Prostate Cancer

Activation of the Thromboxane A2 Pathway in Human Prostate Cancer Correlates with Tumor Gleason Score and Pathologic Stage

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Article info

Article history:
Accepted January 15, 2006
Published online ahead of print on February 23, 2006

Keywords:
Prostate
Cancer
Cyclooxygenase
Thromboxane
Prognosis

Abstract

Objective: We investigated the potential involvement of the thromboxane A2 (TXA2) pathway in human prostate cancer (PCa).
Methods: Expression of cyclooxygenase-2 (COX-2), TXA2 synthase (TXS), and TXA2 receptors (TPRs), the main actors of the TXA2 pathway, was analyzed on serial tissue sections from 46 human PCa specimens.
Results: The expression levels of COX-2, TXS, and TPRs were significantly higher in malignant than in corresponding nontumoral prostatic epithelial cells. Increased immunoreactivity for these antigens was also observed in high-grade prostate intraepithelial neoplasia (HGPIN) glands. COX-2, TXS, and TPR proteins usually displayed a coordinated overexpression pattern in PCa lesions, as assessed in serial tissue sections. Increased levels of these proteins in the tumors were all significantly associated with higher Gleason scores and pathologic stages.
Conclusions: Proteins specifically involved in the TXA2 pathway are up-regulated in human PCa and their level of expression is associated with tumor extraprostatic extension and loss of differentiation. Our study is the first to examine simultaneously all key proteins involved in this pathway including TXA2 receptors and results suggest that the TXA2 pathway may be a potential target for PCa prevention/therapy.

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2 V.C. and D.W. codirected this work.

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1. Introduction

Intake of nonsteroidal anti-inflammatory drugs (NSAIDs), which act as inhibitors of cyclooxygenases, has been associated in humans with a significantly reduced risk of developing several types of cancer including prostate cancer (PCa) [1–4]. A recent comprehensive review of 91 epidemiologic studies, assessing the impact of daily intake of NSAIDs, has indicated that such a treatment may result in cancer development risk reduction of 39% for PCa [1]. Use of NSAIDs has also been associated with a significantly reduced incidence of colon, breast, lung, esophageal, stomach, and ovarian cancers [1]. For most patients, NSAID anticancer preventive effects become apparent after ≥5 yr of use, with a positive association between intake duration and the importance of risk reduction [1]. These data support the observations that prostanoids, which are derived from arachidonic acid (AA) through the activity of cyclooxygenases (COXs), usually display anti-apoptotic, growth-promoting, and proangiogenic properties [5]. It is thus assumed that the chemopreventive effects of COX inhibitors are predominantly achieved as a result of the inhibition of AA conversion into prostanoids (see Fig. 1 for a schematic description of the prostanoid pathway). However, prostanoids may exert opposing roles in tumor development/progression. For example, in the study by Pradono et al., retroviral vectors carrying thromboxane A2 (TXA2) synthase cDNA, or prostacyclin (PGI2) synthase cDNA were transduced to colon cancer cells and each transformant was inoculated to mice. Tumors derived from TXA2 synthase transformants grew almost three times faster and showed more abundant vasculature, whereas tumors from PGI2 synthase transformants presented opposite effects. These effects were reversed by administration of specific inhibitors [6]. Therefore, the profile of COX metabolites in cancer cells can be a significant determinant for tumor development. Results from several other studies have largely supported the implication of TXA2 in tumor invasiveness, angiogenesis, and metastasis [7–15]. TXA2 is thus currently considered as a valuable anticancer target [11–13, 15,16]. In this respect, it is important to consider that the selective targeting of downstream COX-2 pathways, such as the TXA2 pathway, may appear as a promising strategy bearing the potential of avoiding COX-2 inhibitors cardiovascular toxicity while maintaining their anticancer properties.

Several studies on the human prostate have yielded contradictory results regarding the possible overexpression of COX-2 in PCa lesions [17–29]. On the other hand, TXS has been shown to be upregulated in PCa and its increased expression has been associated with advanced disease [8]. To the best of our knowledge, no data on expression of TXA2 receptors (TPRs) in PCa are currently available. Two different TPRs, named TPα and TPβ receptors, have been identified and are generated by alternative splicing [30]. TPRs are transmembrane receptors belonging to the G protein-coupled receptor superfamily. Although no differences were observed in ligand binding and coupling of TPα and TPβ receptors, the β splice variant becomes internalized to a greater extent than the α variant on exposure to agonist. TPα and TPβ form homo- and heterodimers/oligomers [31].

