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Review – Prostate Cancer

Inflammation and Chronic Prostatic Diseases: Evidence for a Link?

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Abstract

Objectives: Emerging evidence indicates that prostatic inflammation may contribute to prostate growth either in terms of hyperplastic (benign prostatic hyperplasia [BPH]) or neoplastic (prostate cancer [PCa]) changes. We propose two questions: Does prostate inflammation represent a significant factor for the development and the progression of both BPH and PCa? Are data available now to sustain the identification of prostate inflammation as a risk factor for prostate diseases?

Methods: We reviewed the recent international literature using a PubMed search to analyze new findings supporting a role for inflammation in BPH and PCa growth and progression.

Results: On histologic examinations from patients with BPH, inflammatory aspects are present in approximately 40% of cases. The men with inflammatory aspects inside the prostate have a significantly higher risk for BPH progression and acute urinary retention. Evidence shows that a cyclooxygenase-2 (COX-2) inhibitor can increase the apoptotic activity in human BPH tissue. Analyses on the bacterial colonization in PCa and normal prostate tissue showed a highly suggestive correlation between bacterial colonization/chronic inflammation and the diagnosis of PCa. Evidence from genetic studies supports the hypothesis that prostate inflammation may be a cause of PCa development. Proliferative inflammatory atrophy has been considered as an early histologic precursor to prostatic intraepithelial neoplasia and PCa.

Conclusion: The concept that inflammation can promote chronic prostatic diseases, such as BPH or PCa, is actually supported by several new significant findings; however, no specific oncologic surveillance for these cases is justified at the moment.

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1. Introduction

Prostate cancer (PCa) in United States and similarly in most European countries is now the most common cancer among men. Benign prostatic hyperplasia (BPH) very significantly increases in incidence according to the age of men [1,2].

Benign prostatic hyperplasia (BPH) and PCa are chronic diseases with a long period for their development and progression. BPH develops from a simple micronodular hyperplasia to a macroscopic volume enlargement and then to a clinical expression. Similarly, PCa evolves through early and late precancerous modifications.

In both BPH and PCa, an imbalance exists between prostate cell growth and apoptosis because some factors minimize cell apoptosis (immortalizing factors) and others stimulate proliferation. Intrinsic (in particular, growth factors) and extrinsic (in particular, steroid hormones) factors directly and indirectly regulate prostate tissue growth and differentiation. The microenvironment around prostate cells also significantly influences their growth and differentiation [3].

We must also remember that BPH and PCa are progressive diseases. The Medical Therapy of Prostate Symptoms (MTOPS) study [4] showed that, if untreated, a significant percentage of BPH cases will develop disease progression, either in terms of hyperplastic growth or of clinical complications, such as symptom progression, quality of life deterioration, bladder dysfunction, acute urinary retention, and, finally, need for surgery.

As a neoplastic disease, risk of progression of PCa can be actually stratified on the basis of clinical nomograms.

The first question is: Does inflammation associated with prostate tissue represent a significant factor for the development and, in particular, for the future progression of both BPH and PCa diseases?

The second question that we propose is: Are clinical data now available that can guarantee the identification of prostate inflammation as a risk factor for chronic prostatic diseases?

This review article presents recent evidence that suggests a link between inflammation and prostate proliferative diseases such as BPH and PCa.

2. Methods

Because several reviews related to this topic have been published [3,5–7], here we focus on new findings and suggestions. In particular, we reviewed the recent international literature using a PubMed search (prostate inflammation and BPH or PCa), and we analyzed new findings supporting a role of inflammation on BPH and PCa growth and progression. We have included ''Remarks'' sections to stress results obtained and limits evidenced.

3. Epidemiologic data: a real causal relationship?

Why are several clinical prevention trials for neoplasms focusing on antioxidants or anti-inflammatory agents? The reason is because the role of infection or inflammation is sustained in different cancer sites and also because in PCa infection or inflammation may be involved.

Using a meta-analysis, Dennis et al [8] examined the consistency of the observed associations between prostatitis and PCa. They found 11 studies that assessed this relationship.

Analyzing the odds ratio (OR), the association between prostatitis and PCa was significant among population-based, case-control studies (OR = 1.8; $p = 0.005$) and overall (OR = 1.6; $p = 0.0005$).

