Journal of Cancer Therapy, 2014, 5, 836-844
Published Online August 2014 in SciRes. http://www.scirp.org/journal/jct
http://dx.doi.org/10.4236/jct.2014.59092

Inflammation and Its Role in Prostate Cancer

Rakesh K. Mishra, Ashutosh K. Tewari*

Department of Urology, Icahn School of Medicine at Mount Sinai, New York, USA
Email: *ashtewari@mountsinai.org

Received 18 June 2014; revised 13 July 2014; accepted 5 August 2014

Abstract

Infections and inflammatory responses are linked to 20% - 300% of all deaths from cancer worldwide. Inflammatory responses play crucial roles at different stages of tumor development, including initiation, promotion, malignant conversion, invasion, and metastasis. Several studies point to an important role of inflammation in prostate growth, although the contribution of inflammation to benign prostate cancer is not completely understood. The basic and clinical research in the area, trying to understand the etiology of prostatic inflammation and its signaling pathway may help to develop the novel therapeutic interventions against prostate cancer development triggered by inflammation.

Keywords

Prostate Cancer, Inflammation, Signaling

1. Introduction

Inflammation is a fundamental physiological process that can arise in any tissue in response to infectious, post-ischemic, toxic, or autoimmune injury. In the setting of tissue damage resulting from microbial pathogen infection or other noxious stimuli, these processes lead to eradication of pathogens, clearing of debris, epithelial regeneration and stromal remodeling. Inflammation induces cellular and genomic damage and promotes cellular turnover associated with a sustained inflammatory microenvironment that provides a constant supply of a variety of reactive nitrogen and oxygen species, reactive aldehydes, cytokines, chemokines, and growth factors, which can alter crucial biological processes responsible for maintaining normal cellular homeostasis, leading to uncontrolled proliferative response and genomic instability and risk of prostate cancer development [1]. The American Cancer Society estimates that approximately 218,000 men will be diagnosed with, and 32,000 men

*Corresponding author.

How to cite this paper: Mishra, R.K. and Tewari, A.K. (2014) Inflammation and Its Role in Prostate Cancer. *Journal of Cancer Therapy*, **5**, 836-844. http://dx.doi.org/10.4236/jct.2014.59092

will die of, prostate cancer in the United States in 2010 [1]. On the basis of these numbers, prostate cancer (PCa) is the most commonly diagnosed cancer in men and is responsible for the second highest number of cancer-related deaths in men in the United States. PCa represents 27.6% of new cancer cases in men and 10.7% of cancer-related deaths in men [2]. An estimated 1 in 3 men will be diagnosed with PCa or a precancerous prostatic lesion in their lifetime. In Europe, there are approximately 346,000 new PCa cases and 87,000 deaths per year [3].

There is a poorly understood, but longstanding, observation and epidemiologic link between inflammation and cancer. It was in 1863 that Rudolf Virchow reported for first time leucocytes in neoplastic tissues and made a connection between inflammation and cancer. He suggested that the "lymphoreticular infiltrate" reflected the origin of cancer at sites of chronic inflammation. Recent estimates suggest that about 20% of all human cancers are caused by chronic infection or chronic inflammatory states [4]. Prominent examples for this phenomenon are the strong associations between chronic gastritis, hepatitis, prostatitis or colitis and increased risk of primary carcinoma in the corresponding organ. Almost 30% of people who suffer from inflammatory bowel disease will develop colorectal cancer, and around 18% of people who suffer from inflammation of the prostate will develop prostate cancer [5].

Prostate cancer remains a significant health concern for men throughout the world. Recently, there has developed an expanding multidisciplinary body of literature suggesting a link between inflammation and prostate cancer [6]. The prevalence of both prostate cancer and prostatic inflammation is at nearly epidemic levels in the United States and in "westernized" countries [7]. Prostate cancer development is thought to be mediated in part by genetics, and also by environmental exposures, as evidenced by the apparent increase in prostate cancer risk when men from geographic areas with low prostate cancer incidence immigrate to western countries [8]. Some of the environmental exposures that may confer this increase in prostate cancer risk likely include the same exposures that may contribute to the development of prostatic inflammation, including, prostatic infections [9].