The present study investigated whether the TXA2 pathway may be activated in PCa. The expression of the main proteins involved in TXA2 biosynthesis and activity (COX-2, TXS, and TPR) was assessed using immunohistochemistry in serial tissue sections of human PCa samples.

2. Methods

2.1. Tissue samples

Tissue samples from human PCa were surgically obtained from 46 patients who had undergone a radical retropubic prostatectomy for localized PCa. All radical prostatectomy specimens used in this study had been entirely submitted for histopathologic examination (complete sampling), as
previously described [32]. Most of the tissue sections analyzed in our study contained portions of both peripheral and transitional zones. No patient who had received prior hormonal therapy, chemotherapy, or radiation therapy was included in the investigation. The age of the patients and the pathologic stage of their disease are shown in Table 1.

### 2.2. Antibodies

Polyclonal anti-TXS and anti-TPR antibodies, their corresponding blocking peptide, and monoclonal antihuman COX-2 antibodies were purchased from Cayman Chemical (Ann Arbor, MI). TXS- and TPR-blocking peptides correspond to the peptides against which their respective antibodies were raised. TXS-blocking peptide corresponds to amino acids 359–377 (TNPDCEKLLREVDVFKEK) of human TXS. TPR blocking peptide corresponds to amino acids 275–279 (VMSFSGQLLRATEHQ) of human TXS. TPR blocking peptide corresponded to the peptides antibodies were purchased from Cayman Chemical (Ann Arbor, MI). TXS- and TPR-blocking peptides correspond to the peptides their corresponding blocking peptide prior to their use in the immunoperoxidase assay.

### 2.3. Immunohistochemistry

One tissue block per patient containing the most representative tumor-bearing areas was selected considering the capsular status (pathologic stage) and the Gleason score stated in the pathologic report, as previously described [33–35]. Serial tissue sections, 5 μm thick, were cut from paraffin blocks and placed on silane-coated slides for immunohistochemical analysis. Immunoperoxidase staining was performed as previously described [33,35] with the use of the ABC Vectastain Kit (Vector Laboratories, Burlingame, CA). For antigen retrieval, slides were heated in a water-bath at 95 °C for 40 min in 10 mM citrate buffer. Anti-COX-2 antibody (1:60), anti-TXS antibody (1:300), or anti-TPR antibody (1:200) was applied onto the slides and incubated overnight at 4 °C. Control experiments included omission of the first antibody and preincubations of anti-TXS and anti-TPR antibodies with their corresponding blocking peptide prior to their use in the immunoperoxidase assay.

### 2.4. Evaluation of immunohistochemical staining

The immunohistochemically stained sections were reviewed by two independent observers. All discrepancies were resolved by joint review of the slides. The importance of anti-COX-2, anti-TXS, and anti-TPR immunoreactivity in noncancerous and non–high-grade intraepithelial neoplasia (HGPIN) epithelial cells (herein referred to as “nontumoral”) was analyzed without segregating the expression data between benign prostatic hyperplasia (BPH) glands from the transitional zone and histologically normal glands that are adjacent to cancer cells in the peripheral zone. Anti-COX-2, anti-TXS, and anti-TPR immunoreactivity was scored in nontumoral and HGPIN glands when at least 10 glands were present in the tissue sections. Scoring of the staining was done according to immunostaining intensity and extent using arbitrary scales ranging from 0 to 3 and 0 to 4, respectively, as previously described [33,35,36].

### Table 1 – Characteristics of 46 patients with clinically localized prostate cancer treated by retropubic radical prostatectomy

<table>
<thead>
<tr>
<th>Age, yr</th>
<th>No. of patients</th>
<th>Organ confined (pT2)</th>
<th>Extracapsular (pT3a)</th>
<th>Seminal vesicle invasion (pT3b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>67.1</td>
<td>100</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>SD</td>
<td>6.2</td>
<td>55.2</td>
<td>31.9</td>
<td>13.8</td>
</tr>
</tbody>
</table>

Pathologic stage, %

- Organ confined (pT2): 100%
- Extracapsular (pT3a): 0%
- Seminal vesicle invasion (pT3b): 0%