Also though lower, the OR between sexually transmitted (most evidence involves syphilis and gonorrhea) prostatic infections and PCa was significant (OR = 1.4; $p = 0.003$) in this meta-analysis [8]. These results could reflect an etiologic connection between prostatitis and PCa but also a detection bias if men with prostatitis are more likely to be screened for PCa.

In contrast with the meta-analysis of Dennis et al [8] are the recent results of Karakiewicz et al [9], who examined the association between needle biopsy tissue inflammation and coexistent PCa, as well as high-grade prostatic intraepithelial neoplasia (HGPIN). Of 4526 patients assessed with systematic prostate biopsies, an inflammatory infiltrate was seen in 7.7% and PCa in 36.1% of cases. The authors [9] showed that men with chronic inflammation exhibited HGPIN (2.7% vs. 20.3%, $p < 0.01$) and PCa (13.6% vs. 43.5%, $p < 0.01$) less frequently than their counterparts without chronic inflammation. In their experience, the OR of 0.20 indicated that inflammatory aspects on needle biopsy are 80% less likely to have coexistent PCa than men without chronic inflammation. Similar results were found between inflammation and HGPIN (OR = 0.11) [9].

Epidemiologic data suggest also a relationship between inflammation and BPH. It is well recognized by both urologists and pathologists that BPH and inflammation very frequently coexist [10]. Di Silverio et al [11], on 3942 histologic examinations from BPH patients, described inflammatory aspects in 43% of cases, in particular, chronic inflammation in 30% of cases.

Irani et al proposed that inflammatory aspects associated with prostate tissue can be classified

Table 1 – Histologic grading and histologic aggressiveness of inflammatory aspects in prostate tissue

Histologic grading		Histologic aggressiveness	
Grade	Histologic finding	Grade	Histologic finding
0	No inflammatory cells	0	No contact between inflammatory cells and glandular epithelium
1	Scattered inflammatory cell infiltrate without nodules	1	Contact between inflammation and epithelium
2	Nonconfluent lymphoid nodules	2	Interstitial infiltrate with glandular disruption
3	Large inflammatory areas with confluence	3	Glandular disruption on >25%

This is a hypothetical histologic grading system proposed by Irani et al [12] and includes histologic examination from 111 consecutive prostate biopsies.

using a hypothetical histologic grading, on the basis of extension of inflammatory cells [12] (Table 1). Otherwise, a different classification can be obtained using a histologic aggressiveness grading, on the basis of the effect that these inflammatory cells produce on prostate tissue (12) (Table 1). This last histologic aggressiveness grading seems to have more clinical relevance, demonstrating also a correlation with prostate-specific antigen (PSA) serum levels. In fact, a positive association between PSA levels and the histologic aggressiveness grading has been described, but PSA ranges for each grades of the system have not be included [12]. This aspect underlines a possible correlation between the effect that inflammation produces in prostate tissue and a clinical marker of prostate tissue proliferation and progression such as PSA.

REMARKS:

Different possible confounding factors make epidemiologic evidence difficult to analyze [13]:

1. The real incidence of prostatitis or prostatic inflammation is uncertain. The reported incidence of prostatitis in men older than 40 yr is 5–10%, but several men may have the condition without clinical symptoms.
2. Symptomatic men with prostatitis are more likely to be screened for PCa or to undergo a needle biopsy. Therefore, in this population PCa may be over-diagnosed.
3. Even the epidemiologic evidence that inflammation is associated with BPH may be open to major bias. In fact, BPH causing urinary retention may facilitate prostatic inflammation and infection.

Epidemiologic evidence suggesting a causal link between inflammation and chronic prostatic diseases is at now limited by significant detection and selection bias.

4. Hypothesis for a pathogenetic mechanism: inflammation or infection?

4.1. *Genetic aspects*

To understand the molecular basis of the association between inflammation and prostate proliferative diseases, Nelson et al analyzed this aspect from a genetic viewpoint [3].

Can genetic aspects support this hypothesis? Actually PCa has the greatest inherited contribution of any common cancer. PCa genes appear to confer increased susceptibility to PCa in certain families. In particular one of these genes, *RNA–SEL* (linked to *HPC1* gene) encodes an enzyme that degrades viral RNA on viral infection; a second gene, *MSR1*, encodes subunits of a macrophage-scavenger receptor capable of binding bacterial lipopolysaccharides [3]. Macrophages are abundant at sites of prostate inflammation. The possibility that viral or bacterial infections or inflammation might lead to PCa has been linked with the identification of these two familial PCa genes [3].