Inflammation is a process that involves both an innate and adaptive immune response following infection or injury. The innate immune system initiates the inflammatory response by producing a large number of cytokines, reactive oxygen (ROS), and nitrogen species (RNS) [10]. This process is essential, not only to eliminate pathogens and repair tissue damage, but also to activate the adaptive immune response. Even though inflammation acts as a host defence and usually is a self-limiting process, failure leading to inadequate resolution of inflammatory responses may be pathologically conductive. Chronic inflammation has been linked to tumour promotion and progression by several mechanisms, including increased cell proliferation, enhanced angiogenesis, and evasion from apoptosis [10].

2. Mechanisms of Inflammation Induced Carcinogenesis

Chronic or recurrent inflammation is responsible for the development of many human cancers, including those affecting the liver, esophagus, stomach, large intestine, and urinary bladder [11]. Inflammation might influence the pathogenesis of cancers by 1) inflicting cell and genome damage, 2) triggering restorative cell proliferation to replace damaged cells, 3) elaborating a portfolio of cytokines that promote cell replication, angiogenesis and tissue repair.

Oxidative damage to DNA and other cellular components accompanying chronic or recurrent inflammation may connect prostate inflammation with prostate cancer. In response to infections, inflammatory cells produce a variety of toxic compounds designed to eradicate microorganisms. These include superoxide, hydrogen peroxide, singlet oxygen, as well as nitric oxide that can react further to form the highly reactive peroxynitrite [11]. These reactive species can alter protein structure and function, cause lipid peroxidation and induce somatic gene changes. Free radicals have been shown to cause post-translational modifications of several key proteins, including those involved in DNA repair, apoptosis, cell signaling and essential enzymatic pathways.

3. Inflammation and Prostate Cancer

Inflammation involves the induction of complex, coordinated chemical signals and associated physiological processes following injury that promote "healing" of damaged tissues [12] [13]. Early responses include increases in vascular permeability and activation, together with the directed migration of leukocytes (neutrophils, monocytes and eosinophils) towards the site of injury, where the ground-work is being laid for the formation of a new extracellular matrix. The directional migration is mediated by secreted chemokines that form a concentra-

tion gradient towards the site of inflammation [14]. Normally, inflammation is a self-limiting process due to the production of anti-inflammatory cytokines, which buffer the effect of pro-inflammatory cytokines. The cytokine/chemokine pattern persisting at the inflammatory site is important in the development of chronic disease. Deregulation of any of the cooperating factors can lead to prolonged inflammation with chronic exposure to cytotoxic mediators [15]. Chronic inflammation can be caused by a variety of factors, including bacterial, viral, and parasitic infections, chemical irritants, and non-digestible particles, but often the underlying cause is unknown. The longer the inflammation persists, the higher the risk of associated carcinogenesis [16].

The molecular mechanisms that prime the pathogenesis of cancer-related inflammation are complex and involve a delicate interplay between tumor and its microenvironment. To address the details of transition from inflammation to cancers and the further development of inflammation-associated cancers, it is necessary to investigate specific roles of key regulatory process involved in this process. Constant activation of NF-κB has been found in several cancers including PCa. NF-κB might be linked to tumour development through induction of pro-inflammatory cytokines, such as IL-6, TNF-α, and COX-2, and may also contribute to genomic instability by promoting release of ROS and RNS.

1) The oxidative stress imbalance in the prostrate tumor, and

2) The cytokine & chemokine orchestration in prostate cancer.

3.1. The Oxidative Stress Imbalance in the Prostrate Tumor

The oxidative stress associated with infection and inflammation has also been regarded as a possible cause of prostate carcinogenesis because the induction of iNOS (inducible nitric oxide synthase) might activate reactive nitrogens and oxygen reactive species that are released during the inflammatory response.

