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Prostate cancer and inflammation: the evidence

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Abstract

Chronic inflammation is now known to contribute to several forms of human cancer, with an estimated 20% of adult cancers attributable to chronic inflammatory conditions caused by infectious agents, chronic noninfectious inflammatory diseases and / or other environmental factors. Indeed, chronic inflammation is now regarded as an ‘enabling characteristic’ of human cancer. The aim of this review is to summarize the current literature on the evidence for a role for chronic inflammation in prostate cancer aetiology, with a specific focus on recent advances regarding the following: (i) potential stimuli for prostatic inflammation; (ii) prostate cancer immunobiology; (iii) inflammatory pathways and cytokines in prostate cancer risk and development; (iv) proliferative inflammatory atrophy (PIA) as a risk factor lesion to prostate cancer development; and (v) the role of nutritional or other antiinflammatory compounds in reducing prostate cancer risk.

Keywords

cytokines; diet; infections; inflammation; proliferative inflammatory atrophy; prostate cancer

Introduction

Prostate cancer will be diagnosed in approximately 240 890 US men in 2011, and an estimated 33 720 men will die from this disease.[1] While the death rate has been decreasing somewhat over the last decade, the absolute number of men with prostate cancer is projected to increase substantially as a result of the ageing baby boomer population. Thus, there is a critical need for a better understanding of the aetiological factors that drive prostate cancer development; knowledge which may be utilized for cancer prevention and treatment strategies.

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The most well-recognized risk factors for the development of prostate cancer are advanced age, family history and African American ancestry; however, there is also a distinct geographic distribution to prostate cancer incidence, and an apparent increase in risk with the adoption of a 'westernized' lifestyle. Clearly, the pathogenesis of prostate cancer involves environmental factors in addition to hereditary factors. One such potential environmental factor which has gained a great deal of recent attention is the development of chronic inflammation in the prostate due to a number of potential causes including infections, dietary factors, hormonal changes and / or other unknown environmental exposures.[2] The aim of this review is to summarize the current literature regarding a role for chronic inflammation in prostate cancer aetiology, with a specific focus on potential stimuli for prostatic inflammation, prostate cancer immunobiology, inflammatory pathways and cytokines in prostate cancer risk and development, proliferative inflammatory atrophy (PIA) as a risk factor lesion to prostate cancer development and the role of nutritional or other anti-inflammatory compounds in reducing prostate cancer risk.

Prevalence of prostatic inflammation

There are multiple different lines of evidence suggesting that inflammation is very common within the adult prostate. Prostatitis is a heterogeneous and complex entity which the National Institutes of Health (NIH) consensus classification refers to as chronic prostatitis / chronic pelvic pain syndrome (CPPS). CPPS is divided into the following four categories, the first three of which relate to men with symptoms of disease: (I) acute bacterial prostatitis; (II) chronic bacterial prostatitis; (III) chronic prostatitis / CPPS; and (IV) asymptomatic inflammatory prostatitis.[3] Bacterial prostatitis accounts for only an estimated 5–10% of prostatitis cases, with the most commonly implicated microorganisms being *Escherichia coli* and *Enterococcus* spp.[4,5] In terms of symptomatic 'prostatitis' (e.g. NIH categories I–III), it is estimated that up to 16% of men in the US population are afflicted at some time in their life.[4,6] The prevalence of asymptomatic prostatic inflammation (i.e. 'histological prostatitis') appears to be in fact much higher, as evidenced by studies examining men who undergo biopsy for prostate cancer due to elevated prostate-specific antigen (PSA) levels and test negative for cancer,[7–10] autopsy studies[11] and findings from transurethral resections for benign prostatic hyperplasia (BPH).[12] A recent example of this stems from results published from the baseline data of the REDUCE (REduction by DUtasteride of prostate Cancer Events) trial, where 80% of patient biopsies were found to have some degree of inflammation. [13] Similarly, results from a prospective randomized controlled trial of 328 men with PSA levels between 2.5 and 10 ng / ml and normal digital rectal examination (DRE) indicated that more than 45% of the patients had leucocytes in expressed prostatic secretions (EPS).[9] Finally, histological specimens of prostate cancer tissue frequently exhibit unexplained acute and chronic inflammation and inflammation-associated lesions.[2]

Evidence suggests there is also a racial and geographical difference in the prevalence of prostatic inflammation in adult men, which falls in line with the geographic distribution difference in prostate cancer incidence. For example, studies have reported an increased incidence of inflammation in biopsy specimens [14] and increased expression of immune-related genes in tumour tissues[15] from African American men compared to European

American men. Also, recent findings from our own group from an autopsy study revealed less inflammation in the prostates of Asian men as opposed to European American men (C. Joshu, A.M. De Marzo, M.S. Lucia, J.K. Parsons, C. Maggi-Galluzzi and E.A. Platz, unpublished data).

As will be discussed below in the section regarding the immunobiology of prostate inflammation, preliminary work indicates that there may also be a difference in the prevalence of prostatic inflammation which correlates to risk of high-grade prostate cancer (B. Gurel, M.S. Lucia, E.A. Platz and A.M. De Marzo, manuscript in preparation). These preliminary studies revealed that chronic inflammation in benign tissue of a needle biopsy was predictive of a higher risk for prostate cancer diagnosis and specifically with higher-grade (Gleason score 7–10) disease.

Contributors to prostatic inflammation

Multiple different aetiological agents are thought to contribute to the initiation of prostatic inflammation, including infections, dietary factors, corpora amylacea (and associated physical trauma), hormonal changes and urine reflux.[2] Here we focus on recent evidence regarding the role of infections, diet and corpora amylacea in prostatic inflammation and cancer development.

A POTENTIAL LINK BETWEEN PROSTATITIS, PROSTATE INFECTIONS AND PROSTATE CANCER

Multiple different bacterial species are known to infect the human prostate and induce inflammation, and many of these organisms have been identified from studying patients with bacterial prostatitis. Interestingly, in the study referred to above by Ugurlu *et al.*[9] regarding the incidence of leucocytes in EPS from patients with elevated PSA levels, the patients with leucocyte-positive EPS were randomized into antibiotic (levofloxacin), anti-inflammatory (naproxen sodium) and control treatment groups. Only the antibiotic-treated patients exhibited a significant decrease in PSA levels, suggesting a potential contribution from an unrecognized prostatic infection.

