The Lack of Epithelial Interleukin-7 and BAFF/BlLyS Gene Expression in Prostate Cancer as a Possible Mechanism of Tumor Escape from Immunosurveillance

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Abstract

Purpose: The human prostate is endowed with intraepithelial and stromal lymphocytes, which may develop lymphoid follicles (LF) and allow a local immune response. We sought to investigate whether interleukin (IL)-7 and BAFF/BlLyS, two fundamental survival factors for T and B cells, are expressed in the normal and neoplastic prostate and affect intraprostatic lymphocyte homeostasis.

Experimental Design: We have used real-time reverse transcription-PCR of microdissected prostatic glands and confocal microscopy to detect cytokine production, combined with immunohistochemistry to characterize intraprostatic lymphocytes.

Results: Prostatic epithelia constitutively produce IL-7 and, to a lesser extent, BAFF/BlLyS. Indeed, we show that IL-7 receptor α is expressed by intraepithelial T lymphocytes and parafollicular T cells, whereas BAFF-R is found on periglandular B lymphocytes and mantle zone B cells of LFs. Prostate-homing B and T lymphocytes are scarcely proliferating, whereas most of them express the antiapoptotic protein bcl-2 and reveal a low apoptotic index in the terminal deoxynucleotidyl transferase–mediated dUTP nick end labeling assay. The transition from normal to neoplastic glands in prostate cancer (PCa) is marked by a dramatic decline of IL-7 and BAFF/BlLyS production. Accordingly, PCa is characterized by a significant reduction of intraprostatic lymphocytes and loss of LFs. B-cell and T-cell expression of bcl-2 decrease, whereas the apoptotic events increase. The remaining PCa-infiltrating lymphocytes are mostly CD8+ T cells that lack terminal differentiation and barely penetrate neoplastic glands.

Conclusions: These results suggest that epithelial IL-7 and BAFF/BlLyS production support intraprostatic lymphocyte survival. Its loss in PCa is associated with a severe depletion of prostate-associated lymphocytes and points to a novel tumor escape mechanism.

Prostate tissue is composed of a mixture of glands and intervening fibromuscular stroma (1). We have recently characterized a third element, namely, the prostate-associated lymphoid cell population (2). This is embedded in both components in the form of intraepithelial lymphocytes, mainly CD8+ T cells, and stromal lymphocytes, sometimes arranged (as observed in a significant number of subjects) in lymphoid follicles (LF), which are CD20+ B-cell follicles that may develop a germinal center (GC) surrounded by parafollicular CD3+ T-cell areas and are located adjacent to the double-layered glandular epithelium (2). This anatomic setting strongly suggests the possibility of an intimate cross-talk between glandular epithelia and associated lymphoid cells and leads to speculation on the local production of cytokines endowed with a lymphoid cell growth, differentiation, or survival function.

Interleukin (IL)-7 is a pleiotropic cytokine with central roles in modulating T-cell and B-cell development, and peripheral naive and memory T-cell homeostasis (3–5). Binding of IL-7 to its receptor (IL-7R), which consists of two components, the α chain (IL-7Ra) and the γ chain, shared by receptors for IL-2, IL-4, IL-9, IL-15, and IL-21, activates multiple pathways that regulate lymphocyte survival, proliferation, and differentiation. IL-7 is primarily important for the survival of memory CD8+ T cells through its antiapoptotic effect via up-regulation of bcl-2 (6–9). The physiologic role of IL-7 as a trophic factor for developing B cells through the modulation of bcl-2 family members has not yet been definitively determined (4), at least in humans.

The key role of the B-cell–activating factor of the tumor necrosis factor family (BAFF; also called BlLyS, TALL-1, zTNF-4, or THANK; ref. 10) in B-cell biology includes immunoglobulin isotype switching, GC maintenance, and expression of surface molecules (11), whereas its prime function is the control of
B-cell maturation and homeostasis (12) by stimulating the expression of prosurvival proteins bcl-2 and bcl-xl and decreasing that of proapoptotic factors such as Bak and, potentially, Blk (13–15). Signals through BAFF-R/BR3, the BAFF-specific receptor (16), increase bcl-2 expression in both T cells (17) and B cells (13), which may result in enhanced basal T-cell survival, particularly by BAFF-R+ T cells, such as effector and central memory subsets.

