common somatic genome alteration described for human prostate cancer [19]. Lack of GSTP1 expression is characteristic of human prostate cancer cells in vivo. In one study investigating GSTP1 CpG island DNA hypermethylation in prostate cancer DNA, there were almost exclusively hypermethylated GSTP1 alleles in each prostate carcinoma cells. GSTP1 CpG island DNA hypermethylation was thus responsible for the lack of GSTP1 expression by prostate carcinoma cells. Perhaps GSTP1 inactivation might render prostatic cells susceptible to additional genome alterations, caused by electrophilic or oxidant carcinogens, that provide a selective growth advantage [19].

Other detoxifying enzymes investigated with lower expression in PIN and prostate carcinoma lesions were copper-zinc superoxide dismutase, manganese superoxide dismutase and catalase [20]. The expression of the DNA adduct 8-hydroxy-2-deoxyguanosine as a marker of oxidative stress in that study was no different among benign epithelium, PIN and prostate cancer, which might indicate that oxidative stress is an early event in prostate carcinogenesis. However, the antioxidative capacity was markedly decreased in premalignant and malignant lesions [20].

The vast majority of proliferative epithelial cells in the normal prostate reside in the basal compartment, with multiple genomic protection mechanisms intact. Therefore the basal cells are well protected from incurring large amounts of genome damage and genomic instability [21]. The stem cell model introduced by De Marzo et al. [21] implies that prostatic carcinoma initiates from an abnormal increase in replication of transiently proliferating cells within the secretory compartment that are poorly protected against DNA damage. However, these transiently proliferating cells abnormally retain stem cell-like features, e.g. unlimited self-renewal, which is described by the term ‘topographic infidelity of proliferation’. The breakdown of the protective mechanisms probably occurs early in the stage of PIA and is inferred by oxidative stress, which might be caused by an infectious process.

FINDINGS ASSOCIATING INFECTION AND PROSTATIC CARCINOMA

DETECTION OF BACTERIA IN PROSTATIC SPECIMENS

In one study, sterile prostate biopsies were obtained from patients with prostate cancer, and using a perineal approach from 170 with CPPS; the samples were tested for 16S rRNA [22]. Bacterial DNA sequences were detected in 19.6% of patients with prostate cancer and 46.4% of those with CPPS ($P < 0.001$). These bacteria included urogenital pathogens, other described microorganisms and bacterial sequences not reported previously [22]. Thus bacterial DNA sequences might be identified in prostate tissue from many patients, but bacterial detection rates in prostate tissue appear to differ among populations, with higher rates among patients with the CPPS than among those with prostate cancer.

In another analysis, 28 prostate samples from organ donors, patients with prostate cancer or those with BPH were investigated, detecting bacterial 16S rRNA gene sequences by PCR [23]. There was a focal and heterogeneous distribution of inflammation and infection in the RP specimens. In the prostate cancer and BPH groups there was a strong association of inflammation with positive PCR findings. The presence of bacteria and/or inflammation in RP specimens was a localized process. Concordance between inflammation and positive PCR results in RP specimens suggests that bacteria might often have a role in histologically inflammatory prostatitis caused by bacteria detectable through 16S rRNA [23].
EXPERIMENTAL STUDIES IN MICE

In a mouse model of chronic bacterial prostatitis induced by Escherichia coli it was shown that chronic inflammation induced by bacterial infection incites varying degrees of atypical hyperplasia and severe dysplasia in the prostate. This reactive hyperplasia and dysplasia occurred 12 weeks after inoculation and were associated with strong staining for oxidative DNA damage, and increased expression of Ki-67, a marker of epithelial cell proliferation [24]. Thus, that study suggests that chronic bacterial prostatic infection and inflammation can lead to neoplastic tissue alterations in the prostate.

DETECTION OF VIRAL PATHOGENS IN PROSTATIC SPECIMENS

Genomic screening of viral sequences in prostatic specimens of patients with prostatic carcinoma was done using a viral detection DNA microarray composed of oligonucleotides corresponding to the conserved sequences of all known viruses. There were γ-retroviral sequences in samples from seven of 11 Arg462Gln homozygous, vs one of eight Arg462Gln heterozygous and homozygous wild-type cases [25].

A further expanded survey of 86 tumours detected this viral genome in 40% of homozygous vs only 1.5% in heterozygous or wild-type cases. This new virus is closely related to xenotropic murine leukaemia viruses, and was therefore called xenotropic murine leukaemia-related virus. Interestingly, the viral sequences were found in 1% of stromal cells, predominantly fibroblasts and haematopoietic elements in regions adjacent to the carcinoma, but not in epithelial cells [25]. This finding also underlines the possible role of the stromal cells in the microenvironment for prostatic carcinogenesis, by producing proliferative signals or promoting oxidative stress.

CONCLUSION

Genetic and environmental factors influence the pathogenesis of prostatic carcinoma. Bacteria or viruses, or both, might be infectious triggers of an inflammatory cascade. Several gene products, e.g. RnaseL, MSR1 or TLR4, influence the susceptibility of prostate cells to infectious agents. The subsequent chronic inflammation produces inflammatory oxidants and could thus induce cell-and genome damage.

A new patho-morphological lesion, PIA, could be a connection between prostatitis and prostatic carcinoma. The loss of the GSTP1 detoxification function in the transition from PIA to PIN leads to an increased susceptibility of the prostatic cells to genomic damage by inflammatory oxidants or nutritional carcinogens. Consecutive somatic genome damage arises which modulates the further pathogenesis of prostatic carcinoma. These new findings could possibly significantly influence the prevention and treatment of prostatic carcinoma.

CONFLICT OF INTEREST

The authors state that there is no conflict of interest.

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Correspondence: Florian M.E. Wagenlehner, Department of Urology, Justus-Liebig-University Giessen, Rudolf-Buchheim-Str. 7, 35385 Giessen, Germany. e-mail: wagenlehner@aol.com

Abbreviations: CPPS, chronic prostatitis/pelvic pain syndrome; RP, radical prostatectomy; PIN, prostatic intraepithelial neoplasia; PIA, proliferative inflammatory atrophy; RNaseL, 2′-5′-oligoadenylate (2–5 A)-dependent RNase; MSR1, macrophage scavenger receptor 1; TLR4, Toll-like receptor 4.