Recent Role of Inflammation in Prostate Diseases: Chemoprevention Development Opportunity

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ABSTRACT

The role of inflammation in prostate diseases is suggested by the presence of inflammatory cells within the Benign Prostatic Hyperplasia (BPH) and Prostate Cancer (PC). Inflammation suggests influence a balance between prostate cell growth and apoptosis by increasing microenvironment around prostate factors such as cytokines, COX-2 and oxidative stress. These factors stimulate proliferation and minimize cell apoptosis. In vitro studies showed an over expression of these inflammatory markers in BPH and PC compared normal tissue. There were also inflammatory marker differences between BPH and PC, which was more severe inflammation process in PC. Another basic difference was a gene polymorphism in PC. Targeting the microenvironment may represent a promising therapeutic approach for prostate disease. Many epidemiological studies showed a beneficial effect of drug that influences inflammation such as non steroidal anti-Inflammatory drugs, antioxidant compound in food or supplements and vitamin D receptor (VDR) agonists. These drugs need more investigation to prove their function as chemoprevention of prostatic disease.

Key words: prostate, inflammation, chemoprevention.

INTRODUCTION

Both prostate diseases, Benign Prostate Hyperplasia (BPH) and Prostate Cancer (PC), are chronic diseases that need a long period for development from small lesion to become clinical manifestation. In these both prostate diseases, there was an imbalance between prostate cell growth and apoptosis. This imbalance was complex and influenced by microenvironment around prostate such as growth factors, cytokines and steroid hormones. These factors stimulate proliferation and minimize cell apoptosis.

The role of inflammation in prostate diseases is suggested by the presence of inflammatory cells within the prostate in BPH and PC patients. This role has been noted since 1937, but Virchow already hypothesized that the origin of cancer was at sites of chronic inflammation in 1863. Many studies showed more than 92% incidences of inflammatory lesions in prostate tissue in BPH and PC. Another histopathologic investigation confirmed that inflammation is much more common in the transition and peripheral zones of the prostate, that is a predilection for BPH and PC.

Clinically, many studies found correlation between inflammation and prostate disease. A large scale study showed that the odd ratio for BPH was 8.0 for history of prostatitis. Gerstenbluth et al found that patients with BPH unassociated with prostatitis had significantly smaller prostate weight and were younger than those associated with prostatitis. Two large studies by Di Silverio et al and Roehrborn et al demonstrated a correlation higher inflammatory infiltrates present in bigger prostate volume and more prone to progression of symptoms, risk of acute urinary retention (AUR) and risk for surgery. These data suggest that the more serious the inflammation, the larger the prostate growth. A meta-analysis of many articles found a
and involves a broad spectrum of immune responses components.2,20 of a humoral (cytokines) and cellular (leukocytes, disease prevention.16-19 inflammation to the prostate.16-19 inflammatory reaction to the prostate.16-19 Furthermore, any of these can break in immune tolerance and the development of an inflammatory reaction to the prostate.16-19 This review is aimed to explore the mechanism of inflammation in prostate, the differences of inflammation process between BPH and PC and the possibility of drug development against inflammation for prostate disease prevention.

**INFLAMMATION NETWORK IN PROSTATE DISEASE**

Inflammation is a complex phenomenon consisting of a humoral (cytokines) and cellular (leukocytes, monocytes and macrophages) components.2,20 Cytokines that promote inflammation and act to make disease worse are called pro-inflammatory cytokines, whereas other cytokines that serve to reduce inflammation and promote healing are called anti-inflammatory cytokines.21 Inflammation is usually a self-limited event, with initial pro-inflammatory cytokines and growth factor release and angiogenesis followed by anti-inflammatory cytokine–mediated resolution.22 In normal tissues, anti-inflammatory cytokines are synchronically upregulated after the pro-inflammatory cytokines are produced, leading to inflammation resolution.23 In chronic inflammation, mainly composed of chronically activated T cells and mononuclear phagocytes (monocytes and macrophages), there are persistence of promoters or a failure in mechanisms required to resolve inflammation. This will release more pro growth cytokines as well as various growth factors and attract additional immune cells to the inflammation site which amplifies the inflammatory response.19,22