In this study, we set out to determine whether IL-7 and BAFF are expressed in the human prostate and affect intraprostatic T and B lymphocyte homeostasis. Our approach was based on laser capture microdissection (LCM), a technology that allows isolation of individual cell populations, followed by reverse transcription-PCR (RT-PCR) and real-time RT-PCR. In addition, immunofluorescence and laser scanning confocal microscopy were used to investigate protein production, combined with immunohistochemistry to characterize intraprostatic lymphocyte populations.

**Materials and Methods**

**Patients and samples.** Normal prostates were obtained from 12 untreated patients ages 57 to 63 following prostatectomy for bladder cancer (control patients). They were histologically negative for prostate cancer (PCa) or benign prostatic hyperplasia. PCAs were from 46 patients (PCa patients) ages 64 to 74 following radical prostatectomy for histologically verified adenocarcinomas at biopsy. Both normal and cancer specimens, from each PCa patient, were collected.

Preoperative androgen deprivation had not been used. PCA samples were graded as Gleason score 5 (n = 9), 6 (n = 7), 7 (n = 13), 8 (n = 10), and 9 (n = 7) and staged as pT2 [organ-confined cancer; n = 27 (7 T2a, 12 T2b, and 8 T2c)] and pT3 [capsular penetration; n = 19 (17 T3a and 2 T3b)].

One half of each sample was fixed in 4% formalin and embedded in paraffin, and the other was embedded in Killik frozen section medium (Bio-Optica), snap frozen in liquid nitrogen, and preserved at -80°C.

For histology, paraffin-embedded samples were sectioned at 4 μm and stained with H&E. Single and double immunohistochemistry was done on paraffin-embedded sections, combined with immunohistochemistry to characterize intraprostatic lymphocyte populations.

**Antibodies and immunohistochemistry.** For immunohistochemistry on the formalin-fixed, paraffin-embedded samples, sections were treated as previously reported (18) with the primary antibodies listed in Table 1.

For immunohistochemistry on the frozen samples, cryostat sections were fixed in acetone for 10 min. After washing in PBS/Tween 20, sections were stained as reported (18) with the primary antibodies listed in Table 1.

**Translational Relevance.**

This article reports novel findings in the area of Human Cancer Biology and particularly in the immunopathology of prostate cancer. We believe that these findings, obtained from investigations carried out on a fairly large number of patient tissue samples, are of relevance in the development of vaccines and forms of immunotherapy for prostate cancer.
vial. RNA was immediately isolated with RNeasy Mini kit (Qiagen). RT and PCR were done using the iScript cDNA Synthesis kit and the iQ RT-PCR was done using the iCycler iQ real-time RT-PCR was carried out on an MJ Mini Gradient Thermal Cycler (Bio-Rad) under the following conditions: IL-7, initial denaturation at 95°C for 3 min followed by 35 amplification cycles (denaturation at 94°C for 30 s, annealing at 58°C for 30 s, and extension at 72°C for 30 s); BAFF, initial denaturation at 95°C for 12 min followed by 35 amplification cycles (denaturation at 94°C for 30 s, annealing at 60°C for 30 s, and extension at 72°C for 30 s); GAPDH, initial denaturation at 95°C for 3 min followed by 35 amplification cycles (denaturation at 94°C for 30 s, annealing at 57°C for 30 s, and extension at 72°C for 30 s). For each sample, a mock reaction without reverse transcriptase (RT-) was done. The PCR products were separated on a 2% agarose gel stained with ethidium bromide. DNA bands were visualized with a Transilluminator 2000 (Bio-Rad). All experiments were done in triplicate.

**LCM and real-time RT-PCR.** For LCM, we used the P.A.L.M. Micro Beam System (P.A.L.M. Microlaser Technologies). Frozen sections (10 μm), from normal prostate samples (of both control and PCA patients) and PCA samples, were mounted on polyethylene naphthalate membrane-covered slides (P.A.L.M.), thawed at room temperature, and immersed in cold acetone (5 min). Two sections per sample were analyzed. All reagents were prepared using Ultrapure DNase/RNase-free distilled water (Invitrogen). Immediately after staining, sections were used for LCM. Selected cells were cut and catapulted intact into the cap of an LPC-Microfuge Tube (P.A.L.M.), and RNA was immediately isolated with the RNeasy Micro kit (Qiagen). RT-PCR and visualization of amplified cDNA fragments were done as described above.

