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Immunohistochemical Localization of the Retinoic Acid Receptors in Human Prostate

FRANK RICHTER*, ALINA JOYCE†, FRANK FROMOWITZ†, SHULUN WANG*, JOHN WATSON*, RICHARD WATSON*, ROBERT J. IRWIN, JR* AND HOSEA F. S. HUANG*

*From the Departments of * Department of Surgery, Division of Urology and † Laboratory Medicine and Pathology, UMDNJ-New Jersey Medical School, Newark, New Jersey, and VA Medical Center, East Orange, New Jersey.*

Correspondence to: Dr Hosea F. S. Huang, Department of Surgery, Division of Urology, UMD-New Jersey Medical School, 185 South Orange Ave, Newark, NJ 07103 (e-mail: huanghf{at}umdnj.edu).

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Abstract

Retinoic acid receptors (RARs) are nuclear transcription factors that mediate the effects of retinoids. Aberrant expression and regulation of RARs have been linked to various malignancies, including steroid-related breast and cervical cancers. Our previous results also suggest that prostate cancer is associated with altered RAR signaling. To understand the relationship between RAR signaling and prostate cancer, the current study examined the cellular distribution of RAR-α, -ß, and -γ in human prostate tissues exhibiting different pathologic conditions. In histologically normal epithelium, both RAR-α and -γ were present throughout the epithelium with minimal nuclear accumulation. RAR-ß was present only in basal epithelial nuclei. On the contrary, RAR-α was significantly increased in the nuclei of luminal epithelial cells, and both RAR-ß and -γ were increased in basal and luminal epithelial nuclei in glands exhibiting benign prostatic hyperplasia (BPH). RAR-α was also increased in luminal epithelial nuclei in glands exhibiting prostatic intra-epithelial neoplasia (PIN). In these glands, RAR-ß was persisting in basal epithelial nuclei that were also RAR-γ positive. In low- and intermediate-grade cancerous glands, RAR-α was also significantly increased in luminal epithelial nuclei, and a strong RAR-γ signal was seen in some cells. RAR-ß was absent in these glands. Both RAR-α and -γ were also increased in high-grade cancer cells. In conclusion, current results demonstrated changes in cellular distribution of RAR-α and -γ in human prostate tissues exhibiting different pathologies. These results suggest links between altered RAR signaling and deregulated cell growth and/or tumorigenic transformation of prostate epithelial cells.

Key words: Prostate carcinoma

Prostate cancer poses serious health problems for aging men; its occurrence has been increasing over the past 20 years and is expected to double by the year 2030 (Boyle et al, 1996). Although androgen-related cellular events are involved in the genesis and progress of the disease (Bostwick et al, 1991), disease progression after androgen ablation indicates that androgen-independent mechanisms are involved in these processes (Thalmann et al, 1994). Retinoids are essential for the development and differentiated function of various organs and tissues, including the prostate (De Luca, 1991; Aboseif et al, 1997). The prostate becomes regressed during vitamin A deficiency and is associated with metaplasia of the epithelia (Wolbach and Howe, 1925; Thompson et al, 1964). The latter suggests a link between vitamin A malnutrition and tumorigenic transformation of prostate epithelial cells. Prevention of chemical-induced prostate carcinogenesis by retinoid analogs (Pollard et al, 1991; Pienta et al, 1993; Stearns et al, 1993) also demonstrates chemoprevention and therapeutic efficacy of retinoid in prostate malignancy.

Retinoids exert their cellular effects by binding to and activation of retinoic acid receptors (RARs) and retinoid X receptors (RXRs), which are members of the steroid and thyroid hormone receptor superfamily (Evans, 1988; Chambon, 1995). These receptors are transcription factors that, upon ligand binding, modulate the expression of target genes and result in cascades of biochemical events leading to changes in cellular function (Mangelsdorf et al, 1995). Aberrant expression and signaling of RARs and RXRs have been linked to various malignancies, including those of the breast, lung, cervix, and promyeloytic leukemia (de The et al, 1990; Gebert et al, 1991; Roman et al, 1993; Geisen et al, 1997). While the importance of RAR signaling in prostate cell biology and pathophysiology has also been suggested (Huang et al, 1997; Richter et al, 1999), and abnormal retinoid nutritional states in human prostate cancer tissues have been reported (Pasquali et al, 1995), the function of RAR signaling in the pathogenesis and/or progression of prostate neoplasia remained undefined. By using in situ hybridization, Lotan et al (2000) reported the presence of messenger RNA (mRNA) transcripts for RAR-α and -γ in human prostate epithelium but observed no changes in these transcripts under different pathophysiologic conditions. On the other hand, Gyftopoulos et al (2000a,b) reported increased RAR-α in prostate cancer tissues and a correlation between the abundance of RAR-α and the grades of the disease, thus suggesting a role of RAR-α signaling in the progression of prostate cancer. An overexpression of RAR-α has also been reported in tumorigenic rat prostate epithelial cells (Richter et al, 1999). In order to understand the function of RAR signaling in human prostate cancer biology, the present study examined the cellular distribution of RAR-α, -ß, and -γ in normal and pathologic human prostate tissues. Results of these experiments demonstrated differences in the cellular distribution of these receptors in tissues exhibiting different pathophysiology. These results emphasize the importance of RAR signaling in prostate cell biology and perhaps the genesis and progression of prostate cancer.