Prostate has a fully active immunologic response and involves a broad spectrum of immune responses against foreign antigens and contains scattered stromal and intraepithelial endogenous inflammatory cells such as T and B lymphocytes, macrophages and mast cells.16,24 T-cells increase with age, which correlates with the incidence of prostate inflammation during the aging process.25 T-cells are known to release factors that stimulate matrix formation and secreting potent epithelial and stromal mitogens which could promote prostate stromal and epithelial proliferation/hyperplasia.26

Stromal – epithelial prostate interactions play a pivotal regulatory role in the maintenance of homeostasis in health and development of disease.18,25 Prostate cell itself can induce inflammation reaction because it can express Antigen Presenting Cell (APCs) and all of the Toll-like receptors (TLRs). These expressions can produce pro-inflammatory cytokine and activate immune responses.7,21,24,27-29 Konig et al found a different expression pattern of the TLR in BPH and PC tissue. Most of the BPH tissues showed a strong expression for the TLR 4, 5, 7, and 9, whereas in PCA increased expression was obtained for TLR 1, 2, and 3.30 But it is still unknown how it will influence the inflammatory process in these prostate disease.

T-cells, prostatic stromal and epithelial cells simultaneously secrete higher pro-inflammatory cytokines such as interleukins (IL-1, IL-1α, IL-2, IL-4, IL-6, IL-7, IL-8, and IL-17), the CXC-type chemokine and their receptors in BPH and PC tissues compared to normal prostate tissue.18,21,28,31 These cytokines were thought to induce fibromuscular growth and proliferation of prostatic stromal or epithelial cell by an autocrine or paracrine loop or via induction of COX-2 expression.7,26,31-33 IL-1α produced by epithelial cells induces fibroblast growth factor-7 (FGF-7) in prostate stromal cells that will induce benign growth of the prostate. IL-17 up-regulates the secretion of other proinflammatory cytokines, such as IL-8 and IL-6 as well as of TGF-β. IL-8 and IL-6 are recognized as two potent growth factors for prostatic epithelial and stromal cells, with IL-8 playing a major role in stromal proliferation by the induction of FGF-2.4,28 The expression of pro-inflammatory cytokines was different between BPH and PC. Mechergui et al and Konig et al found IL-6 and IL-8 were more over expressed in PC tissue compared to BPH-tissue.21,30 IL-6 regulates the growth of prostate carcinoma and activates the androgen receptor dependant gene in prostate cancer cells in the absence of androgen.21 Chronic inflammation continuously produces cyclooxygenase-2 (COX-2).2,5,23,34 COX–2 increases
production of Prostaglandin (PG) E2 (an adhesion to the extracellular matrix), concentrations of Bel-2 (pro apoptotic genes), and reduces the E-cadherin protein (with consequent loss of cell-to-cell adhesion). COX – 2 also modulates production of angiogenic factors to induce angiogenesis. At last, COX-2 increases the carcinogenic potential of cells through the oxidation of procarcinogens to carcinogens, increased cell growth, decreased apoptosis, as well as decreased immune response to abnormal or cancer cells matrix-metalloproteinase overexpression with an associated increase in invasiveness.\textsuperscript{4,35-37} COX-2 is up-regulated in a variety of malignancies including prostate cancer, throughout the tumorigenic process from early hyperplasia to metastatic disease.\textsuperscript{23,38} Hsu et al indicate that normal prostate epithelial cells do not express significant levels of COX-2.\textsuperscript{39} Many studies showed more over expression of COX – 2 in prostate cancer compared in BPH. COX-2 over expression was also higher in Prostatic Intraepithelial Neoplasia (PIN) and poorly differentiated tumours.\textsuperscript{22,30,34,38}