The real-time RT-PCR was carried out using the iScript cDNA Synthesis kit for RT and the iQ SYBR Green Supermix for real-time PCR (both from Bio-Rad) with the following primers: IL-7, 5′-AAAAGTGATCTTGTTG-3′ (forward) and 5′-GGTTATGCTTCTTTGGC-3′ (reverse); BAFF, 5′-ATGTAAGGTTCCACAGAAG-3′ (forward) and 5′-TGGCAGCAAGACAGCAGT-3′ (reverse). The housekeeping gene glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was used as a control to assess RT and PCR efficiency using the following primers: forward, 5′-CCACTTCTATGACATGTGCAAG-3′; reverse, 5′-CAGCTCAGTGCTG-3′ (reverse). BAFF mRNA in the prostate tissue (Fig. 2A). Human prostatic epithelium expresses IL-7 mRNA and produces IL-7 protein. Because the human prostate is regularly embedded by lymphocytes, mainly T cells (2), we used RT-PCR to assess the expression of IL-7, a cytokine essential for T-cell development and homeostasis (4), in normal prostate sections from untreated patients following prostatectomy for bladder cancer.

IL-7 mRNA was expressed as shown in Fig. 1A, where the specificity of the amplified band was validated by its predicted size (764 bp). Double immunofluorescent staining and confocal microscopy revealed IL-7 protein production in most of the glandular epithelium in both the apical (CK18) and the basal (p63; ref. 20) epithelial cell layer (Fig. 1B, a-g) and frequently in blood vessel endothelial cells (marked by anti-VWF; Fig. 1B, h). LCM of the whole epithelia, marked by CK5/6/18 immunostaining on frozen sections, followed by RT-PCR analyses of the isolated cells, showed their expression of IL-7 mRNA (Fig. 1C) in accordance with the immunohistochemical findings.

**Lymphocytes and endothelial cells express IL-7Rα.** This demonstration of IL-7 production by prostatic epithelial and endothelial cells prompted us to look for its target by investigating the expression of IL-7Rα (CD127), the specific component of the IL-7R complex (5).

Immunohistochemistry on paraffin sections revealed IL-7Rα expression on peripapillary and intraepithelial small mononuclear cells displaying a lymphocyte morphology (Fig. 1D, a), mostly identified as CD3+, and on stromal lymphocytes, particularly those located at the parafollicular T-cell zone of periglandular lymphoid aggregates (Fig. 1D, b). Expression of IL-7Rα could also be found on stromal microvessels (Fig. 1D, c) and sometimes on vessels with H&E-like features, such as those found in lymphoid aggregates (Fig. 1D, d).

Human prostatic epithelium expresses BAFF mRNA and produces BAFF protein. In view of the B-cell component of the IL-7R complex (5), we investigated the local expression of BAFF, which plays a fundamental role in regulating peripheral B-cell survival and homeostasis (12).

RT-PCR showed BAFF mRNA in the prostate tissue (Fig. 2A). The specificity of the related amplified band was validated by its predicted size (184 bp). Immunohistochemistry on frozen sections disclosed BAFF protein expression in the basal epithelial layers of many glands of the prostate (Fig. 2B and C). RT-PCR examination of microdissected p63+ basal cells supported this result by showing their expression of BAFF mRNA (Fig. 2D).

BAFF protein was also identified as CD3+ T lymphocytes, mostly those with the CD4+CD45RO+ memory phenotype, arranged in loosely or well-organized follicle-like structures, as assessed by confocal microscopy (Fig. 3A, a-i).

**Expression of BAFF-R, mostly by CD20+ cells.** BAFF binds to three receptors, namely, BCMA (B-cell maturation antigen;
ref. 12), TACI (transmembrane activator and calcium modulator and cyclophilin ligand interactor; ref. 12), both of which also bind APRIL (a proliferation-inducing ligand), and BAFF-R/BR3 (16), which is specific for BAFF. We therefore looked for the expression of BAFF-R/BR3 by immunohistochemical analysis of prostate paraffin sections. BAFF-R was expressed by many lymphocytes scattered in the periglandular stroma (Fig. 3B, a), whereas in the LFs it was mainly found on CD20+ B cells and rarely on T cells, as assessed by double immuno-histochemistry (Fig. 3B, b-d). BAFF-R was weakly expressed by GC B lymphocytes and clearly expressed by B cells colonizing the mantle zone, as illustrated in Fig. 3C (a and b).