As mentioned previously, the most commonly implicated microorganisms in bacterial prostatitis are *E. coli* and *Enterococcus* spp.; however, additional organisms such as *Pseudomonas* spp., *Proteus mirabilis*, *Klebsiella* spp. and *Serratia* spp. have also been identified.[4,5] Several sexually transmitted organisms have also been implicated in bacterial prostatitis or prostatic inflammation, and these include *Chlamydia trachomatis*, Gonococcal organisms, *Trichomonas vaginalis* and *Treponema pallidum* (reviewed in Ref. 2,16). *Mycoplasma* spp. have also been implicated in chronic prostatitis.[17,18]

Studies attempting to define a potential correlation between prostatitis and prostate cancer risk have reported both positive[19,20] and negative results[21] (also reviewed in Ref. 22). A very recent study performed in a large, multiracial and ethnic cohort as part of the California Men's Health Study (CMHS) found an increase in risk for prostate cancer with a history of prostatitis [relative risk (RR) = 1.30; 95% confidence interval (CI): 1.10–1.54] and long duration of prostatitis symptoms.[23] This study also found that a self-reported reported

history of sexually transmitted disease (STD) was not associated with overall prostate cancer risk; however, Latinos reporting a history of STDs had an increased risk of prostate cancer compared to Latinos with no STD history. Furthermore, foreign-born Latinos were found to have a greater risk of prostate cancer associated with STD history than US-born Latinos.[23] Although the authors report that this study could have potentially been confounded by detection bias (e.g. men with symptomatic prostatitis may seek medical attention, which may in turn lead to a greater chance for testing and incidental detection of prostate cancer), the association between prostatitis and prostate cancer risk certainly remains an important area for further research.

There are also several lines of evidence that support a potential role for asymptomatic (i.e. subclinical) prostatic inflammation caused by infectious microorganisms and prostate cancer development. An organism of particular interest in this respect is *E. coli*. Apart from being one of the most frequently isolated microorganisms from patients with bacterial prostatitis, *E. coli* has also been identified in both BPH and prostate cancer tissues using both culture-dependent and culture-independent molecular techniques.[24,25] In mouse models, infection of the prostate with uropathogenic strains of *E. coli* (UPEC) has been reported to induce epithelial proliferation and reactive hyperplasia,[26] dysplasia and oxidative DNA damage[27] and a marked reduction of the haploinsufficient prostate cancer tumour suppressor, NKX3.1.[28] A recent study in Wistar rats described prostatic epithelial hypertrophy and atrophy in response to UPEC *E. coli* infection, with a transient upregulation of ErbB2 [human epidermal growth factor receptor 2 (HER2 / *neu*)].[29] Different strains of UPEC *E. coli* produce a number of virulence factors, such as cytotoxic necrotizing factor 1 (CNF1), which has been shown to promote tissue damage in a rat model of prostatitis.[30] Furthermore, strains of pathogenic *E. coli* which harbour a '*pks*' genomic island responsible for synthesis of a peptide–polyketide hybrid cytotoxin (termed colibactin) have been shown to induce DNA double-strand breaks (DSBs) in human cells.[31] Strains of *E. coli* which are implicated in urosepsis have been shown to frequently harbour both CNF1 and the *pks* island.[32] Intriguingly, in a recent study examining *E. coli* isolates from patients presenting with acute bacterial prostatitis, more than 70% of isolates were found to express colibactin and one strain carried the cytolethal distending toxin (CDT) gene cluster.[33] The authors of this study posit that the production of genotoxic toxins by *E. coli* implicated in acute bacterial prostatitis could contribute to subsequent carcinogenesis and potentially explain the epidemiological data suggesting an increased risk for prostate cancer with previous history of prostatitis.[33] For reasons such as those described here, *E. coli* should remain an organism of particular interest in regards to a potential link between prostatic inflammation and prostate cancer development.

Additional microorganisms (both bacterial and viral) have been implicated in stimulating prostatic inflammation that may contribute to the development of prostate carcinogenesis. For example, *C. trachomatis* has been detected in prostatitis,[34] BPH[35] and prostate cancer,[36] although multiple epidemiological studies have reported no association between *C. trachomatis* seropositivity and prostate cancer risk.[37–39] Studies have shown that *C. trachomatis* can infect rat prostate epithelial cells *in vitro*, leading to the production of proinflammatory cytokines and chemokines.[40,41]

Another bacterial species that has gained recent attention in the prostate cancer field is *Propionibacterium acnes*, a proinflammatory bacterium that is considered to be the aetiological agent in the skin condition acne, as well as several other inflammatory conditions including endocarditis and post-surgical infections.[42] *P. acnes* was first reported in association with prostate inflammation and cancer in 2005,[43] and several subsequent studies have also identified *P. acnes* in prostate specimens.[24,44–46] The potential association between acne and / or plasma antibodies to *P. acnes* and prostate cancer incidence and outcomes has been examined in multiple epidemiological studies.[47–49] In 2005, Galobardes *et al.*[47] reported on an investigation involving the Glasgow Alumni Cohort Study whereby a reported history of acne in young adulthood was associated with an increased risk of prostate cancer mortality [hazard ratio (HR) = 1.67, 95% CI: 0.79–3.55]. In 2007, Sutcliffe *et al.*[48] reported that men with a history of tetracycline use for four or more years (as a measure of previous history of severe acne) had a significantly higher risk of prostate cancer (multivariable-adjusted RR = 1.70, 95% CI: 1.03–2.80). In contrast, a study in 2010 by Severi *et al.*[49] reported an inverse association between *P. acnes* antibody titres and prostate cancer risk [e.g. higher concentrations of circulating *P. acnes* antibodies were associated with decreased prostate cancer risk, odds ratio (OR) = 0.73, 95% CI: 0.58–0.91], which was especially pronounced for advanced prostate cancer (OR = 0.59, 95% CI: 0.43–0.81). Here, the authors assert that the potential role that *P. acnes* may play in prostate cancer might be a protective one, in that immune responses elicited against *P. acnes* may be tumoricidal.