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*Summary of the cellular distribution of different RARs in human prostate tissues**

Materials and Methods

Top
Abstract
Materials and Methods

Archived, formalin-fixed, paraffin-embedded human prostate tissues obtained by radical prostatectomies or transurethral resection at the Division of

Results
Discussion
References

Urology, University of Medicine and Dentistry of New Jersey-University Hospital between 1994 and 2000 were used. A total of 25 cases of primary prostatic adenocarcinoma (low grade with Gleason score <7, n = 17; high grade with Gleason score >7, n = 8) from men between the ages of 51 and 79 were examined. None of these patients had undergone prior hormonal treatment. In addition, histologically normal prostates from 5 patients who underwent cystoprostatectomy for bladder cancer were used as control. These tissue blocks were sectioned (4 µm in thickness) and stained with hematoxylineosin (HE) for pathological diagnosis and Gleason grading, as well as for immunostaining of RARs. This study was approved by the Institutional Review Board of both the New Jersey Medical School and the East Orange VA Medical Center.

Specificity of RAR Antibodies

The antibodies used in the present experiment were affinity-purified rabbit polyclonal antibodies raised against peptides mapping at the carboxy terminal of RAR-α, -ß, and -γ of human origin (Santa Cruz Biotechnology Inc, Santa Cruz, Calif). To verify the specificity of these antibodies, recombinant human RAR-α, -ß, and -γ proteins (Wolfgang et al, 1997) were immunoblotted using standard 10% sodium dodecyl sulfate-polyacrylamide gel electrophoresis (BioRad Laboratories, Hercules, Calif).

Immunostaining of RAR-α, -ß, and -γ

The sections were deparaffinized in xylene and hydrated in graded ethanol, and antigens (RARs) were retrieved by boiling the sections in 0.01 M Na citrate (pH 6.0) for 30 minutes. Immunostaining of RAR-α, -ß, and -γ was performed using the DAKO Catalyzed Signal Amplification System by procedures outlined by the manufacturer (DAKO Corp, Carpinteria, Calif). For negative control, the primary antibodies were replaced with antibodies that were incubated with 50-fold excess of corresponding purified peptide or recombinant protein at 4 °C overnight. For each specimen, immunostaining of each RAR was performed at least twice at different times. In each section, 4 to 6 areas of similar pathological conditions were examined independently by 2 individuals (F.R. and H.F.S.H.) to establish the staining pattern for each RAR. The intensity of staining in the nuclei or cytoplasm was scored 0 to 3 arbitrarily to reflect negative, light, moderate, and strong, respectively. The pathological conditions were then diagnosed by 2 pathologists (A.J. and F.F.) using HE-stained adjacent sections.

Results

Top
Abstract
Materials and Methods
Results
Discussion
References

Figure 1 shows the specificity of antibodies used in this experiment. Each of the antibodies interacted only with its respective recombinant receptor protein.

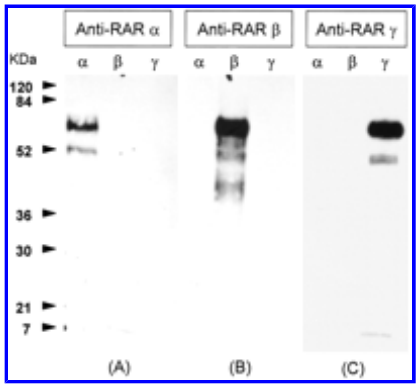

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Figure 1. Immunoblottings of retinoic acid receptors (RARs) α, ß, and γ. Recombinant RAR-α, -ß, and -γ proteins were electrophoresed using standard 10% sodium dodecyl sulfate-polyacrylamide gel electrophoresis and blotted onto polyvinylidene difluoride membranes. The blots were incubated with anti-human RAR-α **(A)**, RAR-ß **(B)**, and RAR-γ **(C)** antibodies and visualized using the ECL$^+$ Western blot detection system.