Chronic Inflammation also produces a free radical substance/oxidative stress such as inducible nitric oxide (i-NOS)/reactive nitric species (RNS) and various reactive oxygen species (ROS).\textsuperscript{2,5,23,34,41,42} These oxidative stress can induce vascular tissue damage, protein structure and function damage, genomic damages and cause post-translational modifications including those involved in DNA repair and apoptosis.\textsuperscript{7} These can lead to oxidative DNA damage in point mutations, deletions, or rearrangements and reduce DNA repair. These oxidative stresses also alter the stem cell population. Genomic alterations in cellular DNA resulting in the modulation of a imbalance between cell proliferation and cell death. A change in the normal regulation of programmed cell death lead to hyperplastic or precancerous transformation.\textsuperscript{15,17,19,22,43} All of these active factors production also induce a repetitive tissue damage and repair with the release cytokines, growth factors and oncogenes, leading to increase epithelial or stromal cell proliferation.\textsuperscript{15} Normally, these highly oxidative stresses are removed by natural protective mechanism, the superoxide dismutase enzyme system, such as superoxide dismutase (SOD), glutathione peroxidase (GPX) and catalase (CAT) enzyme.\textsuperscript{2}

Human prostate tissue is vulnerable to oxidative DNA damage due to more rapid cell turnover and fewer DNA repair enzymes. Balance between oxidative stress and antioxidant component of the cells have a role in developing prostate disease.\textsuperscript{44} There are increases in oxidative stress and decreased antioxidant mechanisms in prostate disease. Sciarra et al characterized NOS expression in human prostate tissue and in particular for the iNOS increased immunostaining in the epithelial cells of cases with BPH and more with high grade PIN (HGPIN) and PC when compared to normal tissue.\textsuperscript{2} Khandrika et al also found increasing ROS generation for more aggressive phenotype in PC cell lines.\textsuperscript{44} Prostate cancer cell expresses lower levels of antioxidant enzymes or almost total inactivation of prooxidant scavenging enzyme than BPH. Compare to normal prostate, activity of antioxidant enzymes is decreased in BPH.\textsuperscript{37,45-49} Age was one of contributing factor changing the oxidant/antioxidant balance is shifted towards oxidative stress. Production of ROS and free radicals in mitochondria was increased during aging. There are also a down regulation, and/or underexpression of antioxidant with increasing age.\textsuperscript{44,50,51}

Oxidative stress then can activate the transcription factor NF-kB (nuclear factor kappa-light-chain-enhancer of activated B cells) by TNF-a/AP-1 transduction pathway and NIK transduction pathway. NF-kB is known as a master inflammatory transcriptional regulator and is highly active in macrophages. Targets of NFkB include genes regulating immune response, inflammation, cell proliferation, cell migration, and apoptosis. The nuclear translocation of NF-kB can activate target genes involved in carcinogenesis.\textsuperscript{1,35} NF-kB potentially can lead to the amplification of the inflammatory response in the tumor environment. Dysregulation of the transcription factor NF-kB has been proposed to be one putative molecular mechanism leading to chronic inflammation and cancer. In a chronically inflamed tumor environment, it is difficult to distinguish whether aberrant NFkB activation originates from tumor cells or from immune infiltrates. Wong CP et al found exposure of prostate epithelial cells to proinflammatory soluble mediators directly activated NFκB and induced local production of proinflammatory cytokines in the prostate epithelial cells.\textsuperscript{19} NFκB was found a significant increase in the PIN and adenocarcinoma.\textsuperscript{19,20} The IL-1b-induced NF-kB pattern of intraprostatic chemoattractive signals might have a capability for maintaining the chronic inflammation and proliferative inflammatory atrophy (PIA) in the prostate, which are recognized as putative precursor lesions in the development of prostate cancer.\textsuperscript{52} In normal prostate, the transduction pathway from NIK to NF-kB seems to be inactive In BPH, there was increasing TNF-a/
AP-1 transduction pathway and also followed by increasing apoptotic pathway to inhibit uncontrolled cell proliferation. In PC, conversely to what occurs in BPH, the proapoptotic effect of TNF-α / AP-1 pathway decreased and also nuclear translocation of NFkB increased which are an active form to stimulate prostate cancer cell proliferation.\(^1,19,20\)