Recent evidence suggests that infection by the protozoan *T. vaginalis*, the causative sexually transmitted infection (STI) agent of trichomoniasis, may contribute to asymptomatic prostatic inflammation as well as prostate cancer risk (reviewed in Ref. 16). A positive association between *T. vaginalis* serostatus and both overall prostate cancer risk (OR = 1.43, 95% CI: 1.00–2.03) as well as high-grade disease (OR = 1.76, 95% CI: 0.97–3.18) was first reported by Sutcliffe *et al.*[50] in 2006 in a case–control study in the Health Professionals Follow-up Study (HPFS). This association was not present in a subsequent study conducted in the Prostate Cancer Prevention Trial (PCPT)[51]; however, a positive association with measures of advanced cancer (extraprostatic extension, metastatic prostate cancer) was again observed in the Physicians' Health Study (PHS).[52] Although attempts to detect *T. vaginalis* via molecular techniques do not indicate that the organism is readily detectable in *ex vivo* prostate tissue biopsies from prostate cancer patients,[24] the epidemiological findings may warrant further investigations into potential mechanisms by which *T. vaginalis* might contribute to prostate cancer risk, and specifically risk of advanced disease.

Another indication that STIs may infect the prostate and contribute to prostatic inflammation stems from recent studies suggesting an increase in serum PSA levels in men with a confirmed diagnosis of an STI. In 2006, Sutcliffe *et al.*[53] reported that men with laboratory-confirmed exudative STIs, including gonorrhoea, chlamydia and trichomonosis, were significantly more likely to have increased PSA levels. In another recent study in 2011, Sutcliffe *et al.*[54] again reported that men with active infections of chlamydia and gonorrhoea were likely to have a large rise in PSA, further indicating prostate involvement with STIs. While it is not entirely clear why serum PSA levels are elevated after infection with these organisms, the most straight-forward mechanism would be that infection of the prostate

leads to prostatic inflammation and damage to prostate epithelial cells, resulting in release of PSA extracellularly that, in turn, is released into the circulation.

It has been suggested that a newly discovered gammaretrovirus, termed xenotropic murine leukaemia virus-related virus (XMRV), may also act as an aetiological agent in prostatic inflammation.[55] This virus was first reported in association with prostate cancer in 2006;[56] however, the likelihood that XMRV ever establishes a true infection in humans has become the subject of intense controversy.[57,58] Indeed, very recent evidence suggests that XMRV originated from a recombination event between two endogenous murine retroviruses during the passage of the CWR22 prostate cancer xenograft in mice.[59,60] Furthermore, mouse DNA contamination of samples and common laboratory reagents has now been shown to be a potential source of false-positive polymerase chain reaction (PCR) results for XMRV.[61–64] Currently, therefore, we suggest that the likelihood that XMRV is playing any role in human prostate cancer initiation or progression is exceedingly small.

DIET

Although a later section of this review will focus on the evidence for anti-inflammatory dietary components in prostate cancer prevention, evidence also exists that suggests a potential role for certain dietary factors in promoting prostatic inflammation and prostate cancer development.[65] In this regard, much attention has been given to a class of dietary mutagens called heterocyclic amines (HCAs), to which humans are exposed under common dietary practices. HCAs are generated in abundance in meats cooked under high temperature conditions and have been linked to cancer of multiple organs including prostate, colon and breast.[66] In prostate cancer, a particular focus has been given to the cancer-inducing capabilities of the heterocyclic amine 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP). Although not all studies are positive, a number of epidemiological studies have linked the consumption of meat and very well-cooked meat with risk of overall prostate cancer and / or aggressive prostate cancer.[66–71] In rodents, dietary intake of PhIP represents one of the few animal models which results in prostatic intraepithelial neoplasia (PIN) lesions and intraductal carcinoma,[72,73] providing further evidence of a potential role of dietary intake of PhIP in human prostate cancer. In a recent study, conducted in a transgenic Fisher344 (Big Blue) rat model, PhIP consumption was shown to induce elevated mutation frequencies in all lobes of the prostate.[73] PhIP-induced cancerous lesions are restricted to the ventral lobe of the rat prostate, however, and in this study an increase in stromal mast cells and macrophages that was restricted to the ventral prostate was observed. This study represents experimental evidence whereby lobe-specific inflammation was shown to be induced in response to PhIP consumption, and it was suggested that this represents a potential new mechanism by which dietary PhIP can increase cancer risk (i.e. by prompting inflammation). Interestingly, while the inflammation did not appear restricted to the ventral lobe, Borowsky *et al.*[74] also reported that PhIP-induced PIN lesions in the rat prostate were preceded by inflammatory infiltrates.

Another line of indirect experimental evidence which supports a role for dietary-induced inflammation in prostate cancer development is contained in reported results from the PCPT. Here, study participants who consumed the highest amounts of polyunsaturated fats were

found to have an increased risk of high-grade (Gleason score 8–10) prostate cancer.[75] Whereas several recent large-scale US and European cohort studies have not found a positive association between high fat intake and prostate cancer risk,[76–78] a study in heavy smokers with a family history of prostate cancer found a substantially increased risk of prostate cancer associated with high polyunsaturated fat consumption.[79] A major constituent of dietary polyunsaturated fats in western diets are n-6 fatty acids, primarily in the form of linoleic acid (LA).[80] LA is metabolized into arachidonic acid, which can in turn be transformed into the proinflammatory eicosanoids prostaglandin E_2 (PGE_2) and leukotriene B_4 (LTB_4). The potential increase in prostate cancer risk found with high dietary intake of n-6 fatty acids may, therefore, be mediated through their effect on oxidative stress and inflammation.

CORPORA AMYLACEA AND CALCULI

Prostatic corpora amylacea and calculi are tiny laminated bodies and calcified stones, respectively, which are observed frequently in the adult prostate. Both corpora amylacea and calculi, which apparently represent calcified corpora amylacea, are postulated to cause physical trauma to glandular epithelium with the subsequent induction of focal acute and chronic inflammation and gland occlusion (Figure 1A).[2,81] A study published in 2009 reported that the organic matrix of corpora amylacea and calculi is largely comprised of proteins involved in acute inflammation, and specifically proteins contained at high levels in neutrophil granules including lactoferrin, calprotectin, myeloperoxidase and α-defensins (Figure 1B,C).[82] These findings suggest that corpora amylacea and calculi, which are highly prevalent in prostates of older men, may represent lasting remnants of past acute inflammatory events. Another study published a few months later reported largely similar findings regarding the identification of proteins involved in acute inflammatory pathways in corpora amylacea.[83] Intriguingly, this study also identified both DNA and proteins from *E. coli* in corpora amylacea samples.