Gleason score

<table>
<thead>
<tr>
<th>2–4</th>
<th>5–7</th>
<th>8–10</th>
</tr>
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<tbody>
<tr>
<td>No. of patients</td>
<td>7</td>
<td>29</td>
</tr>
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</table>

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<tr>
<th>Gleason score</th>
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<tbody>
<tr>
<td>2–4</td>
</tr>
<tr>
<td>No. of patients</td>
</tr>
</tbody>
</table>

### Table 2 – Analysis of expression of COX-2, TXS, and TPR levels using immunohistochemistry in human prostate tissues

<table>
<thead>
<tr>
<th></th>
<th>I score</th>
<th>E score</th>
<th>IE score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-COX-2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N (n = 45)</td>
<td>0.51 ± 0.51 (0–1)</td>
<td>1.29 ± 1.39 (0–4)</td>
<td>1.29 ± 1.39 (0–4)</td>
</tr>
<tr>
<td>HGPIN (n = 22)</td>
<td>2.0 ± 0.52 (1–3)</td>
<td>3.87 ± 0.46 (2–4)</td>
<td>7.73 ± 2.28 (4–12)</td>
</tr>
<tr>
<td>C (n = 46)</td>
<td>2.06 ± 0.64 (1–3)</td>
<td>3.72 ± 0.65 (2–4)</td>
<td>7.79 ± 2.87 (2–12)</td>
</tr>
<tr>
<td>Anti-TXS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N (n = 45)</td>
<td>1.36 ± 0.48 (1–2)</td>
<td>1.36 ± 0.48 (1–2)</td>
<td>2.07 ± 1.45 (1–4)</td>
</tr>
<tr>
<td>HGPIN (n = 22)</td>
<td>2.17 ± 0.58 (1–3)</td>
<td>4.00 ± 0.00 (4–4)</td>
<td>8.70 ± 2.30 (4–12)</td>
</tr>
<tr>
<td>C (n = 46)</td>
<td>2.09 ± 0.73 (1–3)</td>
<td>4.00 ± 0.00 (4–4)</td>
<td>8.35 ± 2.90 (4–12)</td>
</tr>
<tr>
<td>Anti-TPR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N (n = 45)</td>
<td>0.82 ± 0.39 (0–1)</td>
<td>1.22 ± 0.74 (0–2)</td>
<td>1.22 ± 1.22 (0–2)</td>
</tr>
<tr>
<td>HGPIN (n = 22)</td>
<td>1.39 ± 0.72 (0–2)</td>
<td>1.91 ± 0.90 (0–4)</td>
<td>3.09 ± 1.88 (0–8)</td>
</tr>
<tr>
<td>C (n = 46)</td>
<td>1.39 ± 0.88 (0–3)</td>
<td>1.98 ± 1.22 (0–4)</td>
<td>3.48 ± 3.24 (0–12)</td>
</tr>
</tbody>
</table>

COX-2 = cyclooxygenase-2; TXS = thromboxane synthase; TPR = thromboxane receptor; n = number of cases; N = normal prostatic glands; HGPIN = high-grade prostatic intraepithelial neoplasia; C = cancer. I score is an intensity score ranging from 0 to 3; E score is extent score ranging from 0 to 4; IE score is intensity × extent score ranging from 0 to 12. All values are expressed as mean ± standard deviation (minimum to maximum).
Fig. 2 – Detection of cyclooxygenase 2 (COX-2), thromboxane synthase (TXS), and thromboxane A₂ receptors (TPRs) using immunoperoxidase in human prostate tissues. (A) Immunohistochemical detection of COX-2 in human prostate cancer (PCa) cells. The inset in the upper right corner shows a higher magnification of the COX-2–expressing PCa cells. (B) Control experiment using the same tissue sample (serial section) as in panel A, in which anti-COX-2 antibody was omitted in the immunoperoxidase assay. (C) Detection of TXS in PCa cells (same tissue sample as in panel A). (D) Control experiment in which the anti-TXS antibody was incubated with an excess of the corresponding peptide prior to its use in the immunoperoxidase assay. Note the markedly reduced level of anti-TXS immunoreactivity in tumor cells. (E) Detection of TPR in PCa cells. (F) Control experiment in which the anti-TPR antibody was incubated with an excess of the corresponding peptide prior to its use in the immunoperoxidase assay. Note the markedly reduced level of anti-TPR immunoreactivity in tumor cells. Representative examples of moderately (G) and poorly (H) differentiated prostate adenocarcinoma (c) showing strong anti-TPR immunoreactivity. No or a weak detectable level of TPR was found in adjacent nontumoral prostate glands.
2.5. Statistical analysis