The Table summarizes the patterns of cellular distribution of RARs in human prostate under different pathophysiologic conditions. In histologically normal tissues (Figure 2A), RAR-α was uniformly distributed in glandular epithelium (Figure 2B). Of the 61 glands examined, low-moderate intensity of RAR-α was detected in approximately 75% of luminal epithelial cells, and RAR-α containing granules/vesicles were frequently seen at the luminal edge of the epithelium. Immunostaining intensity of RAR-α in the nuclei was not significantly greater than that in the cytoplasm (Figure 2B). In contrast, RAR-ß was seen only in basal epithelial nuclei in more than 80% of normal glands (Figure 2C). Like RAR-α, a low level of RAR-γ was also present in normal epithelium without significant nuclear accumulation (Figure 2D). Frequently, RAR-γ was detected in basal epithelial nuclei of some glandular tissues (Figure 2D).

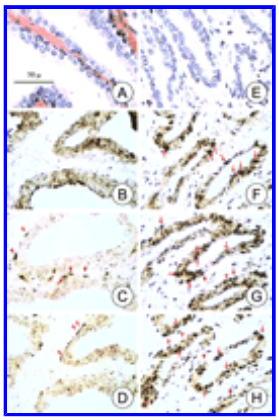

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Figure 2. Immunohistochemical localization of retinoic acid receptors (RARs) α, ß, and γ in human prostate. **(A-D)** Normal epithelium. **(A)** Hematoxylineosin (HE)-stained normal glands. **(B)** RAR-α was uniformly distributed in the epithelium without significant nuclear accumulation but tended to accumulate at the luminal edge in some cells. **(C)** In these glands, RAR-ß was present mainly in the nuclei of basal epithelial cells (arrowheads). On rare occasions, an RAR-ß—positive nucleus of nonepithelial cells (arrow) was observed near the base of the epithelium. **(D)** Low intensity of RAR-γ was detected homogeneously throughout the epithelium. High intensity of RAR-γ was present in basally located nuclei of some glands (arrowheads). **(E-H)** Benign prostatic hyperplasia (BPH) glands. **(E)** HE-stained BPH glands. **(F)** In these BPH glands, RAR-α was present in both the cytoplasm and nuclei of luminal epithelial cells (arrows). **(G)** In addition to luminal epithelial nuclei (arrows), RAR-ß, was also present in the basal epithelial nuclei (arrowheads) of BPH glands. **(H)** This micrograph shows that RAR-γ was present in both the basal (arrowheads) and luminal (arrows) epithelial nuclei of the BPH glands.

Cellular distributions of RARs were altered in glands and cells exhibiting different pathologies. In glands exhibiting BPH, RAR-α was also present throughout the epithelium but with increased intensity of RAR-α in the nuclei of luminal epithelial cells (Figure 2F). Unlike those in normal glands, moderate intensities of both RAR-ß and -γ were present in epithelial cytoplasm, as well as in basal and luminal epithelial nuclei in BPH glands (Figure 2G and H).

In glandular epithelium containing prostatic intraepithelial neoplasia (PIN), there was a significant increase in nuclear RAR-α in luminal epithelial cells. It was estimated that more than 80% of luminal epithelial nuclei of the PIN exhibited a moderate to strong RAR-α signal (Figure 3B). In these glands, RAR-ß was also present in basal epithelial nuclei (Figure 3C) and in nuclei of some basally located cells adjacent to cancerous glands or cells (Figures 3G and 4C). Unlike that in BPH glands, RAR-γ was increased only in basal epithelial nuclei of glands exhibiting PIN. Such increases were seen in 12 of the 15 specimens examined (Figure 3D).