Induction of anti-inflammatory factors such as macrophage inhibitory cytokine-1 (MIC-1) is an early response due to inflammation in the prostate.\(^53\) MIC-1 was down regulated in BPH tissues compared to normal prostate tissue.\(^4,7,54\) However, in PC, there are up-regulation and overexpression of MIC-1 in higher grade and more aggressive prostate cancers.\(^53,54\) Gene expression analysis between normal peripheral zones and transition zones of the specimens obtained from patients with prostate cancer revealed a preferential expression of MIC-1 in the peripheral zone (predominant site of tumor occurrence) compared with the transition zone (site of benign prostatic hyperplasia). MIC-1 in tumor environment is assumed to reduce the tumor killing (functional) activity of macrophage.\(^54\)

Another factor that differentiate between BPH and PC was gene polymorphism. Polymorphisms in innate and adaptive immune genes may affect the nature and extent of the immune response within the prostate, including the likelihood of persistent prostatic infection and chronic inflammation. There are many evidence that BPH has only rare genetic abnormalities.\(^55\) Recently, multiple genes with regulatory roles on inflammatory pathways have been associated with prostate cancer risk, including Ribonuclease L (RNASEL), macrophage scavenger receptor 1 (MSR1), macrophage inhibitory cytokine-1 (MIC-1), interleukins (IL-8, IL-10), vascular endothelial growth factor (VEGF) and intercellular adhesion molecule (ICAM), ELAC2/HPC2, Machropaghe Scavenger Receptor (SR-A/MSR1), CHEK2, Breast Cancer gene (BRCA) 2, Paraoxonase (PON) 1, 8-oxoguanine glycosylase (OGG-1), TLRs and COX-2 promoter. These genes are linked to cellular defenses against inflammation and oxidative stress, and defects in their function may lead to the inability to prevent tumor formation by this pathway.\(^12,14,16,34,56-58\) One study in Swedish population found 9275 single nucleotide polymorphisms (SNPs) in 1086 genes of the inflammatory pathway were associated with the risk of prostate cancer.\(^22,59,60\) There was still a question wether this gene polymorphism change congenitally or after the inflammation, because sporadic prostate cancer consists for about 85% of all prostate cancer.\(^61\) In Table 1, we summarize the inflammation process differences between BPH and PC.

**Table 1. Inflammation process differences between BPH and PC**

<table>
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<th>Compared to BPH, the differences in PC are:</th>
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<tr>
<td>1. Different TLR expression pattern</td>
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<td>2. More overexpressed cytokine, COX – 2 and oxidative stress</td>
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<tr>
<td>3. Lower or until no antioxidant</td>
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<tr>
<td>4. Decreasing apoptotic activity</td>
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<tr>
<td>5. Increasing MIC – 1 expression</td>
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<td>6. Increasing Gene polymorphism</td>
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**MANAGING INFLAMMATION AS A CHEMOPREVENTION OPPORTUNITY**

The association of prostate disease with chronic inflammation offers a framework to design therapeutic approaches.\(^27\) Targeting the microenvironment may represent a promising therapeutic approach for prostate disease. In 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.\(^2\)