The immunobiology of prostate inflammation

The inflammation identified histologically in prostate cancer tissues is most commonly chronic, being chiefly comprised of lymphocytes as well as macrophages, and less frequently of plasma cells and eosinophils. Acute inflammation is present to a lesser extent and is comprised primarily of neutrophils. Just as the stimuli for prostatic inflammation are largely yet to be defined, our understanding of prostate immunobiology is still relatively poor. Over the past few years, however, there have been several recent advances in the characterization of the inflammatory cell types infiltrating the prostate.

IMMUNE REGULATORY CELLS

Regulatory T cells (T_{reg}) are a subset of $CD4^+$ T cells which act in the suppression of autoreactive T cells and prevention of autoimmunity. T_{reg} were identified initially by high coexpression of CD4 and CD25 surface markers ($CD4^+CD25^{high}$ cells); however, CD25 is also elevated on activated T cells. T_{reg} are currently defined by the expression of the forkhead family transcription factor FoxP3. In light of their role in immune suppression, T_{reg} have been investigated for a role as suppressors of antitumour immune responses.[84]

Infiltrating T_{reg} have been identified in a number of solid tumours, and in some instances the presence of these cells correlates with poor prognostic outcome (reviewed in Ref. 85). $CD4^+CD25^{high}$ T cells were first reported in tumour tissues and peripheral blood of prostate cancer patients in 2006.[86] In this study, T cells outgrown from prostate tumour tissues were found to have elevated numbers of $CD4^+CD25^{high}$ T cells in comparison to matched normal prostate tissues. Furthermore, this study reported elevated numbers of $CD4^+CD25^{high}$ T cells in the peripheral blood of prostate cancer patients compared to normal donors. A subsequent study published in 2008 confirmed these findings, showing a relative enrichment of $CD4^+FoxP3^+$ T_{reg} in prostate tissues of cancer patients with respect to peripheral blood.[87] Another study published in 2009 demonstrated $CD25^+$ and $FoxP3^+$ cells in lymphocyte clusters surrounding prostate cancer lesions via immunohistochemistry (IHC).[88] Additional studies have reported an increase in the suppressive function of T_{reg} isolated from the peripheral blood of prostate cancer patients as opposed to normal donors,[89] the expression of FoxP3 in prostate cancer cell lines[90] and the presence of $CD8^+$ $FoxP3^+$ cells in prostate tumours.[91]

While the significance of elevated levels of T_{reg} in the prostate remains unclear, the presence of infiltrating T_{reg} in prostate tumours may have significant implications with regard to the design and potential efficacy of prostate cancer immunotherapy strategies. In the same respect, another molecule of potential interest is the inhibitory receptor programmed death 1 (PD-1), a cell-surface protein associated with inhibition of T cell responses. A number of human tumours have been found to express PD-1L (B7-H1),[92] and expression of PD-1 on cytotoxic T lymphocytes (CTL) inhibits antitumour effector function. [93] Very promising results are arising from clinical trials based on treatment strategies utilizing monoclonal antibodies for PD-1 blockade for multiple forms of advanced malignancies.[94,95] Anti-PD-1 treatment strategies may also prove to be beneficial in prostate cancer therapeutic strategies, as prostate-infiltrating lymphocytes have been found to express PD-1.[88,96] The first study to demonstrate the presence of $PD\text{-}1^+$ cells in prostate cancer tissues utilized IHC with an anti-PD-1 antibody to demonstrate that lymphocyte clusters surrounding prostate tumours contained both $PD\text{-}1^+$ and $B7\text{-}H1^+$ cells.[88] A second study specifically analysed tumour-infiltrating $CD8^+$ T cells and demonstrated by flow cytometry that PD-1 was up-regulated on prostate-infiltrating $CD8^+$ cells in comparison to matched peripheral blood samples. In some patients, up to 90% of prostate-infiltrating $CD8^+$ T cells expressed PD-1,[96] with potentially major implications in prostate cancer immunotherapy strategies.[97]

T HELPER TYPE 17 (TH17) CELLS

A newly discovered $CD4^+$ effector T cell lineage, termed Th17 cells, has been described which develops through distinct cytokine signals [specifically interleukin (IL)-23] and are characterized by the production of IL-17.[98] Th17 cells are thought to be the key mediators in a number of autoimmune diseases, and may play a role in inflammation-associated cancer.[98,99] The role of Th17 cells in cancer is currently a topic of significant debate, as there appear to be conflicting reports as to whether Th17 cells promote carcinogenesis or play a role in antitumour immunity.[100] In prostate cancer, increased expression of IL-17 at the mRNA level was shown in tissue from both prostate cancer and BPH before it was

known that Th17 T cells represent a distinct CD4 effector T cell lineage.[101] A study published in 2008 reported a significant skewing of prostate-infiltrating $CD4^+$ T cells towards a Th17 phenotype.[87] Interestingly, this study found a statistically significant inverse correlation between Th17 skewing and tumour grade. Although this study was conducted in a relatively small patient set ($n = 20$),[87] these findings are in agreement with other studies that find a protective role for Th17 cells with regard to tumour immunity (reviewed in Ref. 100). Another recent study found that the generation of an IL-17-associated progressive autoimmune response resulted in rejection of the TC2 tumour in C57BL / 6 mice.[102] In contrast, in a recent study in patients with advanced prostate cancer who were undergoing immunotherapy, higher levels of $CCR4^-IL\text{-}17^+CD4^+$ T cells in the patient's peripheral blood pre-therapy corresponded significantly to decreased time to disease progression. [103] Although the potential relationship between elevated levels of Th17 cells in the peripheral blood, which can also be due to underlying infection or inflammation, and prostate tumour-infiltrating lymphocyte populations is unclear, these studies warrant further evaluation of the protective versus tumour-promoting roles that Th17 cells may play with regard to prostate cancer immunobiology.