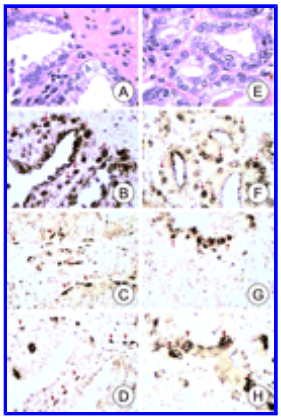

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Figure 3. Immunohistochemical localization of retinoic acid receptors (RARs) α, ß, and γ in human prostate. **(A—D)** High-grade prostatic intra-epithelial neoplasia (PIN). **(A)** Hematoxylin-eosin (HE)-stained high-grade PIN. **(B)** In these glands, a high abundance of RAR-α was detected in luminal epithelial nuclei (arrows). **(C)** On the other hand, RAR-ß was persisting only in basal epithelial nuclei of these glands (arrowheads). **(D)** Unlike that in benign prostatic hyperplasia (BPH) glands, RAR-γ was significantly increased only in basal epithelial nuclei of glands exhibiting PIN (arrowheads). **(E—H)** Intermediate-grade prostate cancer (Pca) glands (Gleason grade 3). **(E)** HE-stained Pca glands. **(F)** In these Pca glands, a moderate to strong RAR-α signal was detected in the nuclei of some of the cancer cells (arrows) but not in the others. While RAR-ß was absent in these Pca glands **(G)**, it was present in some basally located nuclei (arrows) of a nearby gland exhibiting PIN. **(H)** In these Pca glands, RAR-γ was present only in some cells (arrowheads) within each gland.

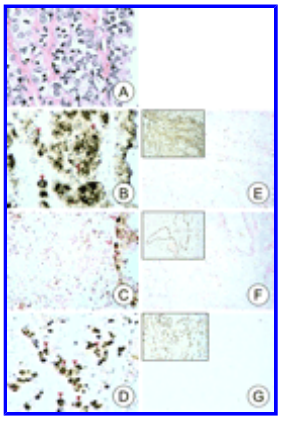

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Figure 4. Immunohistochemical localization of retinoic acid receptors (RARs) α, ß, and γ in human prostate. **(A-D)** High-grade prostate cancer (Pca) cells (Gleason grade 4). **(A)** Hematoxylin-eosin (HE)-stained high-grade Pca cells. **(B)** In most of these cells, a moderate to strong RAR-α signal was detected in both the cytoplasm and nuclei (arrowheads). **(C)** While RAR-ß in these high-grade Pca cells was negligible, it was detected in some basally located nuclei of a nearby prostatic intra-epithelial neoplasia (PIN) gland (arrows). The morphology of these nuclei excluded them as basal epithelial cells. Identity of these cells remained undetermined. **(D)** Unlike the RAR-α, a strong RAR-γ signal was present only in the nuclei of high-grade Pca cells (arrowheads). **(E-G)** Negative controls for the immunostaining of RAR-α, -ß, and -γ, respectively. Preadsorption of each antibody with respective antigen or recombinant protein at 4°C overnight eliminated immunostaining of each RAR. The insert in each photomicrograph shows positive staining of respective RARs in adjacent sections.

In the low- and intermediate-grade cancerous glands, there was a general increase in the RAR-α signal in epithelial cells with 2 distribution patterns that sometimes coexisted within the same specimen. In approximately 90% of the low-grade cancerous glands (Gleason grade 2), a moderate strength signal of RAR-α was present in most nuclei similar to that in the PINs (data not shown). While a moderate to strong signal of RAR-α was also seen in the nuclei of intermediate-grade (Gleason grade 3) cancer cells (Figure 3F), the number of such nuclei appeared to be less than that of the lower grade cancer cells. In approximately 60% of low- and intermediate-grade cancerous

glands, a moderate to strong RAR-α signal was present in the cytoplasm of some cells with or without significant nuclear staining (data not shown). In these glands, RAR-ß was usually absent (Figure 3G), and RAR-γ was present in isolated cells with or without nuclear staining (Figure 3H).

There was an even greater increase in RAR-α in highgrade (Gleason grade 4) cancer cells (Figure 4A). It was estimated that more than 80% of high-grade cancer cells (8 specimens, n = 36 areas) contained high levels of RAR-α in both the nuclei and cytoplasm (Figure 4B). In 7 of 8 specimens, a moderate to strong intensity of RAR-γ was present in the nuclei of high-grade cancer cells (Figure 4D). The presence of RAR-ß in high-grade cancer cells was negligible (Figure 4C). Preadsorption of antibodies with their respective antigen or recombinant protein eliminated the immunostaining of each RAR (Figure 4E through G).