Fig. 1. Expression of IL-7 and IL-7Rα in the human prostate. A, expression of IL-7 in normal prostate tissue as determined by RT-PCR. Lane 1, RT−; lane 2, GAPDH; lane 3, IL-7. B, IL-7 protein was produced (a) by luminal epithelial cells, marked by CK18 (b), of normal prostatic glands, as shown by their partial colocalization (yellow in c and d, which is a magnification of details from c). IL-7 was also produced (e) by the basal epithelial cells (f, detectable through their nuclear p63 positivity), as shown by their green-stained cytoplasm (g) and by vWF+ endothelial cells (h, red) as revealed by the merge image in h. Magnification, ×400 (a–h). C, expression of IL-7 in microdissected CK5/6/18+ epithelial cells as determined by RT-PCR. Lane 1, RT−; lane 2, GAPDH; lane 3, IL-7. D, IL-7Rα expression on periepithelial (inset in a) and intraepithelial lymphocytes (a) and on stromal lymphocytes, particularly those located at the parafollicular T-cell zone of lymphoid aggregates (b). Expression of IL-7Rα can also be found on stromal vessels (c) and, sometimes, on HEV in the context of lymphoid aggregates (d). Magnifications, ×400 (a, b, and d) and ×630 (c).
Prostate-infiltrating lymphocytes display low proliferation but wide expression of the antiapoptotic protein bcl-2. We have recently shown that most prostate-infiltrating T and B cells are located inside (in the form of intraepithelial lymphocytes) or close to (sometimes in the form of LFs) the glandular epithelium (2). In the present study, we have observed that these lymphocytes mostly express IL-7Rα and/or BAFF-R. It can thus be hypothesized that production of IL-7 and BAFF by the prostatic epithelia is involved in modulating intraprostatic lymphocyte proliferation and/or survival.

Intraprostatic lymphocytes were scarcely proliferating, as assessed by Ki-67 immunostaining. As previously described (2), in addition to a few basal cells of the glandular epithelium, Ki-67 positivity was only detected in GC lymphocytes of LFs (Fig. 4A and B).

The vast majority of prostatic lymphocytes, both stromal (organized in LFs, that is, CD20+ B-cell follicle encircled by parafollicular T-cell area, Fig. 4C-H, or not organized, Fig. 4I-K) and intraepithelial lymphocytes (Fig. 4I), strongly expressed the antiapoptotic protein bcl-2. Accordingly, they showed very low apoptotic rate as revealed by their rare positivity in the TUNEL assay (Fig. 4M). Prostate-homing lymphocytes thus have low proliferative and high antiapoptotic activity.

Loss of IL-7 and BAFF production in neoplastic prostatic glands is accompanied by reduction of CD8+ and CD20+ cell infiltrates. To find out whether epithelial production of IL-7 and BAFF and thus their trophic action on intraprostatic lymphocytes are subverted by tumor onset, we next did immunohistochemistry, LCM, and real-time RT-PCR to determine their expression level on prostate adenocarcinoma sections from 46 untreated patients.