At the site of inflammation, caused by either wounding or infection, phagocytic cells (e.g. neutrophils and macrophages) generate reactive oxygen and nitrogen substances, but these cells also synthesize and secrete large quantities of growth factors and a number of potent angiogenic factors, cytokines, and proteases, all of which are important mediators in the tissue regeneration, but can also potentiate neoplastic tumorigenesis. Prostaglandins, cytokines, nuclear factor NF-κB, chemokines and angiogenic factors are the main molecular players that link inflammation to genetic alterations. However, free radical species derived from oxygen (ROI) and nitrogen (RNI) are the main chemical effectors [17] [18].

Human cells have three main systems for protection and repair during the oxidative stress: 1) direct antioxidant enzymes (superoxide dismutase (SOD), catalase, peroxidises), 2) proteases and phospholipases activated by oxidative modification of membranes, 3) lipid and water soluble antioxidants [19] [20]. Both chronic and acute inflammation may lead to events that can cause proliferation within prostatic tissue through a variety of mechanisms, notably oxidative stress [21]. Both tissue damage and oxidative stress may lead to compensatory cellular proliferation with resulting hyperplastic growth. Prostatic inflammation can lead to the generation of free radicals. These include nitric oxide (NO) and various species of oxygen. Both macrophages and neutrophils provide a source of free radicals that can induce hyperplastic transformations through oxidative stress to tissue and DNA [22].

The macrophages in the tumor microenvironment produce ROS and RNS. The increase in reactive radicals causes DNA damage, genetic mutations and initiates/promotes cancer progression. Some molecules implicated in prostate atrophy include p53 and AR mutations, hypermethylation of the CpG island of the promoter of glutathione S tranferase-P1 (GSTP1), decreased activity of manganese superoxide dismutase (MnSOD) and increased expression of NADPH oxidase 1, which initiate high grade prostatic intraepithelial neoplasia (PIN) and progressive prostate cancer [23].

ROS are endogenously generated during cellular metabolic processes. It can also come from external sources. The excessive ROS production or impairment of antioxidant defense systems can induce oxidative stress. This increase in ROS levels may contribute to the initiation and development of various cancers, including prostate cancer, because oxidative stress regulates cellular fate in various systems. ROS are considered to be tumor initiators/promoters given the potential for induction of DNA damage. Furthermore, signaling pathways in response to intracellular changes in ROS levels may trigger proliferation, apoptosis and senescence, events highly implicated in all the stages of the carcinogenic process [24] (**Figure 1**).

The NF-κB family of transcription factors has an essential role in inflammation and innate immunity.