In terms of inflammation being associated with a procarcinogenic environment, a number of studies have suggested that inflammation in and around prostate cancer is associated with worse disease outcome.[104,105] Further, recent work found that chronic inflammation in benign tissue of a patient biopsy was predictive of a higher risk for prostate cancer diagnosis (OR = 1.79, 95% CI: 1.06–3.04), and specifically with higher-grade (Gleason score 7–10) disease (OR = 2.41, 95% CI: 1.17–4.95). The risk of prostate cancer and high-grade prostate cancer also increased with the number of biopsies that were found to contain chronic inflammation (B. Gurel, M.S. Lucia, E.A. Platz and A.M. De Marzo, manuscript in preparation). These data raise the intriguing possibility that chronic inflammation in benign areas of the prostate may contribute to the development of high-grade disease. Further evidence for a role for chronic inflammation and prostate cancer development has been presented above in the context of inflammatory stimuli in the prostate and will be discussed in further detail below in the context of genetic polymorphisms in inflammatory pathways and cytokines in prostate cancer.

Inflammation pathways and cytokines in prostate cancer

A great deal of literature has addressed the role of genetic polymorphisms in inflammation pathways and the production of inflammatory cytokines with regard to prostate cancer risk and promotion. In the following sections we will address recent literature in these areas, as opposed to summarizing the body of literature as a whole, for which there are many relevant review articles.[2,22,106,107]

GENETIC POLYMORPHISMS IN INFLAMMATIONRELATED GENES AND PATHWAYS

Over the past few years, and with recent advances in sequencing and genotyping technologies, the number of studies that have reported on the association between one or multiple single nucleotide polymorphisms (SNPs) in inflammation-related pathways and prostate cancer risk has greatly increased. Licastro *et al.*[108] recently reported an interesting association between a SNP (GG genotype) in the promoter region of alpha-1-

antichymotrypsin (ACT) and increased risk of prostate cancer (age-adjusted OR = 2.676, CI: 1.375–5.205). A correlation between circulating levels of PSA and the ACT GG genotype was also reported in younger prostate cancer patients. ACT is an acute-phase protein which is up-regulated in response to inflammation. ACT is also a serine protease inhibitor, and most circulating PSA is bound to ACT. Another recent case–control study in the Risk Factors for Prostate Cancer Study examined a cytokine-rich region at 5q31.1 which has been implicated previously as a potential prostate cancer risk loci, and found a modest association between two alleles of IL-4 and prostate cancer risk and no association between IL-5 or IL-13.[109] The associations with IL-4 were not present in another large case–control study (the Melbourne Collaborative Cohort Study); however, the authors report that one of the IL-4 alleles (rs2243250 genotype) led to a decrease in IL-4 activity, potentially pointing to an antitumour function of IL-4 in prostate cancer risk.[109]

A number of recent studies have also attempted to correlate the potential interaction of SNPs between multiple different cytokines in conferring an increased risk of prostate cancer. In 2008, Zabaleta *et al.*[110] examined nine SNPs in three cytokines [IL-1B, IL-10, tumour necrosis factor (TNF)] in a case–control study of African American versus Caucasian men. This study found an increased combined risk of prostate cancer in African Americans carrying variants in IL-1B (IL1B–511CT / TT) and IL-10 (IL10–592CC) (OR = 2.56, 95% CI: 1.09–6.02). Similarly, in Caucasians, a higher risk of prostate cancer was associated with the combinations of variants of IL-1B (IL1B–31TT / TC) and IL-10 (IL10–1082AA) (OR = 2.92, 95% CI: 1.13–7.55), as well as IL-10 (IL10–592AA) and TNF (TNF–238GG) (OR = 2.14, 95% CI: 1.05–4.38). In 2009, this same group evaluated 15 SNPs in five cytokine genes (IL-1B, IL-10, TNF-α, IL-6 and IL-8) in relation to risk of aggressive prostate cancer (Gleason sum ≥8 or PSA >20 ng / ml or Gleason sum ≥7 and clinical stages T3–T4) in African Americans and Caucasians.[111] Using the multivariate adaptive regression splines (MARS) form of regression analysis, this study found an association between aggressive prostate cancer and an IL-8 (IL8–47CT) genotype (OR = 3.50; 95% CI: 1.13–10.88) as well as an increased risk with combined genotypes in IL-1B (IL1B–511CC) and IL-10 (IL10–1082GG) (OR = 3.38; 95% CI: 1.70–6.71) in Caucasian men. Unfortunately, the numbers of African American men in this study were not large enough for analysis. Interestingly, both studies found an association between increased risk for prostate cancer or aggressive prostate cancer and the IL10–1082GG variant of IL-10 alone.[110,111] Another recent study which undertook a similar approach examined 143 SNPs in 16 inflammation-related genes [CXC ligand 12 (CXCL12), IL-4, IL-6, IL-6ST, prostaglandin-endoperoxide synthase 2 (PTGS2), signal transducer and activator of transcription 3 (STAT3), TNF, protein kinase B (AKT1), CXCR4, IL-6R, IL-8, IL-10, nuclear factor kappa B (NFκB), phosphatidylinositol 3-kinase (PIK3)R1, PTGS1 and vascular endothelial growth factor (VEGF)] in a case–control study of African American versus Caucasian men.[112] The authors reported that SNPs in IL-4, IL-6ST, PTGS2 and STAT3 were associated significantly and independently with prostate cancer susceptibility, and that SNPs in AKT1, PIK3R1 and STAT3 were associated with aggressive prostate cancer. Furthermore, this study reported that men carrying multiple ‘high-risk’ alleles are at an elevated risk for prostate cancer development. These studies collectively underline the potential importance of the interactions between inflammatory cytokines and inflammation pathways in conferring prostate cancer risk.

COX-2

Another inflammation-related molecule that has generated a great deal of interest with regard to prostate cancer is cyclooxygenase 2 (COX-2, also known as PTGS2). This enzyme is an inducible isoform of the enzymes that convert arachidonic acid to proinflammatory prostaglandins (see previous discussion regarding n-6 fatty acids). Previous reports have indicated that COX-2 may be overexpressed in prostate cancer;[113,114] however, overexpression of this enzyme may in fact be limited to areas of proliferative inflammatory atrophy (PIA), a predicted risk factor lesion to prostate cancer, [115] which will be discussed in detail below. A large range of recent literature has been published regarding the association of SNPs in PTGS2 and prostate cancer risk, and a summary of this literature is provided in Table 1.[112,116–124] The diagnostic and prognostic value of CpG island hypermethylation at PTGS2 is also an area of active current investigation.[125–129] COX-2 remains a molecule of particular interest in the link between inflammation and prostate cancer.