A paired t test was used to compare the immunostaining scores between cancer, HGPIN, and normal prostate glands. The Spearman rank correlation test was performed to evaluate the degree of association between the specific staining scores and the clinicopathologic features of the tumors. A \( p < 0.05 \) was considered as statistically significant. Statistical analyses were carried out using the StatView 5.0 software (Abacus Concepts, Berkeley, CA).

3. Results

3.1. The two main TXA2 biosynthetic enzymes, COX-2 and TXS, and its receptors are overexpressed and colocalized in human PCa

We examined the expression of the main components of the TXA2 pathway in human PCa cells. The expression of the TPRs and that of the 2 enzymes involved in its synthesis, COX-2 and TXS, was evaluated using immunohistochemistry in a series of human PCa lesions. Among the enzymes responsible for TXA2 synthesis, no detectable or a weak level of expression of COX-2 and TXS was observed in nontumoral glands, whereas adjacent cancer cells usually expressed high levels of the enzymes (Fig. 2A and C). All tumor lesions showed a detectable level (intensity score of 1+, 2+, or 3+) of TXS and COX-2 expression (Table 2). In addition, among the 46 PCa lesions analyzed, 39 (85%) and 37 (78%) expressed moderate to strong levels (intensity score of 2+ or 3+) of COX-2 and TXS, respectively. Increased levels of TXS and COX-2 expression were also usually observed in HGPIN glands as compared with nontumoral glands (data not shown).

Positive staining was abolished or strongly reduced by omission of the primary antibodies or preincubation of the primary antibodies with the corresponding synthetic peptides (Fig. 2A–D). As previously described [20,25,26], COX-2 expression was systematically detected in the epithelium lining ejaculatory ducts and seminal vesicles when present in the tissue sections, was observed in scattered inflammatory cells, including macrophages and lymphocytes, but was not detected in endothelial cells (data not shown). Anti-COX-2, anti-TXS, and anti-TPR immunostaining was prominently cytoplasmic.

Fig. 2E–L shows representative photomicrographs of anti-TPR immunoreactivity. Epithelial cells from nontumoral glands usually exhibited no or a low detectable level of TPRs. In contrast, TPR expression levels in HGPIN and cancer glands/cells were generally increased as compared with those found in nontumoral cells (Fig. 2G–J). Most PCa lesions studied (38 of 45, 74.4%) expressed detectable levels of TPR (intensity score of 1+, 2+, or 3+). TPR expression was heterogeneous within the same tumor and the highest levels of immunoreactivity were frequently observed in the most undifferentiated and infiltrating areas (Fig. 2K). In cases showing perineural invasion, neoplastic cells frequently exhibited strong TPR expression (Fig. 2L). Positive TPR staining was abolished by preincubation of the primary antibody with the corresponding synthetic peptide (Fig. 2E and F).

Results of anti-COX2, anti-TXS, and anti-TPR staining intensity and extent scoring are summarized in Table 2. Immunostaining extent and intensity for the proteins tested was higher in cancer cells and HGPIN glands than in nontumoral prostate glands (paired t test, \( p < 0.005 \)). No significant difference in anti-COX-2, anti-TXS, or anti-TPR immunostaining intensity or extent was found between cancer cells and HGPIN glands. As shown in representative examples in Fig. 3, all proteins examined also appeared to be coordinately upregulated within the same tumor. Indeed, all tumors exhibiting detectable levels of TPR also expressed COX-2 and TXS. In addition, among tumors expressing moderate to strong levels (2+ and 3+ intensity scores) of TPR expression, 95% and 90% of them also expressed moderate to strong levels (2+ and 3+ intensity scores) of COX-2 and TXS, respectively (data not shown).

