Abstract

Introduction: There is emerging evidence that prostatic inflammation may contribute to prostate growth either in terms of hyperplastic (BPH) or neoplastic (PC) changes. Inflammation is thought to incite carcinogenesis by causing cell and genome damage, promoting cellular turnover.

Methods: We reviewed our personal experience and the international recent literature on the clinical data supporting a role of inflammation on BPH and PC growth and progression.

Results: BPH: Among those patients with self-reported prostatitis, 57% had a history of BPH. MTOPS study showed that men with inflammation had a significantly higher risk of BPH progression and acute urinary retention. We showed that the use of a COX-2 inhibitor in combination with a 5 alpha reductase inhibitor could increase the apoptotic index in BPH tissue.

Prostate cancer: A PCR-based analysis of bacterial colonization in PC specimens and normal prostate tissue showed highly suggestive correlation of bacterial colonization and chronic inflammation with a diagnosis of PC. Evidence from genetic studies support the hypothesis that prostate inflammation may be a cause of prostate cancer. De Marzo proposed that proliferative inflammatory atrophy (PIA) is a precursor to PIN and cancer.

Conclusion: The concept that inflammation can promote prostate growth either in terms of BPH and PC risk remains highly suggestive.

Keywords: Prostate neoplasm; Benign prostatic hyperplasia; Inflammation; Estrogen
1. Introduction

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

Prostate diseases are chronic diseases that need a long period for development. BPH need a long period for its evolution from a simple micronodular hyperplasia to macroscopic volume enlargement and then clinical expression. Similarly for PC, the evolution needs a long period probably through the development of early and later precancerous modifications and then to the development of a clinical PC (Fig. 1).

In both prostate disease, BPH and PC, there is an imbalance between prostate cell growth and apoptosis, probably because some factors minimize cell apoptosis as 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 [2].

We must also remember that prostate diseases are progressive diseases. The MTOPS study [3] showed that, if untreated, a significant percentage of BPH cases develop a disease progression, either in terms of hyperplastic growth or of clinical complications, such as symptoms progression, quality of life worsening, bladder dysfunction, acute urinary retention and finally need of surgery.

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

The first question that we will try to answer is: may inflammation associated to prostate tissue represent a significant factor able to condition the development and in particular the future progression of both BPH and PC diseases?

And, second question: are there now data that can guarantee the identification of prostate inflammation as a risk factor so as to be integrated in risk stratification analyses for prostate diseases?

Therefore the aim of this review article is to present recent evidences suggesting a link between inflammation and prostate proliferative diseases such as BPH and PC.

2. Epidemiologic data

Why several clinical prevention trials for neoplasms are 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 for PC, infection or inflammation may be involved.

Dennis et al. [4] examined the consistency of the observed associations between prostatitis and PC using a meta-analysis. They found 11 studies that assessed this relationship.

Analysing the odds ratios (OR), the association between prostatitis and PC was significant among the population-based, case control studies (OR = 1.8) and overall (OR = 1.6). Also if lower, the OR between sexually transmitted (most regarding syphilis and gonorrhea) prostatic infections and PC was significant in this meta-analysis. These results could reflect an etiologic connection between prostatitis and PC but also a detection bias if men with prostatitis are more likely to be screened for prostate cancer.

But it is not only a link between PC and inflammation. It is well recognize by both urologists and pathologists that BPH and inflammation very frequently coexist (Fig. 2).

Inflammatory aspects associated to prostate tissue can also be classified using a histological grading on the basis of inflammatory cells extension [5] (Fig. 3).

Otherwise, using a histological aggressiveness grading on the basis of the effect that these inflammatory cells produce on prostate tissue, they can be classified into: simple contact, infiltration, tissue disruption [5] (Fig. 4).

This last histological aggressiveness grading seems to have more clinical relevance demonstrating also a correlation with prostate specific antigen serum (PSA) levels. At the increase in the histological aggressiveness related to inflammation in the prostate, corresponds an increase in mean PSA levels [5]. Therefore, first clinically relevant data, there is a correlation between the effect that inflammation produces in prostate tissue and a clinical marker of prostate tissue proliferation and progression such as PSA.

3. Pathogenetic mechanism: inflammation or infection?

3.1. Genetic aspects

Trying to understand the molecular basis for this association between inflammation and prostate proliferative diseases, one study by Nelson, De Marzo ed Isaacs from the John Hopkins University of Baltimore analyzed this aspect from a genetic point of view [2]. The development of prostate proliferative diseases is sustained by a very complex mechanism involving genetic aspects, transcriptional modifications, growth factors expression and activities. PC cells contain many somatic mutation, gene deletion, gene amplifications and changes in DNA methylation, probably accumulated over a period of several decades [2].