By LCM, we isolated malignant glands from cancer samples and the whole normal glandular epithelium from normal prostate samples (of both control and PCa patients). Real-time RT-PCR revealed that, in contrast to normal prostatic glands, malignant glands showed low to absent, ~60 times lower than in the normal glands (Fig. 5A), IL-7 mRNA expression. In addition, immunohistochemical examination of subsequent serial sections showed that IL-7 protein production was distinct in normal glands and scarce to absent in neoplastic glands (Fig. 5B, a and b). To determine whether this deficiency of IL-7 production was associated with alterations in T lymphocyte content, we next compared the lymphocyte infiltrates of normal (from both control and PCa patients) and neoplastic tissues. In comparison with normal prostate, PCa was largely lacking in the LFs but still detectable in the remaining nonneoplastic tissue. Expression of the chemokines B lymphocyte chemo-attractant, also called CXCL13, and secondary lymphoid tissue chemokine, also known as CCL21, which we previously found (2) associated with LFs, was lost too (Fig. 5B, c-e). Accordingly, CD4+ T lymphocytes, mostly lying in the parafollicular areas of LFs, were scarce in PCa. The remaining T cells were mainly CD8+ (Fig. 5B, f and g), and the vast majority displayed the CD45RA-CD45RO+CCR7- effector-memory phenotype and were CD27+CD28- preterminally differentiated or CD27+CD28+ at an early differentiation stage (21) as assessed by immunohistochemistry (Fig. 5C, a-f). CD8+ T lymphocytes were significantly (P < 0.05) more numerous in the normal prostate, 26.2 ± 5.5 (mean ± SD of positive cells/×400 field), located inside and within glandular epithelium, than in PCa, 17.8 ± 4.2, located within, rather than inside, neoplastic glands (Fig. 5B, f and g). At the same time, the percentage of CD8+ cells with positive cytoplasmic staining for the antiapoptotic protein bcl-2 was decreased in PCa (85.1 ± 5.3%; Fig. 5D, a and b), in comparison with the normal prostate (97.0 ± 2.4%), as assessed by double CD8/bcl-2 staining on paraffin sections.
Accordingly, the percentage of TUNEL+ CD8+ cells was increased in PCa, 16.5 ± 3.7%, when compared with normal prostates, 4.4 ± 2.0% (Fig. 5D, c and d).

LCM followed by real-time RT-PCR examination of neoplastic glands versus normal glands revealed a low to absent, about five times lower than in the normal glands, BAFF mRNA expression (Fig. 5E). Accordingly, a loss of BAFF protein production was assessed by immunohistochemistry (Fig. 5F, a and b). Concomitant decline in the number of periglandular CD20+ B lymphocytes was revealed in PCa, within neoplastic glands, 3.0 ± 2.4, compared with the normal prostate, 13.1 ± 3.9 (Fig. 5F, c and d). The percentage of bcl-2–expressing CD20+ B cells was also reduced in PCa (88.5 ± 4.2%) compared with the normal prostate (95.8 ± 3.0%).

CD8+ and CD20+ lymphocyte counts in PCa were significantly lower than in the normal prostate starting from the lower Gleason score and no significant association was disclosed by Mann-Whitney U test or the χ² test between these counts and the different Gleason scores, tumor-node-metastasis stages, and patient age.

Notably, data about cell counts and IL-7 or BAFF production obtained in normal samples from PCa patients were analogous to those obtained in normal samples from control patients. Furthermore, no significant differences of either IL-7 or BAFF expression emerged, with real-time RT-PCR analyses, by ANOVA test, between groups of patients with different Gleason scores.

**Discussion**

We here provide the first evidence that the prostatic epithelium is a source of both IL-7 and, to a lesser extent, BAFF, two cytokines that are needed for lymphocyte development and homeostasis, and may also act on intraprostatic T and B cells because most of them express IL-7Rα and BAFF-R, respectively.
This observation strongly indicates the existence of an epithelial lymphocyte cross-talk that may be subverted during tumor onset because replacement of the normal epithelium by neoplastic cells implies the dramatic decline of IL-7 and BAFF/BLyS production associated with a reduced lymphocyte bcl-2 expression, increased apoptosis, and consequent impoverishment of intraepithelial and stromal lymphocytes with loss of LFs.

IL-7 is a nonredundant trophic factor for immune cell development that primarily acts by promoting cell survival (22, 23). In humans, it has been identified from thymic stromal cells (primarily MHC class II+ epithelial cells) and subsequently intestinal epithelial cells (24), keratinocytes (25), and hepatocytes (26). It is also produced by follicular (27) and peripheral blood dendritic cells (28), endothelial cells (27), smooth muscle cells (27), and fibroblasts (26). Even so, it is not really clear which cells supply the IL-7 for peripheral T cells nor whether its synthesis by these cells is regulated or constitutive (29). Our study shows that the normal prostate, which is endowed with a discrete number of scattered intraepithelial and stromal lymphoid cells (2, 30, 31), constitutively produces IL-7.