3.2. The expression levels of COX-2, TXS, and TPR are significantly associated with extraprostatic extension and loss of differentiation of human PCa

We then compared COX-2, TXS, and TPR expression levels in tumors with 2 major histopathologic (n). (1) Moderately differentiated prostate adenocarcinoma and adjacent HGPIN glands (p) expressing moderate levels of TPR. Note absence of TPR expression in nontumoral prostate glands. (J) HGPIN glands exhibiting strong anti-TPR immunoreactivity. (K) Strong anti-TPR immunoreactivity in moderately differentiated adenocarcinoma glands (m) with a low detectable level of TPR expression in well differentiated cancer glands (w). (L) Focus of perineural invasion by PCa cells showing strong anti-TPR reactivity. c = cancer; p = HGPIN; n = normal; w = well differentiated adenocarcinoma glands (Gleason score 4); m = moderately differentiated adenocarcinoma glands (Gleason score 6). Original magnification: panels A–D, I, and K, \( \times 100 \); E–G and J, \( \times 200 \); H and L, \( \times 400 \).
Table 3 – Evaluation of the associations between pathologic parameters (pathologic state and Gleason score) and anti-COX-2, anti-TXS or anti-TPR staining intensity and extent in human prostate cancer

<table>
<thead>
<tr>
<th>Associated tests</th>
<th>p value (Spearman rank correlation)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>COX-2</td>
</tr>
<tr>
<td>Pathologic stage vs I score</td>
<td>0.0011</td>
</tr>
<tr>
<td>Pathologic stage vs E score</td>
<td>0.0036</td>
</tr>
<tr>
<td>Pathologic stage vs IE score</td>
<td>0.0029</td>
</tr>
<tr>
<td>Gleason score vs I score</td>
<td>0.0010</td>
</tr>
<tr>
<td>Gleason score vs E score</td>
<td>0.0003</td>
</tr>
<tr>
<td>Gleason score vs IE score</td>
<td>0.0009</td>
</tr>
</tbody>
</table>

COX-2 = cyclooxygenase-2; TXS = thromboxane synthase; TPR = thromboxane receptor; NA = not applicable because all tumors contained a high percentage of cancer cells showing detectable anti-TXS immunoreactivity (immunostaining extent score 4), regardless of their pathologic stage or Gleason score. I score = intensity score ranging from 0 to 3; E score = extent score ranging from 0 to 4; IE score = intensity × extent score ranging from 0 to 12.

4. Discussion

A detailed analysis of the key actors of the TXA2 pathway is definitely warranted to justify the use of existing or future inhibitors of this pathway as preventive or therapeutic agents. Indeed, the administration of such inhibitors would obviously not be recommended if the enzymes belonging to this pathway are not expressed in the targeted tissue.

It is generally accepted that COX-2, an inducible enzyme as opposed to the more constitutively expressed COX-1, is normally undetectable in most tissues. Its expression in certain cell types has been shown to be induced by proinflammatory or mitogenic agents [37,38]. It is also widely recognized that COX-2 expression is up-regulated in many epithelial cancers such as colon, breast, gastrointestinal, and lung cancers.

Whether COX-2 is overexpressed in human PCa cells, as determined by immunohistochemistry, remains a subject of debate at this time. Our study is one among many others that have found an up-regulation of COX-2 expression in human PCa cells. We have searched PubMed for studies in which COX-2 expression was evaluated by immunohistochemistry in human PCa tissues. Strikingly, among 13 identified articles dealing with this issue [17–29], researchers in 11 studies concluded that COX-2 is overexpressed in PCa cells as compared with nontumoral prostate glands [17–19,21–27,29]. One paper showed ‘mixed’ results suggesting that, as compared with nontumoral prostate glands, COX-2 transcript and protein in PCa cells may be underexpressed and overexpressed, in moderately and poorly differentiated PCas, respectively [28]. We have found only one study, in which COX-2 is described to be expressed neither by PCa cells nor by normal secretory cells, unless they are involved in an inflammatory process (or postinflammatory atrophy areas) [20]. In this latter study, Zha et al. have tested the same antibody as the one that was used in our study [20]. Intriguingly, in their hands, this antibody has generated a striking plasma membrane staining pattern, which we have not seen in our analysis of COX-2 expression. Similarly to Zha et al. [20], we have found high levels of COX-2 expression in the epithelial lining of ejaculatory ducts and seminal vesicles. It is likely that contradictory data may have been the result of the different methodologies used (e.g., various antibodies or different batches of the same antiseraum, hormonal status, tissue processing, immunohistochemistry procedures used). In our study, we have further found, as previously described [19,24,26,28], an...
inverse and significant association between COX-2 levels and tumor differentiation.