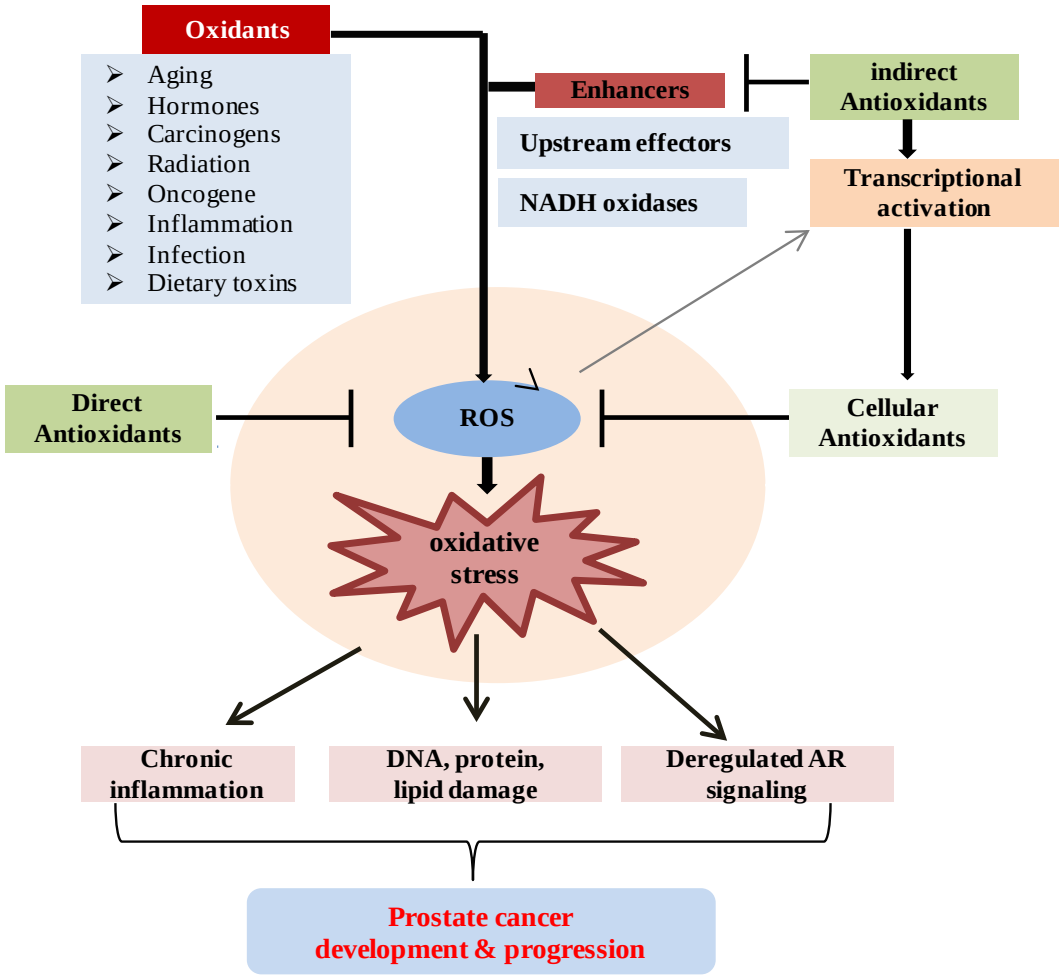

Figure 1. Inflammation and PCa. Inflammation can be triggered by a variety of stresses and stimuli such as infection, radiation, inflammatory stimuli and changes in hormonal status. Cancer-related inflammation is characterized by the presence of inflammatory cells at the tumor sites and the over expression of inflammatory mediators such as cytokines, chemokines, reactive oxygen species (ROS), and nitric oxide (NO) in tumor tissue. These pro-inflammatory mediators promote malignant transformation and prostate cancer progression.

Furthermore, NF-κB has been recognized as the major transcription factor that involves prostate cancer initiation and progression [25].

The NF-κB family of transcription factors plays a crucial role in inflammation as well as in the development and progression of cancer. Extensive evidence indicates that the NF-κB pathway is implicated in controlling the expression of genes involved in cell survival, proliferation, angiogenesis, and invasion [26]. NF-κB is a dimer formed by proteins of the Rel family (RelA/p65, RelB, c-Rel, NF-κB1/p50, and NF-κB2/p52) that is retained in the cytoplasm as a complex with inhibitory IκB proteins. In the canonical pathway, external stimuli such as proinflammatory cytokines promote the dissociation of the ternary complex (mainly that composed of IκBα-p50-p65), an event triggered by phosphorylation of IκBα by IκBα kinase (IKK), followed by proteasomal degradation of IκBα. The released NF-κB dimer is subsequently translocated into the nucleus where it binds specific elements in the promoters of NF-κB-responsive genes [27]. Abnormally high NF-κB activity and aberrant expression of NF-κB-regulated gene products are clinical hallmarks of chronic inflammation and have been widely linked to the cancer phenotype. Inflammation has indeed been shown to contribute to prostate cancer development via multiple mechanisms such as oxidative stress, genomic instability, and DNA damage or indirectly by increasing levels of proinflammatory factors such as tumor necrosis factor α (TNFα), which themselves affect cancer risk [27]. NF-κB hyperactivation may result from enhanced production of tumor-promoting cytokines,

enhanced stimulation of growth factor receptors, and/or aberrant expression/activation of upstream NF-κB kinases such as IKK and NF-κB-inducing kinase (NIK).