Then, can genetic support our hypothesis? PC actually has the greatest inherited contribution of any common cancer. There are PC genes that appear to confer increased susceptibility to PC in certain families. Two of these genes have been named, one as RNA-SEL which encodes an enzyme that degrades viral RNA upon viral infection (linked to HPC1), the second as MSR1, which encodes subunits of a macrophage scavenger receptor capable of binding a variety of ligands including bacterial lipopolysaccharide [2]. Macrophages are abundant at sites of prostate inflammation. The possibil-
Fig. 1. Long period progression from normal tissue to low grade (LGPIN) and high grade (HGPIN) prostatic intraepithelial neoplasia, and then to PC.

Fig. 2. Pathological aspects related to the histological diagnosis of BPH. Inflammatory aspects and premalignant lesions.

Fig. 3. Histological grading of inflammatory aspects in prostate tissue [5].

Fig. 4. Histological aggressiveness grading of inflammatory aspects in prostate tissue [5].
It is well accepted that regions of prostatic inflammation will generate free radicals, such as nitric oxide and various species of oxygen. Macrophages and neutrophil infiltration provide a source of free radicals that can induce hyperplastic or precancerous transformation through the oxidative stress to the tissue and DNA [8].

Normally, these highly reactive oxygen species are removed by the superoxide dismutase enzyme system, the body’s natural protective mechanism. A feature of these oxidative stress reactions is the production of arachidonic acid from membranes, a process associated with the generation of reactive oxygen radicals [8]. It induces oxidative damage to vascular tissue, as well as being converted by the cyclo-oxygenase (COXs) to various eicosanoids, in particular prostaglandins that have long been recognized as important factors in the regulation of cell proliferation. Inflammation is a complex phenomenon consisting on humoral (cytokines) and cellular (leukocytes) components. Inflammation can produce a tissue microenvironment with the production of free radicals, nitric oxide (NO), linked to deleterious oxidative effects of inflammation. These factors can alter protein structure and function, induce gene changes and cause post-translational modifications including those involved in DNA repair, apoptosis. Lipid peroxidation can trigger prostaglandin synthesis via activating COX-2. COX-2 reaction produces reactive oxygen species (ROS) and genomic damage [9] (Fig. 5).

It is important that estrogens, through the estrogen receptor beta (ER-beta) appear to influence the protective activity of glutathione transferase on free radicals production [10].

A modern context highlights that 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 could be related to the cellular events that surround the induction of an inflammatory response within the prostate and the possibility that this may involve the induction of early preneoplastic lesions associated to inflammation. The spontaneous inflammatory response that is induced in animals by estrogens can be prevented by increasing soy intake or enhancing the levels of genistein [10].

### 3.3. COX and NO activity

In this pathogenetic scenarios 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 one that activates reactive nitrogen that can damage cells [11]. These are inflammatory cells in the prostate epithelium expressing this enzyme.

We also characterized NOS expression in human prostate tissue and in particular for the iNOS we found an increased immunostaining in the epithelial cells of cases with BPH and more with high grade PIN (HGPIN) and PC when compared to normal tissue [12] (Fig. 6). Cytotoxicity of macrophages and tumor-induced immunosuppression are associated with iNOS.
Fig. 7. Increased apoptotic activity in human BPH tissue using COX-2 inhibitor. Immunohistochemical analysis [13].

NO enhances also COX activity, the second actor. COX-2 has been detected in all inflammatory cell in the epithelium and interstitial space and it is increased in proliferative inflammatory lesions, generating pro-inflammatory prostaglandins [8,9].

Similarly in BPH we showed that the COX-2 inhibition can produce a significant increase in prostate cell apoptosis [13] (Fig. 7).

4. Inflammation as a early preneoplastic lesion

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

Inflammation itself may represent a very early premalignant change. The glutathione S-transpherase (GST) gene methylation produces the loss of this protective enzyme system and could be implicated in the transition from inflammation to PIN and therefore to PC [8]. Lee et al. [14] identified GST methylation in nearly 70% of PIN lesions and in more than 90% of cancers. GST defends prostate cells against genomic damage induced by various oxidants found at the sites of inflammation.

4.1. Focal atrophy

It has been stressed that the focal atrophy may represent the histological key in these processes. Inflammatory infiltrates in prostate tissue can produce focal atrophy. Sometimes areas of proliferation develop from the atrophic epithelium, which has a pattern that resembles the structure of small acinar carcinoma. More convincingly, a specific mucin, a sulphated sialomucin, normally recognized in cancer, is seen in the acini in areas of post-sclerotic hyperplasia [15].

In 1999 De Marzo [15] proposed that a prostatic lesion called proliferative inflammatory atrophy (PIA) could be considered a precursor to PIN and prostate cancer.