Overall, our data provide additional evidence that COX-2 is overexpressed in HGPIN [18,23] and PCa glands and support the potential use of COX-2 inhibitors as chemopreventive or therapeutic agents of PCa. Although most preclinical investigations have provided compelling and converging evidence that both selective COX-2 inhibitors and nonselective NSAIDs may effectively reduce or inhibit chemically induced carcinogenesis of epithelial tumors and angiogenesis [39–41], the implementation of cancer prevention strategies, based on these findings, has been hampered by the recognized toxicity of NSAIDs chronic use [42]. In addition, the recent withdrawal of specific COX-2 inhibitors due to cardiovascular toxicity [43–45] represents a new serious obstacle to the targeting of COX-2 for cancer prevention or treatment [46]. Therefore, the selective targeting of downstream
COX-2 metabolites, such as TXA₂, may appear more judicious. TXA₂, a powerful aggregation mediator involved in thrombotic disorders, has been recently demonstrated to participate in cancer progression [7–10]. TXA₂ is a key mediator of cancer cell-induced platelet aggregation, a process that favors blood-borne metastasis [11]. It also acts as a potent angiogenesis stimulator, both directly and by inducing platelet vascular endothelial growth factor (VEGF) and platelet derived growth factor (PDGF) secretion following platelet aggregation [12–15]. Our data indicate that human PCas overexpress TXS and receptors, with a significant association between the expression levels of these proteins and higher Gleason score and pathologic stage of the tumors. We have also observed that TXS and TPR are usually up-regulated in HGPIN glands, indicating that overexpression of these proteins may be an early event in prostate carcinogenesis. In addition, because these proteins are predominantly co-expressed, they may contribute to PCA development in an autocrine manner.

Anti-TPR immunoreactivity was observed to be mainly cytoplasmic. This result is not unexpected because previous studies have shown that TPRs become internalized upon agonist exposure [47–49]. In fact, our observation that TPRs are mainly found in the cytoplasmic compartment of PCA cells supports the hypothesis of an autocrine loop, in which the cells synthesize TXA₂ that subsequently binds and activates its receptors. Another explanation for the cytoplasmic localization of TPRs is that TPRs can also be found in the endoplasmic reticulum and the Golgi complex [50]. It has also been shown that TPβ receptor can be constitutively endocytosed and that constitutive endocytosis of TPβ receptors may form a pool of receptors in perinuclear recycling endosomes from which they recycle to the cell surface, a process involved in preserving receptor sensitivity to agonist stimulation [51].
The mechanisms by which COX-2-derived prostanoids might contribute to carcinoma development or progression are not precisely defined, but potentially include protection against apoptosis [52] and contribution to tumor angiogenesis [53–55]. Furthermore, at this time it is not known why PCa cells do overexpress enzymes participating in the TXA2 pathway. Accumulating evidence suggests a role for inflammation in prostate carcinogenesis [56]. Epidemiology data have correlated prostatitis with increased PCa risk and intake of anti-inflammatory drugs with decreased PCa risk. Proliferative inflammatory atrophy lesions containing activated inflammatory cells and proliferating epithelial cells may also be precursors to HGPIN lesions and PCa. COX-2 has been linked to inflammation in the normal and malignant prostate [20]. It has been recently shown that elevated COX-2 expression levels in PCa cells may be associated with increased inflammatory cell density, both of T lymphocytes and macrophages, suggesting that COX-2 expression may be up-regulated focally in tumor areas with chronic inflammation [26]. It has therefore been proposed that proinflammatory cytokines, released by T-lymphocytes and macrophages, may up-regulate COX-2 in adjacent tumor cells. In line with this concept, mutations of one of the putative PCa susceptibility genes, MSR1 (encoding macrophage scavenger receptor-1), may contribute to prostate carcinogenesis through a macrophage-mediated effect [57–61]. Regarding TXS and TPRs, their over-expression in PCa cells may obviously be the result of epigenetic or genetic alterations, which remain to further investigated. Whether expression of TXS and TPRs in prostate epithelial cells may be affected by cytokines should be the focus of further studies.

5. Conclusions

In conclusion, the results of the present study indicate for the first time that the expression of the key proteins involved in the TXA2 pathway are up-regulated in HGPIN and PCa cells. In PCa lesions, overexpression of these proteins is associated with tumor extraprostatic extension and loss of differentiation. Overall, these findings identify the TXA2 pathway as a potential target for PCa prevention or treatment or both.