The Cancer Prostate Sweden Study (CAPS) is a case-control study of PCa in Sweden [5,14]. The large size of this study and the genetic homogeneity of the Sweden population make it an ideal analysis to identify genetic variants associated with PCa. In particular, the analysis of PCa cases and controls in CAPS has led to the identification of several genes in inflammation-related pathways. The *MIC1* gene is a member of the transforming growth factor β superfamily and is recognized to have an important role in inflammation by regulating macrophage activity. In CAPS [14], a significant difference ($p = 0.006$) in the genotype frequency for the non-synonymous change H6D of this gene was observed between patients and controls.

The *IL1RN* gene is related to the interleukin 1 (IL-1) cytokine family and its product acts as an inhibitor of the proinflammatory IL-1α and IL-1β. The most common haplotype across the *IL1RN* gene was observed at a significantly higher frequency in PCa cases compared with controls ($p = 0.009$) [5].

Table 2 – Identification of several genes involved in both prostate cancer and inflammatory-related pathways

Gene type	Chromosomal location	Activities
RNASEL	1q25	Encodes 2′,5′-oligoisoadenylate synthetase-dependent ribonuclease activated by interferon. Required for antiviral and antiproliferative roles of interferons.
MSR1	8p22	Encodes subunits of trimeric membrane receptor (scavenger receptor) expressed by macrophages.
GST–P1	11q13	Encodes the enzyme that catalyses the conjugation of glutathione to electrophilic substrates. It detoxifies carcinogens.
GDF15	19p13.1-13.2	Encodes macrophage inhibitory cytokine-1.
TLR4	9q32-33	Encodes pathogen binding toll-like receptor in macrophages.
TLR1-6-10	4p14	Encodes lipoprotein in macrophages.
MIC1		Is a member of transforming growth factor β family, regulating macrophage activity.
IL1RN		Encodes proteins in the interleukin 1 family. Inhibitor of the proinflammatory IL-1α and IL-1β.
IL8	4q13-21	Encodes IL-8 as mediator of inflammation.
IL10	1q31-32	Encodes IL-10 as mediator of inflammation.

IL = interleukin.

Also Zheng et al [15] suggested that sequence variants in different genes involved in the inflammatory pathway might be associated with PCa. They evaluated 9275 single nucleotide polymorphisms (SNPs) in 1086 genes of the inflammatory pathways among PCa cases and controls from CAPS. They found that more than the expected numbers of SNPs were significant at a $p < 0.05$, providing overall support for their hypothesis.

REMARKS:

If inflammation is an important etiologic factor for prostate growth and PCa development, then allelic variants of the genes involved in inflammation are candidates for genetic determinants of PCa risk. All these data suggest that a genetic basis for our hypothesis has been found. Several results are consistent with the suggestion that variation in many genes related to inflammatory pathways might affect the likelihood of developing PCa (Table 2). Future strategies may correlate more specifically genetic polymorphisms with the extent and pattern of prostatic inflammation.

4.2. *Inflammation or infection?*

An important issue to be addressed is: which factor can directly influence prostate growth and PCa development—inflammation, in particular the chronic exposure to inflammatory agents, or infection, viral or bacterial, which must be present? Genomic damage can be mediated by the infection itself or by oxidant carcinogens elaborated by inflammatory cells. Often the cause of prostatic inflammation is unclear. Several sources exist, including infection, urine reflux with chemical trauma, dietary factors, steroid hormones, or combinations of different factors [5].

Recently, a study from the University of Medison suggested that in mice the bacterial colonization of the prostate, possibly through the reflux of urine into the prostatic ducts of the peripheral zone, could play a role in the genesis of chronic inflammation and prostatic tumorigenesis [16]. The authors hypothesized that the oxidative stress induced by a chronic *Escherichia coli* infection and subsequent inflammation might induce a reactive dysplasia that could evolve into a neoplastic process in the mouse prostate. Male mice prostate tissue inoculated by *E. coli* showed acute inflammation at 5 d and chronic at 20 wk with infiltrates in the stroma and a progressive atypical hyperplasia and dysplastic changes in the prostate glandular epithelium. In particular, in these prostates, chronic inflammation produced histologic changes similar to a PIN lesion [16].