Interestingly, focal prostatic glandular atrophy occurs in close association with chronic inflammation. Both focal atrophy and PC occur principally in the peripheral zone of the prostate. While 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, a decreased expression of p27 in secretory cells have been shown. Similarly expression of Bcl-2 in PIA has been demonstrated, such as heterogeneous areas of GSTP1 and COX-2 expression in particular in secretion cells, as signal of a stress-induced response in these cells [15].

On the basis of these data we may suggest that PIA may give rise to carcinoma directly or considering the strong association between PIA and PIN development and characteristics, indirectly via development into PIN.

Different findings provide supportive evidence that PIA may represent a PIN precursor: a shift in the topographic fidelity of proliferation from basal to secretory cells in both PIA and PIN, high prevalence in the peripheral zone for both lesions. It is possible that oxidant carcinogens elaborated by inflammatory cells, if not detoxified from GSTP1 of the basal epithelial cells, produce genomic damage and therefore the development of PIN. Regions of PIA that are unable to adequately defend themselves against oxidative genome damage may subsequently progress to PIN or PC [15].

Then, a possible cascade may be this, with chronic inflammation as a very early step able to induce regenerative proliferation of prostate epithelial cells in response to injury caused by inflammatory oxidants. Loss of GSTP1 probably as a result of hypermethylation, may define the transition between inflammation, PIA and PIN (Fig. 8). In this model it is hypothesized that many, although not all, HGPIN lesions may develop by first proceeding through a period of atrophy [15].

5. Clinical practice aspects

Then, we have genetic data supporting our hypothesis, we know a possible mechanism involved and we also know a possible event cascade for the evolution. In the last part of the review, we will try to translate these aspects in a clinical practice point of view. The first clinical aspect is: how com-
mon is the presence of inflammation in the prostate of our patients?

On 3942 pathologic BPH examinations reviewed, the incidence of inflammation was significantly, 43% of cases, in particular chronic inflammation in 30% of cases [16]. Similar, also if variable, data are reported in the literature [17].

Considering only the aspect of inflammation, its distribution significantly varied according to prostate volume and regarding chronic inflammation, there was a trend to increase from small to larger prostates, suggesting a possible relationship between inflammation and prostate hyperplastic growth [16] (Fig. 9).

Considering inflammation associated to acinar atrophy there was a trend to increase with decades of age in a way similar to the distribution of HGPIN and PC [16] (Fig. 10).

Also if more interest is directed on a possible role of inflammation on prostatic carcinogenesis we must remember that inflammation may also simply condition hyperplastic proliferation of prostate tissue and the risk of BPH progression.

Clinically, using the data of the voluminous MTOPS study [18], it has been proposed to consider inflammation as a risk factor for BPH progression. Patients with prostatic inflammation inside BPH tissue showed higher percentage of disease progression and in particular, at 4-year follow up, only BPH patients with inflammation developed episodes of AUR [18].

5.1. Preventive strategies

As clinical practice, patients with chronic inflammatory aspects in the prostate gland could be stratified as cases at higher risk of BPH progression or, in particular if associated to focal atrophy, at higher risk of carcinogenic development in the prostate. In both cases the finding of chronic inflammation in the prostate may indicate the need of a preventive strategy (Fig. 11).

In case of BPH patients, as secondary prevention with the aim to block progression, we recently proposed a new combination therapy able to target not only prostate cells but also the microenvironment involved with inflammation processes [13].

In terms of PC prevention, the data on chronic inflammation, PIA as an early preneoplastic lesions, guarantee the...
rational 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 and increased prostaglandin synthesis could induce a resistance to apoptosis and a greater propensity for PC initiation [19]. Unfortunately, this trial has been stopped for the events all that we know related to rofecoxib use.

Another possible rationale for preventive strategy in PC is based on Coffey’s studies [10] supporting a potential beneficial influence of dietary phyto-estrogens like genistein, in preventing the adverse inflammatory response in the prostate. Estrogens, through the ER-beta, appear to influence the activity of GST. This may explain the beneficial effect and antioxidant role of phyto-estrogens, an action mediated through its association with ER-beta. Estrogens may also influence the production of COX-2 isoform, highlighting the role that they exercise in oxidative stress and inflammatory reaction. (COX-1 protective, COX-2 inducing mitogenesis) [10].

6. Conclusion

Probably it is to early to definitely integrate inflammation in risk stratification analysis for prostate diseases, but all these data are very suggestive and certainly prostate inflammation cannot be more considered as a simple tissue inflammation.

Chronic inflammation as an isolated phenomenon or secondary to infection may have a role to induce prostate growth and BPH progression. If associated in PIA lesion, through the loss of GSTP1 function and the oxidative stress damage, gives rise to cells of PIN and increases the prostate’s vulnerability to develop cancer.

References