Acknowledgments

The authors thank Pascale Heneaux for technical assistance. D. Waltregny and L. de Leval are Research Associates and T. Dassesse is a Télévie research Fellow at the National Fund for Scientific Research (FNRS, Belgium).


References

Masferrer JL, Leahy KM, Koki AT, et al. Antiangiogenic and...HPC1, and MSR1 with PCa severity in European American...the thromboxane A2 pathway in the prostate. Characterisation of key-members of this pathway as is currently reported, offers a rationale for the further development of chemopreventive targets in prostate cancer.

References


Clinical, epidemiological and molecular biological studies all imply involvement of inflammatory pathways in prostate cancer [1]. Intake of NSAIDs is generally associated with an inverse association with prostate cancer development [2]. The mechanisms underlying these chemopreventive effects are still poorly understood.

First, inhibition of inflammatory pathways might directly affect prostate cancer cells. The data currently presented by Dassesse et al. support this hypothesis as they clearly demonstrate over-expression of cyclo-oxygenase-2, thromboxane A2 synthase and its receptors in malignant prostate epithelium. Inhibition of these enzymes or receptors by NSAIDs would accordingly have apoptotic or anti-proliferative effects, resulting in remission of latent tumours. Concomitantly, anti-inflammatory drugs potentially prevent progression of pre-malignant lesions. The authors namely demonstrate expression of these inflammatory pathways in PIN, which is generally assumed to represent the precursor of prostate cancer.

Second, besides direct effects on tumour cells, reduction of prostatic inflammation might contribute to the chemoprevention of prostate cancer. Although prostatitis is generally considered a clinical diagnosis, microscopic prostatic inflammatory foci are almost invariably encountered in normal patients. These foci are often associated with morphologic atrophy of adjacent epithelial glands, which paradoxically demonstrate enhanced proliferative activity and have therefore been referred to as ‘proliferative inflammatory atrophy’ [3]. Although these lesions are not considered to be malignant precursors per se, early (epi)genetic alterations are identified in subsets of atrophic epithelial glands presumably in consequence of their continuous exposure to inflammatory oxidants such as nitric oxide and superoxide [4]. Direct targeting of the inflammatory responses by anti-oxidative and -inflammatory drugs would therefore logically represent another chemopreventive mechanism.

Unfortunately, the authors did not specifically consider atrophic lesions in their analysis of the thromboxane A2 pathway in the prostate. Characterisation of key-members of this pathway as is currently reported, offers a rationale for the further development of chemopreventive targets in prostate cancer.

References


Editorial Comment
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First, inhibition of inflammatory pathways might directly affect prostate cancer cells. The data currently presented by Dassesse et al. support this hypothesis as they clearly demonstrate over-expression of cyclo-oxygenase-2, thromboxane A2 synthase and its receptors in malignant prostate epithelium. Inhibition of these enzymes or receptors by NSAIDs would accordingly have apoptotic or anti-proliferative effects, resulting in remission of latent tumours. Concomitantly, anti-inflammatory drugs potentially prevent progression of pre-malignant lesions. The authors namely demonstrate expression of these inflammatory pathways in PIN, which is generally assumed to represent the precursor of prostate cancer.

Second, besides direct effects on tumour cells, reduction of prostatic inflammation might contribute to the chemoprevention of prostate cancer. Although prostatitis is generally considered a clinical diagnosis, microscopic prostatic inflammatory foci are almost invariably encountered in normal patients. These foci are often associated with morphologic atrophy of adjacent epithelial glands, which paradoxically demonstrate enhanced proliferative activity and have therefore been referred to as ‘proliferative inflammatory atrophy’ [3]. Although these lesions are not considered to be malignant precursors per se, early (epi)genetic alterations are identified in subsets of atrophic epithelial glands presumably in consequence of their continuous exposure to inflammatory oxidants such as nitric oxide and superoxide [4]. Direct targeting of the inflammatory responses by anti-oxidative and -inflammatory drugs would therefore logically represent another chemopreventive mechanism.

Unfortunately, the authors did not specifically consider atrophic lesions in their analysis of the thromboxane A2 pathway in the prostate. Characterisation of key-members of this pathway as is currently reported, offers a rationale for the further development of chemopreventive targets in prostate cancer.

References