Fig. 4. Expression of Ki-67 and bcl-2 in prostate-infiltrating lymphocytes. In the normal prostate, rare lymphocytes, a few basal cells of the glandular epithelium (A) and GC lymphocytes of LFs (B) showed Ki-67 positivity. A ring of parafollicular CD3+ T cells (C) surrounding a central core of CD20+ B lymphocytes (D) form the LF (E). Both CD3+ T cells (F) and the remaining lymphocytes forming LF (mostly B cells lying in the white traced area) were bcl-2+ (G), hence the imperfect overlaying in the merge image (H). Unorganized stromal scattered CD3+ T lymphocytes (I) were also bcl-2+ (J), as revealed by the merge image (K). On paraffin sections, areas showing normal glands were surrounded and infiltrated by lymphocytes expressing bcl-2 (L). These areas were negative in the TUNEL assay (M). Magnifications, ×200 (A and B), ×400 (C–H), ×630 (I–K), and ×400 (L and M).
in the whole glandular epithelium as the major source with various degrees of cooperation on the part of the vessels. In the light of the myriad effects of IL-7 on mature T cells and antigen-presenting cells, along with its proven ability to modulate the immune response in infections and malignancies (32, 33) by inducing antitumor immunity, its modulation of this response in prostate-associated lymphocytes during prostatitis and PCa should not be surprising. Whether alterations of the prostate microenvironment by inflammatory stimuli regulate epithelial and/or endothelial IL-7 production, as observed for keratinocytes (34) or intestinal epithelial cells (35), remains to be investigated. This production is certainly impaired in PCa because neoplastic glands express \( \times 60 \) times less IL-7 mRNA than their normal counterparts and hence fail to produce detectable levels of IL-7 protein. This, in fact, may only be found in the remaining nonneoplastic glandular epithelia where the prostate-associated lymphoid cell population is substantially unaffected, whereas it is clearly altered in cancer as shown by a significant decrease in T and B cells and loss of well-organized LFs that was dramatically evident starting from the lower Gleason score. The PCa T-cell infiltrate is mainly composed of effector-memory CD8+ cells devoid of terminal differentiation (21) possibly as a result of IL-7 deficiency (4, 8), an issue we are currently investigating. They are mainly confined to the stroma, undergo apoptosis more frequently than in the normal prostate, and, like B cells, display reduced bcl-2 expression.

Periglandular B lymphocytes and B-cell follicles, along with production of CXCL13 by follicular-like dendritic cells
CCL21 at the site of HEV-like vessels in LFs, usually disappear in the neoplastic areas together with the epithelial production of BAFF because of the loss of p63+ basal cell layer in neoplastic glands. PCa may lack the upstream modulators of CXCL13 and CCL21 production that are needed for basal cell recruitment into LFs (36, 37), and naive T-cell recruitment, and enter the para-follicular T-cell zones of LFs (38). BAFF also affects the formation of LFs supporting B-cell differentiation and GC development (11, 12), but it essentially functions as a regulator of B-cell survival via bcl-2 antiapoptotic protein (12). Initially believed to be produced solely by cells of the myeloid lineage (39), BAFF has now been shown to be expressed by cells of nonhematopoietic origin, such as fibroblast-like synoviocytes, osteoclasts, and ductal epithelial cells of salivary glands in Sjögren’s syndrome (11, 40). By contrast, in the normal prostate, BAFF is produced by the basal layer of the gland in the absence of evident signs of inflammation and by memory CD4+ T lymphocytes arranged in follicle-like structures. These are lost too in PCa, resulting in a further decrease of BAFF available for local B-cell survival.

Taken together, our data suggest that in the human prostate, IL-7, essentially, and BAFF, to a lesser extent, regulate the local mucosal immune system by sustaining T-cell and B-cell survival via bcl-2 up-regulation and thus cooperate to preserve the prostate-associated lymphoid cell arrangement and functions. In addition to the already known mechanisms influencing lymphocyte survival in prostate as in other types of cancer (41, 42), the dramatic decline in the production of these two key lymphotrophic molecules in PCa is clear evidence of a new pathway (i.e., deficiency in the prostate-associated lymphocyte population), enabling a tumor to escape from surveillance from the part of the immune system.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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