Several lines of evidence suggest that activation of NF-κB pathway is dysregulated in prostate cancer and has been implicated in the progression to the androgen-independent state that ultimately leads to patient death. Constitutive NF-κB activation has been reported in prostate tumors tumors [28]. Nuclear p65 NF-κB can be observed in organ-confined prostate tumors, suggesting that constitutive NF-κB activation may be an early event in prostate cancer development [28] [29]. NF-κB has been shown to mediate the effect of proinflammatory cytokines in prostate cancer cells, including TNFα, IFNγ, and IL-1β [30]. Binding of TNFα to its receptor TNFR-I in cancer cells, including prostate cancer cells, leads to the recruitment of adaptor proteins (TRADD, TRAF2, RIP) and the formation of a signaling complex that regulates NF-κB activation and transcriptional activation of inflammatory, survival, and anti-apoptotic genes such as *BCL*2, *BCL2L*1, *PTGS*2 (*COX*2), and *XIAP*.

Collectively, the available evidence confirms that NF-κB activation is a key event in PC pathogenesis. Constitutive or induced activation of NF-κB may lead to amplification of the inflammatory response by providing a positive feedback signal to immune cells present in the tumour microenvironment, thereby increasing the production of molecular mediators such as various proinflammatory cytokines & chemokines which contribute to carcinogenic and inflammatory processes (**Figure 2**).

3.2. The Cytokine Orchestration in Prostate Cancer

Cytokines are a family of cell-signaling protein molecules that are secreted by various cell types and are a category of signaling molecules used extensively in intercellular communication. Cytokines can be classified as proteins, peptides, or glycoproteins. A variety of cytokines are secreted by cells in the tumor microenvironment and can impact on prostate cancer growth [31].