Discussion

- Top
- Abstract
- Materials and Methods
- Results
- Discussion
- References

Because of the importance of RAR signaling in normal differentiation (De Luca, 1991), links between abnormal RAR expression and malignancies (de The et al, 1990; Gebert et al, 1991; Geisen et al, 1997), and effectiveness of RAR analogs in cell growth inhibition (Houle et al, 1993; Lotan et al, 1995; Lu et al, 1999), the mechanisms mediating the RAR signaling in cell growth and therapeutic efficacy have been studied extensively. While in vitro growth inhibition of human prostate cancer cells by RAR or retinoid analogs has been reported (Jones et al, 1997; Lu et al, 1999; Hammond et al, 2001), findings regarding the in vivo therapeutic efficacy of these compounds remained limited and controversial (Trump, 1994). In order to facilitate the use of retinoid/RAR-based therapies in prostate malignancy, an understanding of the cellular distribution of different RARs in prostate cells under normal and pathologic conditions is essential. Lotan et al (2000) found no differences in the level of mRNA transcripts for RAR-α and -γ among tissues with distinct pathologies and postulated that RAR-α and -γ perhaps had no significant role in prostate malignancy. On the other hand, Gyftopoulos et al (2000a,b) reported an increased RAR-α protein level that correlated with the grades of prostate cancer, thus suggesting a link between altered RAR-α signaling and progression of the disease. Results of the current experiment were consistent with the latter and further demonstrated increases of RAR-α in cells that were associated with BPH and PIN. In addition, we observed differences in the expression and cellular distribution of RAR-ß and -γ in human prostate cells that were associated with different pathophysiologic conditions.

The presence of RAR-α in normal epithelium with relatively weak nuclear localization suggests that perhaps a minimal RAR-α signaling is sufficient for normal epithelial functions. The frequent appearance of granular RAR-α at the luminal edge of the epithelium might be due to the crowding of the epithelium and has been reported previously (Gyftopoulos et al, 2000b). On the contrary, increases in nuclear RAR-α in epithelial cells that were associated with BPH, PIN and various grades of cancer imply that RAR-α signaling events might have been exaggerated in these cells. Of note, increases in nuclear RAR-α in BPH glands occurred while cytoplasmic RAR-α persisted, whereas that in the PIN, and the low- and intermediate-grade prostate cancer glands occurred without the significant presence of cytoplasmic RAR-α. Such differences suggest variations in the intracellular shuttling of RAR-α protein. These effects were dictated by disease states of the cell and could be attributed to the induction or posttranslation modification of RAR-α. Energy metabolism and ligand availability have been shown to affect nucleotranslocation of the progesterone receptor (Guiochon-Mantel et al, 1991), and increased nuclear localization of RAR-α has been observed in rat prostate epithelial cells after castration (Huang et al, unpublished data). The biphasic changes in RAR-α intensities among low-, intermediate-, and high-grade cancer cells were consistent with the findings of

Gyftopoulos et al (2000a). These findings, together with an overexpression of RAR-α mRNA in tumorigenic rat prostate epithelial cells (Richter et al, 1999), emphasize the involvement of RAR-α signaling in tumorigenic transformation and/or deregulated cell growth of prostate epithelial cells. A correlation between the expression of the Ki-67 antigen and RAR-α in prostate cancer cells (Gyftopoulos et al, 2000a) is consistent with a role for RAR-α in deregulated cell growth.

The presence of RAR-ß in basal epithelial cells of normal tissues was consistent with its mRNA distribution (Lotan et al, 2000). Because of the absence of RAR-ß mRNA in malignant prostate glands and its decrease in basal epithelial cells of adjacent normal glands, Lotan et al (2000) postulated that tumorigenic transformation of prostate cells was associated with a decrease in RAR-ß expression. This postulate was based on the reported efficacy of RAR-ß in growth suppression of lung cancer cells (Houle et al, 1993) and correlates between clinical outcome and increased RAR-ß in premalignant oral lesions after isotretinoin administration (Lotan et al, 1995). Results of the current study, however, demonstrated the persistence of RAR-ß in basal epithelial nuclei in epithelium exhibiting BPH and PIN. The cause for such a discrepancy perhaps can be attributed to feedback regulation of transcription and translation of the RAR-ß gene. In the rat prostate, postcastration increases in RAR-α mRNA were preceded by a decrease in RAR-α protein (Huang et al, unpublished data). Of note, RAR-ß protein was also increased in epithelial cytoplasm and nuclei of luminal epithelial cells in BPH glands. Such a phenomenon was not seen in normal glands or in those exhibiting PIN. This finding thus suggests a distinct relationship between RAR-ß signaling and BPH. The lack of RAR-ß in low-grade cancer glands is consistent with the absence of basal epithelial cells in such glands. In addition, RAR-ß was also detected in some basally located cells in epithelium containing PIN neighboring cancerous cells or glands. While the identity of these cells remains to be determined, increased nuclear RAR-ß in these cells might reflect their response to the presence of tumorigenic cells in their surroundings.