Chemical irritation from the urine reflux has been proposed as an etiologic agent for the development of chronic prostatic inflammation. In support of this concept a recent work has involved crystalline uric acid (particularly damaging for prostate epithelium) as a ‘‘danger signal’’ released from dying cells, able to directly engage the caspase-1–activating NALP3 ‘‘inflammasome’’ (a multiprotein complex primarily present in macrophages) [17]. The result of this process is the production of inflammatory cytokines that can increase the influx of other inflammatory cells.

Another possible aspect is the production of corpora amylacea [18] in the prostate. They seem to contribute to prostate inflammation and prostate carcinogenesis and they are frequently observed adjacent to the damaged epithelium and focal inflammatory infiltrates [5,18]. An epidemiologic

analysis described a higher proportion of calculi in the prostate tissue from patients with PCa compared with patients with BPH [19], but this observation is not confirmed by other analyses [20].

4.3. *Oxidative stress*

Data show that chronic inflammation can induce proliferative events and posttranslational DNA modifications in prostate tissue through oxidative stress [21]. In fact, repeated tissue damage and oxidative stress related to this event may provoke a compensatory cellular proliferation with the risk of hyperplastic growth or also of neoplastic modifications [22,23].

It is well accepted that regions of prostatic inflammation can generate free radicals, such as nitric oxide (NO) and various species of oxygen. In particular, macrophages and neutrophil infiltrations provide a source of free radicals that can induce hyperplastic or precancerous transformations through the oxidative stress to the tissue and DNA [22].

A feature of these oxidative stress reactions is the production of arachidonic acid from membranes, a process associated with the generation of new reactive oxygen radicals [22]. It can also be converted by the cyclooxygenase (COX) enzymes to various eicosanoids, in particular, prostaglandins that have long been recognized as important factors in the regulation of prostate cell proliferation [22].

Normally, prostate tissue is protected by oxidative stress reactions, free radicals, and highly reactive oxygen species by the superoxide-dismutase and the glutathione-S-transferase (GST)–P1 enzyme systems, the body's natural protective mechanisms. It is important that estrogens, through the estrogen receptor β (ER-β), appear to influence the protective activity of GST on production of free radicals [24]. A modern context highlights that the transplacental transmission of an estrogen signal can promote cancer induction in later life. Estrogens can initiate molecular events, referred to as gene imprinting or gene silencing, that are related to the induction of an inflammatory response within the prostate and to the possibility that inflammation could induce preneoplastic lesions.

Estrogens given to neonatal rodents result in a ''developmental estrogenization'' in which there are developmental defects, including a reduction in prostatic growth. This treatment also results in the development of lobe-specific inflammation, dysplasia, or PIN [5]. The spontaneous inflammatory response that is induced in animals by estrogens can be prevented by increasing soy intake or enhancing the levels of genistein [24].

4.4. *COX and NO activity*

In this pathogenetic hypothesis, NO and COX activity may both play an important role in determining the association between inflammation and prostate growth.

In all the inflammatory cells that arrive in the prostate, the inducible NO synthase (iNOS) is the principal factor activating reactive nitrogens that can damage cells [25].

Gradini et al [26] characterized NOS expression in human prostate tissue and, particularly for iNOS, they found an increased immunostaining in the epithelial cells of cases with BPH and more with HGPIN and PCa, when compared to normal tissue.

NO also enhances COX activity, the second factor. COX-2 activity has been detected in all inflammatory cells in the epithelium and interstitial spaces of human prostate tissue and it is increased in proliferative inflammatory lesions, generating proinflammatory prostaglandins [22,23]. In human BPH tissue, Di Silverio et al [27] showed that COX-2 inhibition can produce a significant increase in prostate cell apoptotic activity [27] (Fig. 1).

REMARKS:

Inflammation is a complex phenomenon consisting of humoral (cytokines) and cellular (leukocytes) components. Inflammation can influence the tissue microenvironment through the production of free radicals, COX activity, and NO synthesis, all linked to the deleterious oxidative effect of inflammation on prostate tissue. These factors can alter protein structure and function, induce gene changes, cause posttranslational modifications, including those involved in DNA repair and apoptotic processes, and provoke cellular proliferation. All these aspects generate an important link between inflammatory processes and the induction of prostate growth or of preneoplastic and neoplastic lesions (Fig. 2).

The mechanism used by inflammation to influence the development and progression of chronic prostatic diseases (BPH and PCa) has been suggested and well supported by scientific evidence.