CYTOKINES IN PROSTATE CANCER

Aside from genotyping studies, multiple inflammatory cytokines have been identified as potential mediators in an interplay between prostatic inflammation and prostate carcinogenesis. One such cytokine is macrophage inhibitory cytokine 1 (MIC-1), a member of the transforming growth factor-β (TGF-β) superfamily identified initially using a subtraction cloning approach used to discover genes associated with macrophage activation.[130] Studies have demonstrated the up-regulation of MIC-1 in prostate cancer,[131,132] and recent evidence also suggests that circulating levels of MIC-1 predicts poor prostate cancer prognosis.[133] It has been suggested that MIC-1 may be a key molecule linking macrophages to prostate cancer pathogenesis.[134]

IL-6 is a multifunctional cytokine which is involved in numerous innate and adaptive inflammatory processes, including B cell activation, acute-phase inflammatory response and thrombopoiesis.[135] IL-6 is produced by multiple cell types, including macrophages, endothelial cells and T lymphocytes. Deregulation of IL-6 is also known to play a role in multiple disease processes, including autoimmune disorders, rheumatoid arthritis, osteoporosis, psoriasis, diabetes, atherosclerosis and cancer.[136,137] In prostate cancer, multiple lines of evidence point to a contributory role of IL-6 in cancer initiation and / or progression: (i) IL-6 and IL6-R can be produced by prostate cells and up-regulation of IL-6 and IL-6R has been detected in malignant epithelium and high-grade prostatic intraepithelial neoplasia (PIN),[138] (ii) circulating levels of IL-6 are elevated in patients with metastatic prostate cancer and hormone-refractory prostate cancer (reviewed in Ref. 139), (iii) IL-6 has been shown to be correlated with measures of prostate cancer morbidity[140] and (iv) IL-6 may function in activation of androgen receptor (AR).[141] Furthermore, an intriguing study was published recently by Iliopoulos *et al.*[142] that presented evidence for a positive feedback loop between inflammation and IL-6 activation, STAT3 activation and NF-κB activation in cancer which maintains cells in an ‘epigenetic transformed’ state. IL-6 remains a particular cytokine of interest in prostate cancer aetiology, and especially with regard to a potential contribution of deregulated and / or systemic IL-6 levels to advanced prostate cancer and disease progression.

In 2010, a study from the laboratory of Michael Karin was published regarding a potential role for B cell-derived lymphotoxin in the development of hormone-refractory prostate cancer.[143] This group found that IKK-β ablation in prostate epithelial cells in the transgenic adenocarcinoma of the mouse prostate (TRAMP) mouse model had no effect on the development or progression of androgen-independent cancer. In contrast, ablation of IKK-β in bone marrow-derived cells in animals allografted with myc-CaP cells delayed the development of castration-resistant cancer after castration. The authors discovered that regressing tumours in castrated animals were infiltrated with T and B lymphocytes. Interestingly, previous studies in human prostate cancer patients have also demonstrated that androgen ablation results in the infiltration of leucocytes into the prostate.[144] It was determined that IKK-β ablation in bone marrow-derived cells abrogated lymphotoxin expression by B cells. Further studies involving transplanted bone marrow from mice lacking lymphotoxin in either B or T cells into irradiated mice demonstrated that lymphotoxin-β ablation in B cells delayed the growth of castration-dependent cancer.[143] Very few studies regarding lymphotoxin and prostate cancer had been published prior to the *Nature* paper in 2010. Intriguingly, a study published by Zhou *et al.*[145] in 2009 demonstrated that a targeted deletion of lymphotoxin-α in T cells in TRAMP mice inhibited the development of spontaneous tumours and had a profound impact on metastasis. A study by Liu *et al.* in 2006[146] reported that a functional polymorphism in the lymphotoxin-α gene conferred increased protection from prostate cancer development with non-steroidal anti-inflammatory drug (NSAID) use. Lymphotoxin may, therefore, be an important inflammatory cytokine driving prostate cancer progression.

PIA as a precursor lesion to prostate cancer

In response to unknown stimuli, regions of prostatic atrophy, which are generally associated with inflammatory cell infiltrates, develop at a very high frequency to encompass large regions of the prostate in some men (Figures 2 and 3). These regions, referred to as proliferative inflammatory atrophy (PIA), contain atrophic epithelial cells that appear to be regenerating in response to cellular damage.[147] Furthermore, these atrophic lesions, which frequently merge with the recognized direct precursor to many prostatic adenocarcinomas, high-grade PIN, have some of the hallmark somatic genome alterations found in prostate cancer and PIN and have been proposed as ‘risk factor lesions’ for the development of prostate cancer.[2,148,149] Morphological transitions between PIA, PIN and prostate cancer have been described previously.[149] In 2009, a report by Wang *et al.*[150] also documented the morphological transition between PIA and PIN as well as PIA and prostate cancer. In this study, serial sections of whole-mount prostates were examined from 50 cases, and 17% of PIN lesions were found to be in the morphological process of merging with PIA in 70% of the prostates examined. Furthermore, instances of PIA directly merging with cancer were identified in 28% of the cases. The authors state that merging lesions were ‘closely adjacent to areas with chronic inflammation, suggesting that it may have a role to play in this process’.[150]

As mentioned previously, further evidence that PIA may be a direct precursor to PIN and / or cancer stems from the fact that PIA has some of the hallmark gene expression changes found in prostate cancer and PIN. For example, two genes which are highly expressed in

normal prostate epithelium and frequently down-regulated or absent in PIN and prostate cancer, NKX3.1 and p27, are down-regulated in prostate atrophy. [2,147,151] Another recent study reported increased p53 immunostaining in PIA lesions, especially in areas of acute inflammation.[152] Although the technique used could not differentiate between wild type and mutated p53, the authors showed that p53-positive areas correspond to a high proliferation index (Ki-67), CK5 expression, overexpression of COX-2 and high levels of glutathione *S*-transferase-π (GSTP1) in the same lesion. Nakayama *et al.*[153] found previously that methylation of deoxycytidine residues within the cytosine–guanine– dinucleotide (CpG) island near the *GSTP1* promoter region, which occurs in nearly all prostatic adenocarcinomas (approximately 90% in this study) and most PIN lesions (approximately 70%), occurred in 6.4% of atrophy lesions. While this is relatively infrequent, as atrophy / PIA is highly prevalent and often quite extensive in the peripheral zone of the prostate these findings are consistent with the possibility that a significant fraction of PIN and / or adenocarcinoma lesions may indeed originate in these atrophic lesions.[153]