**NON STEROIDAL ANTI INFLAMMATORY DRUGS (NSAID)**

The best evidence for the significance of inflammation during neoplastic progression comes from the study of cancer risk among long-term users of Non Steroidal Anti-Inflammatory drugs (NSAIDs). The ability of NSAIDs to inhibit COX-1 and -2 underlies their mechanism(s) of chemoprevention. COX-2 inhibition can produce a significant increase in prostate cell apoptosis through release of cytochrome C from mitochondria and subsequent activation of caspase-9 and -3.\(^2,5,23\) NSAIDs can also promote apoptosis by inhibiting NF-kB.\(^35\) Aspirin use has provided 10–39% risk reduction for prostate cancer.\(^40,62\) A systematic review of many studies found an odd ratio for aspirin and prostate cancer risk of 0.9–0.95 (95% CI 0.82–0.99), but reduction in risk with the use of other NSAIDs was less consistent with a combined OR 0.87–0.92 (95% CI 0.61–1.23).\(^63\) The differences between aspirin and other NSAIDs probably due to underlying differences in their mechanisms of action, for instance aspirin may exert protective effects independently of its ability to inhibit COX, or in the way these medications are prescribed.
and used. Aspirin is typically used on a regular basis for extended periods (e.g. when used in the prevention of coronary heart disease), whereas the other NSAIDs are typically prescribed to be used occasionally, as required (e.g. for pain relief). Selective COX-2 inhibitors, such as celecoxib, also reduces expression of COX-2, PGE2 and NF-in and induction of apoptosis in prostate cancer cell. However, Fowke et al reported Prostate Specific Antigen was significantly lower in aspirin users with latent cancer, so it can affect prostate cancer detection.

**ANTIOXIDANT**

Antioxidant compounds that scavenge oxidative stress may be useful in helping to overwhelm its mutagenic effects. Dietary components/supplements that have antioxidant compound include carotenoids such as lycopenes (in tomato) and b-carotene (in yellow orange vegetables), vitamin A, retinol, vitamin C and vitamin E, and selenium. Another additional food-derived antioxidant compound may also be beneficial in prevention of prostate cancer including thioallyl components (garlic), sulphorophane (cruciferous vegetables), grees tea polyphenol and soy. Many study in vitro, vivo and epidemiology showed a significant effect of these antioxidant dietary components to prevent BPH and PC development. But there are still controversies for the effectiveness of vitamin C and E. Latest study showed neither vitamin E nor C supplementation did not reduce the risk of prostate cancer. One last large study, SELECT (Selenium – Vitamin E Cancer Prevention Trial) study shown no differences in preventing prostate cancer in the generally healthy and heterogeneous population so this study was discontinued earlier. It is due to probably the formulation given in this study was less active compare than other study.

**VITAMIN D RECEPTOR (VDR) AGONISTS**

Vitamin D receptor (VDR) agonists, such as calcitriol, can promoting innate immunity and regulating adaptive immune responses, exert anti-inflammatory and immunoregulatory properties potentially useful in the treatment of diseases characterized by chronic inflammation and cell proliferation. The prostate is a target organ of VDR agonists and represents an extrarenal synthesis site of 1,25-dihydroxyvitamin D3, there are marked inhibitory activity of the VDR agonist elocalcitol on basal and growth factor induced proliferation of human prostate cells. Many mechanism that could be proposed are (1) inhibition of the RhoA/ROCK pathway, a calcium sensitizing pathway, to produce IL-8 (2) inhibition of the expression of COX-2 (3) decreasing PGE production and its receptors, (4) prevention of NF-kB nuclear translocation. The combination of calcitriol and NSAIDs result in a synergistic inhibition of BPH and PC cell growth and offers a potential therapeutic strategy by acting on a separate anti-inflammatory pathway.

**CONCLUSION**

In all prostatic diseases, inflammation processes have a role in pathogenesis as potential triggers of disease progression. There are differences in inflammatory process or markers between BPH and PC development. There is still a question on what mechanism can trigger this different mechanism in BPH or PC development. Drug development based on controlling inflammatory environment is promising to become preventive agent in prostate disease development.

**REFERENCES**