5. Inflammation: an early preneoplastic lesion?

An important issue is to verify a possible association between inflammation and the development of preneoplastic lesions in the prostate. Could

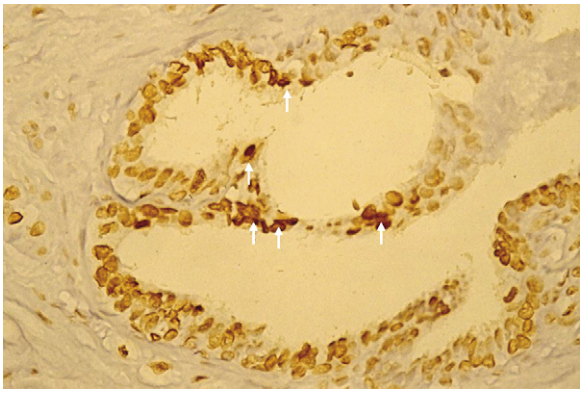

Fig. 1 – Increased apoptotic activity in human benign prostatic hyperplasia tissue using a cyclooxygenase-2 inhibitor. Immunohistochemical analysis [25]. Arrows indicate increased apoptotic activity at epithelial cells level (TdT-mediated dUTP nick-end labeling method).

inflammation itself represent a very early premalignant event?

5.1. *GST activity*

Normally, GST activity defends prostate cells against the genomic damage induced by the various oxidants isolated at sites of inflammation. GST gene methylation produces the loss of this protective enzyme system and it could be implicated in the transition from inflammation to preneoplastic lesions and therefore to PCa [22]. Lee and colleagues [28] identified GST methylation in nearly 70% of HGPIN lesions and in >90% of cancers.

5.2. *Focal atrophy*

It has been stressed that at the prostate tissue level a focal atrophy may represent the histologic key for these processes. Inflammatory infiltrates in prostate tissue can produce focal atrophy [29]. Histologically, most lesions that contain either acute or chronic inflammatory infiltrates in the prostate are associated with focal epithelial atrophy [5]. Sometimes areas of proliferation develop from the atrophic epithelium, which has a pattern that resembles the structure of a small acinar carcinoma. More convincingly, a specific mucin, a sulfated sialomucin, normally recognized in cancer, is seen in the prostatic acini of areas of postsclerotic hyperplasia [30]. Both focal atrophy and PCa occur principally in the peripheral zone of the prostate [5].

In 1999, De Marzo [30] proposed that a prostatic lesion called proliferative inflammatory atrophy (PIA) could be considered a precursor to HGPIN and PCa. Interestingly, in PIA a focal prostatic glandular atrophy occurs in close association with chronic inflammation. Although most focal prostatic atrophy lesions have been considered to be quiescent, cells in some atrophy lesions appear proliferative. In PIA an increased expression of proliferation-associated markers such as Ki67 and a decreased expression of p27 in secretory cells have been shown [30]. Similarly, the expression of Bcl-2 such as heterogeneous areas of GST–P1 and COX-2 expression, in particular in secretory cells (signals of a stress-induced response), have been demonstrated [30].