Anti-inflammatory compounds and prostate cancer risk

DIETARY ANTIOXIDANTS

Some intriguing epidemiological evidence for the role of inflammation in prostate cancer aetiology comes from studying the correlation between dietary or medicinal intake of anti-inflammatory compounds and prostate cancer risk. In this respect, both soy and green tea have anti-inflammatory properties and have been shown to be associated with decreased prostate cancer risk in human epidemiology studies and to decrease prostate cancer in animal studies (reviewed in Ref. 154). Interestingly, a recent study in prostate cancer cell lines demonstrated that treatment with phytoestrogens (genistein and daidzein) resulted in demethylation of GSTP1 and ephrin B2 (EPHB2) promoter regions.[155] The authors of this study suggest that the protective effects of soy in prostate cancer prevention may involve epigenetic modifications to DNA. Previous studies have also shown a significant correlation between the consumption of tomato products and decreased prostate cancer risk (reviewed in in Ref. 156). A study published in 2010 reported increased survival, delayed progression from PIN to cancer and decreased incidence of poorly differentiated cancer in TRAMP mice fed a diet enriched with processed whole tomatoes.[157] Interestingly, this study found that serum concentrations of several cytokines (such as IL-6-family cytokines IL-6, oncostatin M and IL-11) were reduced significantly in animals fed the tomato-enriched diet. Just as proinflammatory n-6 polyunsaturated fatty acids (PUFA) may confer an increased risk of prostate cancer, the anti-inflammatory n-3 (omega 3) PUFA has been associated with a decreased risk (reviewed in Ref. 158), although dietary n-3 polyunsaturated fatty acids failed to reduce prostate tumorigenesis in a preclinical mouse model.[159] A recent case–control study found a strong association between high intake of long chain n-3 PUFA and decreased risk of aggressive prostate cancer.[158] Furthermore, this study identified a SNP in the COX-2 gene that, along with low dietary intake of n-3 PUFA, had an increased risk of prostate cancer (OR = 5.49; 95% CI: 1.80–16.7). Interestingly, this association was decreased with increased intake of n-3 PUFA.[158]

NSAIDS

Multiple epidemiological studies have reported a reduced risk of prostate cancer with NSAID use, possibly by inhibition of the COX-2 enzyme. However, other studies have reported no association. A recent meta-analysis of the reported literature on this topic concluded that NSAID use may reduce the risk of prostate cancer; however, the effect is small.[160] Another large case–control study recently found a reduction in prostate cancer risk for current aspirin users, daily users of low-dose aspirin and long-term users of aspirin, as opposed to non-users.[161] There was an effect modification identified for a COX-2 SNP; however, prostate cancer risk was not reduced by any other form of NSAID or acetaminophen.

Summary and conclusions

In summary, a number of separate lines of research have pointed to a potential role for inflammation in prostatic carcinogenesis and tumour progression. These lines involve epidemiological, genetic, histopathological, molecular pathological and animal studies. Future studies in all of these areas will be needed to ultimately elucidate the precise mechanisms that may prove useful for the development of novel strategies to target the inflammatory process in preventing either prostate cancer outright or preventing progression of established prostate cancer.

Abbreviations

ACT	alpha-1-antichymotrypsin
BPH	benign prostatic hyperplasia
CNF1	cytotoxic necrotizing factor 1
CPPS	chronic pelvic pain syndrome
DRE	digital rectal examination
EPS	expressed prostatic secretins
HCA	heterocyclic amine
IHC	immunohistochemistry
LA	linoleic acid
MIC-1	macrophage inhibitory cytokine 1
NSAID	non-steroidal anti-inflammatory drug
PAH	post-atrophic hyperplasia
PCPT	Prostate Cancer Prevention Trial
PD-1	programmed death 1
PhIP	2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine
PIA	proliferative inflammatory atrophy

PIN	prostatic intraepithelial neoplasia
PSA	prostate-specific antigen
PUFA	polyunsaturated fatty acids
SNP	single nucleotide polymorphism
STD	sexually transmitted disease
STI	sexually transmitted infection
UPEC	uropathogenic strains of *E. coli*
XMRV	xenotropic murine leukaemia virus-related virus

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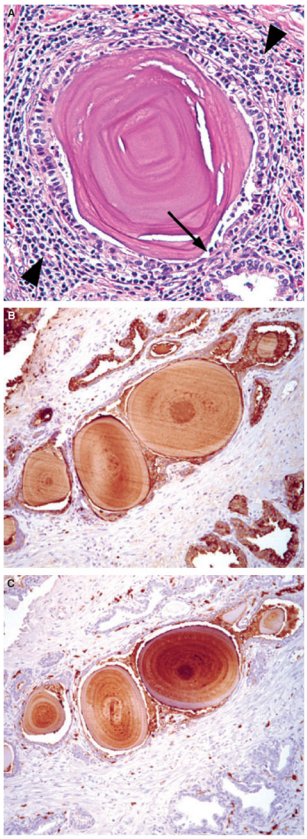

Figure 1.

(**A**), Example of prostatic corpora amylacea. Note physical trauma to glandular epithelium (arrow) and associated surrounding focal chronic inflammation (arrowheads). Immunohistochemistry (IHC) for lactoferrin (**B**) and calprotectin (**C**) on prostate tissue sections containing corpora amylacea.