An increase in RAR-γ in basal epithelial nuclei of high PIN and BPH glands suggests that basal epithelial cells of these glands might share certain similarities and could contribute to the genesis of these pathologic conditions. This postulate is based on a recent finding demonstrating that estrogen-induced metaplastic transformation of mouse prostate cells involved the proliferation of cells with basal cell phenotype (Risbridger et al, 2001). Alternatively, such an increase might reflect the response of basal epithelial cells to abnormal or deregulated cell growth in the luminal compartment. Of note, RAR-γ was also increased in luminal epithelial nuclei of BPH glands but not of the PINs and most low-grade cancer cells. Such a difference again distinguishes cells that associated with benign deregulated cell growth and those with tumorigenic potential. Significant increases of RAR-γ in some low-grade cancerous cells suggest that they might be undergoing further tumorigenic changes, since a strong RAR-γ signal was also detected in the nuclei of high-grade cancer cells.

RARs, as dimeric partners with RXRs, interact with the retinoic acid-responsive element on the promoter of target genes to modulate the expression of these genes causing changes in cellular activities (Mangelsdorf et al, 1995). The retinoid—RAR complex could also affect cellular function by interfering with gene expression via the c-jun/c-fos (AP-1) signaling pathway (Schule et al, 1991; Pfahl, 1993; Saatcioglu et al, 1994) that has been linked to oncogenesis (Angel and Karin, 1991). The AP-1 signaling pathway has been reported to mediate the cell growth effect of retinoid on human lung cancer cells (Wan et al, 1997), as well as the cell suppression effect of retinoid on ovarian cancer cells (Soprano et al, 1996) and Calu-6 human lung cancer cells (Fanjul et al, 1994; Chen et al, 1995).

Retinoic acid has been shown to stimulate cell growth in human prostate tumor lines, including PC-3,

LNCaP, and DU-145 (Fong et al, 1993; Esquenet et al, 1996; Jones et al, 1997), but to inhibit cell growth in primary human prostate cell lines (Peehl et al, 1993), canine prostate adenocarcinoma, and normal canine prostate epithelium (Jones et al, 1997). These results suggest that the tumorigenic transformation of prostate cells may alter their growth response to retinoic acid. Dose-dependent and opposite effects of testosterone on the expression of RAR-α and -γ mRNAs in nontumorigenic and tumorigenic rat prostate epithelial cells (Richter et al, 1999) further suggest that RAR signaling may mediate some of the effects of testosterone on prostate cells; such effects may be altered after tumorigenic transformation. The reported modulation of the growth of LNCaP cells by RXR analogs (De Vos et al, 1997) and DU145 cells by the RAR-γ agonist and antagonist (Fanjul et al, 1996; Lu et al, 1999) is also consistent with the involvement of RAR and RXR signaling in prostate cancer cell growth. In addition, interaction between RAR and other members of the receptor family such as the vitamin D receptor (Blutt et al, 1997; Campbell et al, 1998) could also affect the growth response of prostate carcinoma cells to retinoids. A reduced retinoid concentration in cancerous tissue (Pasquali et al, 1995) could, on the one hand, trigger metaplasia and/or tumorigenic transformation of the neighboring epithelial cells and result in new foci of cancer cells. On the other hand, it could initiate feedback mechanisms and result in compensatory increases of RAR proteins and alter the balance of different RAR signaling events and downstream cellular effects. A combination of these changes could thus contribute to the progression of the disease.

In summary, current results demonstrate distinct cellular distributions of RAR-α, -ß, and -γ in human prostate tissues that exhibit BPH, PIN, and low- or high-grade cancer. These results implicate the RAR signaling events in neoplasia of human prostate epithelial cells. The distinct distribution pattern of these receptors under different pathologic conditions may qualify them as adjuvant markers for specific disease states. Since retinoids exert their cellular effects through RAR signaling, increased nuclear RARs in prostate cancer cells may render these cells more vulnerable to RAR analogs. In this regard, specific RAR-α and -γ analogs have been found to be effective in the suppression of prostate carcinoma cells (Lu et al, 1999; Hammond et al, 2001).

Acknowledgments

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Footnotes

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- Top
- Abstract
- Materials and Methods
- Results
- Discussion
- References

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