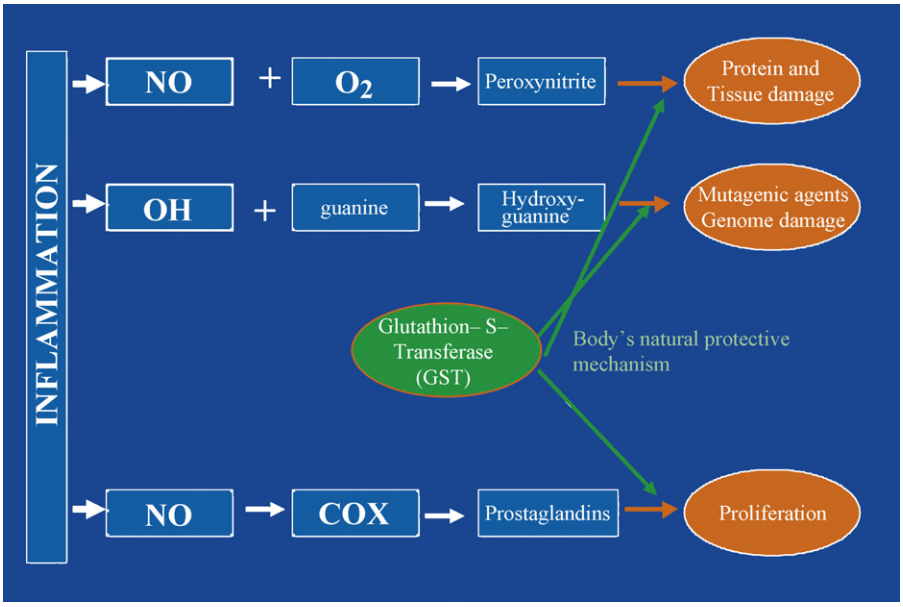

Fig. 2 – Inflammation and prostate growth: a possible pathogenetic mechanism. Role of oxidative stress by oxidant electrophiles, nitric oxide and cyclooxygenase activity; protective role of glutathione-S-transferase.

Several molecular pathways involved in PCa have also been shown to be altered in PIA lesions. For example, three prostate tumor-suppressor genes, *NKX3.1*,*CDKN1B*, and *PTEN* are all down-regulated in focal atrophy lesions [5]. These genes are highly expressed in normal prostate tissue and often decreased or absent in HGPIN and PCa [5]. Other authors showed that chromosomal abnormalities similar to those found in HGPIN and PCa occur in atrophic lesions (increases in chromosome 8 centromere signals, loss of chromosome 8p, and a gain of chromosome 8q24) [5,31,32].

Another question is whether PIA may give rise to PCa directly or, considering the strong association between PIA and HGPIN characteristics, indirectly through HGPIN development.

Different findings provide supportive evidence that PIA may represent an HGPIN precursor, specifically, a shift in the topographic fidelity of proliferation from basal to secretory cells in both PIA and HGPIN and a high prevalence in the peripheral zone for both lesions [30]. It is possible that oxidant carcinogens elaborated by inflammatory cells, if not detoxified from GST–P1 enzyme in the basal epithelial cells, may induce genomic damage and therefore the development of HGPIN. Regions of PIA that are unable to adequately defend themselves against oxidative genome damage may subsequently progress to HGPIN and PCa [30].

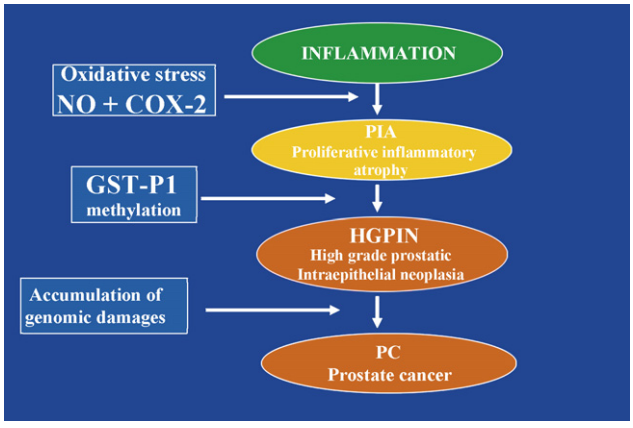

Fig. 3 – Possible event cascade for prostate cancer: inflammation as early event, proliferative inflammatory atrophy (PIA), prostatic intraepithelial neoplasia (PIN), and prostate cancer. Role of oxidants, nitric oxide, and cyclooxygenase-2 activities in the transition from inflammation and PIA. Role of glutathione-S-transferase–P1 methylation and inactivation in the transition from PIA to high-grade PIN and therefore to prostate cancer.

REMARKS:

Repeated injuries to the prostate epithelium occur either as a result of oxidant damage from inflammatory cells or of toxins derived from the diet or from urine that are refluxed into the prostate [5]. The morphologic manifestation of this injury is a focal atrophy or PIA. A possible cascade of events may include: (1) chronic inflammation as a very early step able to induce a regenerative proliferation of prostate epithelial cells in response to the injury caused by inflammatory oxidants; (2) the loss of GST–P1 protective activity, probably as a result of hypermethylation, may define the transition between inflammation, PIA, and HGPIN (Fig. 3). In this model it is hypothesized that many, although not all, HGPIN lesions may develop by first proceeding through a period of atrophy [30].

The cascade of events proposed may recognize a new possible histologic premalignant lesion related to inflammation, such as PIA.

6. Clinical information

All these data suggest that, in men with a genetic predisposition, PCa might be induced by inflammation or, in other cases, inflammation may simply stimulate prostate growth. To support this hypothesis, genetic evidence has been found, and a possible mechanism of action and a possible cascade of events have been proposed. Can we translate this information into clinical practice? The first clinical aspect is: How common is the presence of inflammation in the prostate of our patients?