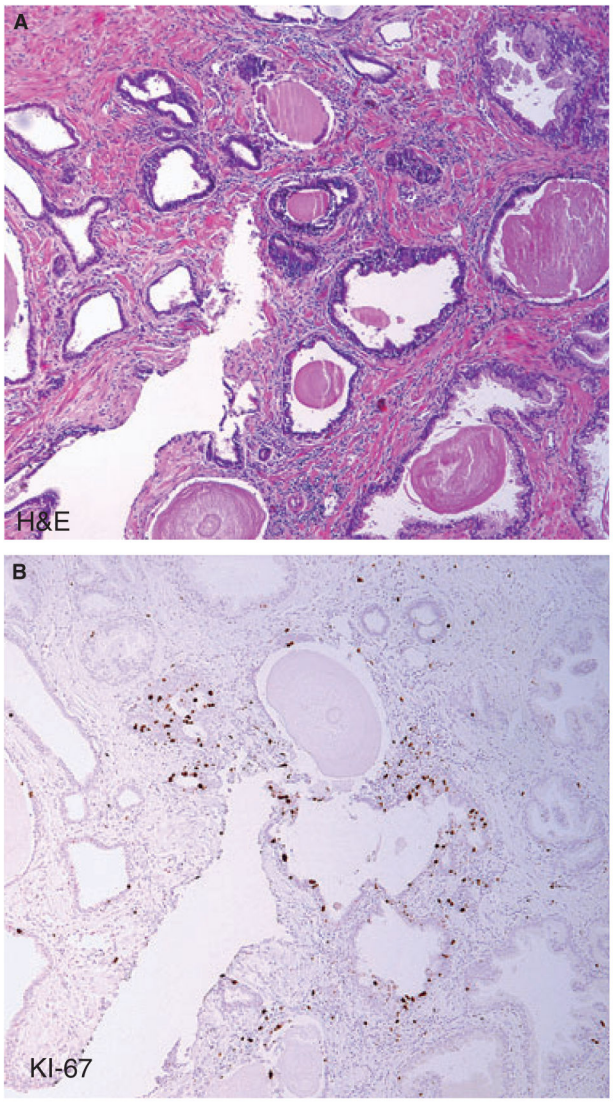

Figure 2.

Example of proliferative inflammatory atrophy (PIA) lesion. **A**, Haematoxylin and eosin (H&E) and **B**, immunohistochemistry (IHC) for Ki-67 proliferation marker shows relatively high fraction of luminal epithelial cells staining (compared to normal appearing epithelium which is not shown).

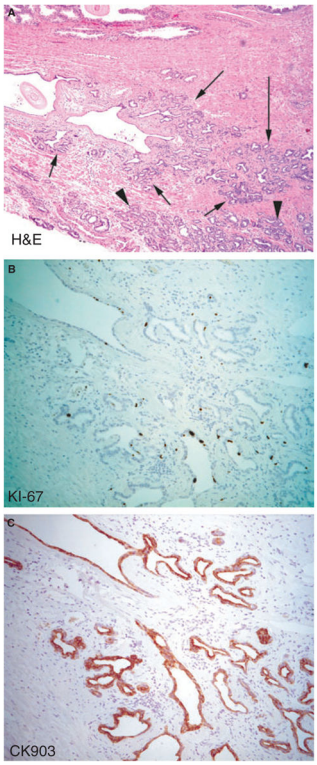

Figure 3. Example of post-atrophic hyperplasia (PAH), a form of PIA

A, Haematoxylin and eosin (H&E) arrows point to PAH, which shows mild stromal inflammation. Arrowheads point to carcinoma.

B, Immunohistochemistry (IHC) for Ki-67. **C**, IHC for 'basal specific' cytokeratin (CK903). Note that, as is characteristic of most forms of prostatic atrophy, many cells in the luminal cell layer stain positive with this antibody as well as other antibodies against keratin 5.

Table 1

Summary of single nucleotide polymorphism (SNP) studies involving cyclooxygenase 2 (COX-2) in prostate cancer

Study population	Size*	SNP(s)	Result	OR, CI	References
Caucasian	1309, 1266	rs2206593 (G / A)	+	1.69, 1.14–2.5	112
		rs2745557 (G / A)	−	0.78, 0.62–0.97	
		rs6685280 (A / C)	+	1.16, 1.01–1.33	
African American	149, 85	rs2206593, rs2745557, rs6685280	NA		
South African	151, 134	rs3918304 (AG and GG)	+	3.53, 2.14–5.90†	116
		rs20415 (CT and TT)	+	3.01, 1.82–5.02†	
		rs5270	NA		
Caucasian, non-Hispanic	2321, 2560	rs5277, rs20432, rs4648276, rs5275, rs689470	NA		117
Primarily Caucasian	8008, 8604	rs5275, rs5277, rs20417, rs689466, rs2206593, rs2383529, rs2745557, rs4648261, rs4648298, rs7550380, rs10911902, rs12042763	NA		118
Primarily Caucasian	1608, 3058	rs20417	NA		119
Caucasian (non-obese)	585, 585	rs2745557	NA		120
Sicilian	50, 125	rs20417	NA‡		121
Taiwanese	218, 436	rs689466, rs5275, rs2745557, rs16825748, rs2066826	NA		122
		rs20417 (GC)	−	0.52, 0.31–0.88	
Caucasian	416, 417	rs689466, rs20417, rs5277, rs2066826, rs5275, rs689470, rs4648310	NA		123
		rs2745557 (GA)	−	0.67, 0.50–0.90	
		rs2206593 (CT)	−	0.58, 0.38–0.89	
African American	89, 88	rs689466, rs20417, rs2745557, rs5277, rs2066826, rs5275, rs2206593, rs4648310	NA		
		rs689470 (AA)	+	2.79, 1.17–6.64	
Caucasian	92, 92	ss5112604, ss5112605, ss5112606	NA		124
		ss5112607 (CG / GG)	−	0.33, 0.1–0.9	
African American	124, 164	ss5112604	NA		
		ss5112605 (GA / AA)	+	2.72, 1.3–5.8	
		ss5112606 (GC / CC)	+	3.67, 1.4–9.9	
		ss5112607 (CG / GG)	−	0.51, 0.2–0.9	

Study population	Size*	SNP(s)	Result	OR, CI	References
Nigerian	154, 110	ss5112604, ss5112605, ss5112606, ss5112607	NA		

+: Positive association; −: inverse association; NA, no association.

*Cases, controls.

†Age-adjusted.

‡No association between cases and age-matched controls.

An association was observed between cases and centenarians [odds ratio (OR) = 2.1, 95% confidence interval (CI): 1.1–3.9].