Of 3942 pathologic BPH examinations reviewed, the incidence of inflammation was significant, 43% of cases, in particular for chronic inflammation in 30% of cases [11]. Similar, although variable, data are reported in another experience [33]. Considering the aspect of a histologically proven inflammation, its distribution in the prostate gland significantly varies according to the prostate volume and, regarding chronic inflammation, there is a significant trend to increase from small to larger prostates, suggesting a simple relationship between inflammation and prostate hyperplastic growth [11].

Considering the aspect of a histologically proven inflammation associated with acinar atrophy, there is a significant trend to increase with the decades of

age and a significant association with the distribution of HGPIN and PCa [11].

Also if more interest is directed to a possible role of inflammation in prostatic carcinogenesis, we must remember that inflammation may simply condition a hyperplastic proliferation of the prostate tissue and the risk of BPH progression. Using the MTOPS data [34,35], it has been proposed to consider inflammation as a risk factor for BPH progression. Patients with a histologically proven prostatic inflammation showed a higher risk of BPH progression and, in particular, at the 4-yr follow-up, a higher risk for acute urinary retention [34,35].

REMARKS FOR THE FUTURE:

Additional analyses need to be performed to determine which proposed mechanism is correct. Recently, De Marzo et al [5] underlined some points to be developed.
First, we need to improve the ability to diagnose and clinically define ''prostatic inflammation'' [5]. In this way an important issue is the improvement in the imaging of the prostate, with new strategies to image inflammation and atrophy and their relationships. Second, we need studies that also quantify asymptomatic inflammation in the prostate to better determine the relationship between prostatic inflammation and prostate growth, preneoplastic lesions, and PCa. We also need an improved understanding of the types of inflammatory cells, their biologic properties, and their aggressiveness in the normal prostate and in BPH, PIA, PIN, and PCa lesions [5].

7. Preventive strategies for the future

Hypotheses for future preventive strategies can be suggested. Patients with chronic inflammatory aspects in the prostate gland could be stratified as cases at higher risk for BPH progression or, in particular, if associated with focal atrophy or a genetic predisposition (eg, GST gene methylation), at higher risk for a carcinogenic evolution in the gland. In both cases the finding of chronic inflammation in the prostate may indicate the need for a preventive strategy.

In terms of secondary prevention of BPH progression, Di Silverio et al [27] speculated on the effect of a combination therapy with a 5α-reductase inhibitor and a COX-2 inhibitor [27]. In particular, at the BPH tissue level the combination of finasteride with rofecoxib produced a significant increase in the apoptotic index when compared to cases treated with finasteride alone [27].

In terms of primary prevention of PCa, the data on inflammation and PIA as an early precancerous lesion can guarantee the rationale for preventive trials with antioxidant agents or, more specifically, with NOS inhibitors or COX-2 inhibitors. The VIP trial tried to verify whether COX-2 up-regulation can induce a resistance to apoptosis in PCa tissue and whether COX-2 inhibition can reduce the risk for PCa development [36]. Unfortunately, this preventive trial has been stopped for possible relationships between chronic administration of rofecoxib and cardiovascular side effects.

Another possible rationale for a preventive strategy in PCa is based on Coffey's studies [24], supporting a potential beneficial influence of dietary phytoestrogens in preventing the adverse inflammatory response in the prostate. As previously shown, estrogens, through ER-β, appear to influence the activity of GST enzyme; this may explain the beneficial effect and the antioxidant role of phytoestrogens. Estrogens may also influence the production of COX-2 isoforms, highlighting the role that they exercise in oxidative stress and inflammatory reactions [24].

8. Conclusion

Probably it is too early to definitely integrate inflammation in a risk stratification analysis for prostate diseases because (1) a reliable, reproducible diagnosis of prostate inflammation is not possible at the moment and (2) men suspected of having prostate inflammation cannot be clinically assumed eligible for a specific oncologic surveillance. However, all data presented are very suggestive and certainly prostate inflammation cannot now be considered only as a simple tissue inflammation. Prostatic inflammation may have a role in the induction of prostate growth and BPH progression. If associated in PIA lesions, through the loss of GST activity and the development of oxidative stress damage, inflammation may give rise to cells of PIN and may increase the prostate's vulnerability to developing cancer.

Conflicts of interest

The authors have nothing to disclose.

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