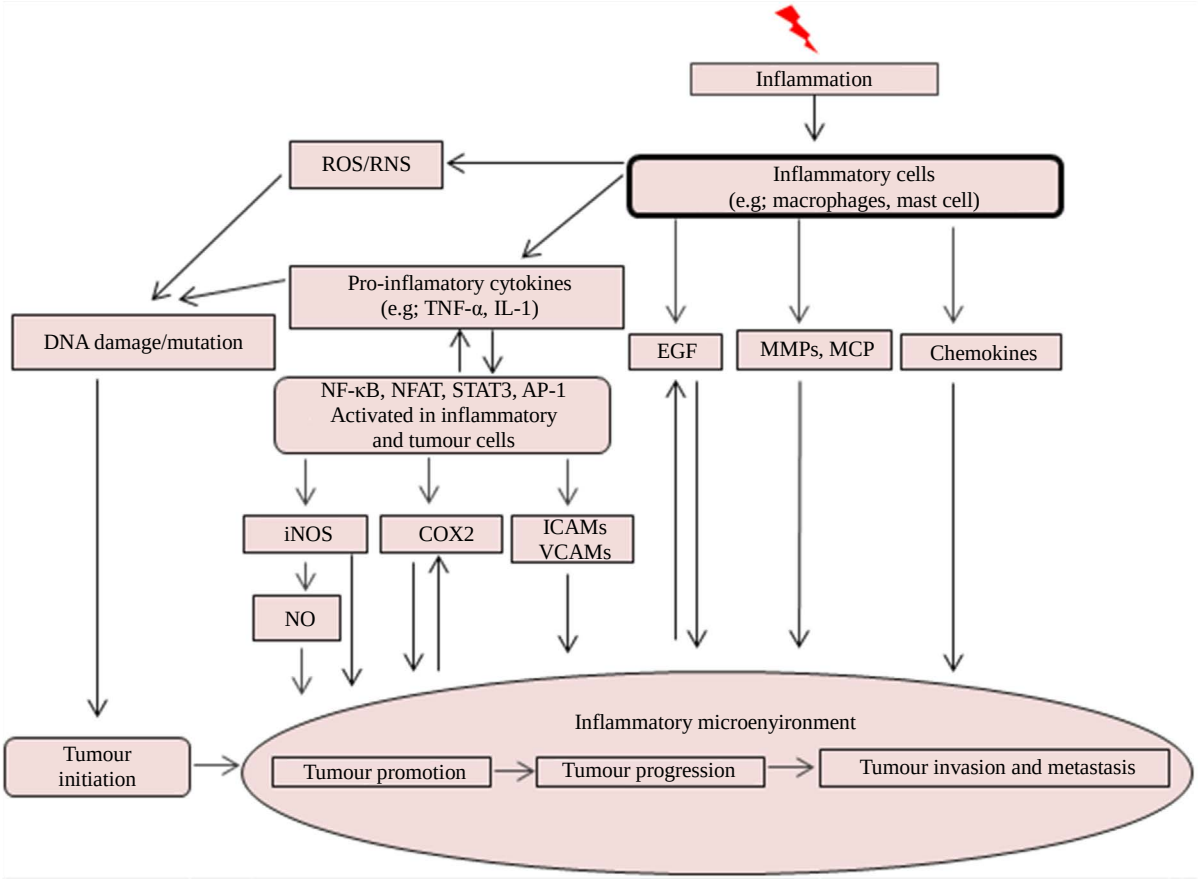

Figure 2. Summary of mechanisms for the involvement of inflammation in cancer development.

Cytokines, including TNF-*α*, IL, growth factors, and differentiation factors (colony-stimulating factors), are secreted or membrane-bound molecules that play a regulatory role in the growth, differentiation, and activation of immune cells (100). Cytokine signaling could contribute to the progression of prostate tumors of altered cells at the inflammatory site [32].

A large number of evidences suggest that TNF and chemokines are candidate linking molecules between inflammation and prostate cancer [33]. TNF, produced mainly by activated macrophages but also by tumor cells, binds to membrane-bound homotrimeric receptors TNFRI and TNFRII [33]. In inflammation, TNF plays a critical role in both tissue destruction and damage recovery, maintaining the reversibility of microenvironments, stimulating cellular change, and tissue remodeling.

TNF-*α* is not released from prostate cancer cells themselves but from associated macrophages after a relapse in disease. Studies have shown that patients with hormone-refractory prostate cancer demonstrate high serum TNF-*α* levels as compared with untreated patients [34] [35]. The relationship between TNF-*α* sensitivity and hormone responsiveness has not yet been explored. However, androgen-insensitive prostate cancer cells, PC-3 and JCA-1, have proven to be TNF-*α* insensitive, whereas androgen-sensitive prostate cancer cells, LNCaP, are TNF-*α* sensitive [36].

The recent publication from Davis *et al.* [37] explains the dichotomy of TNF*α* effect on the control of apoptosis in prostate cancer cells. These authors propose a physiologic role for TNF*α* in prostate regression after androgen withdrawal. This factor is required for castration-induced prostate regression, but membrane-bound TNF*α* protein and stromal cell specific TNF*α* mRNA levels increase in rat prostate after castration, which is coincident with a paracrine effect of TNF*α* in prostate cancer regression.

Moreover, inflammatory cytokines have also been reported to facilitate the spectrum of tumor development. For example, one of the most interesting mediators clearly implicated in prostate cancer is IL-6, a multifunctional cytokine, produced by inflammatory cells, osteoblasts and even prostate cancer cells. There are multiple lines of clinical and experimental evidence preponderantly showing that IL-6 contributes to prostate cancer progression. Both, patients with prostate cancer and patients with advanced metastatic disease display high expression levels of IL-6 and its soluble receptor in the circulating plasma [38]. There is accumulating evidence-linking IL-6 to prostate cancers [39]. In prostate cancer patients, IL-6 serum levels were found to be strongly elevated and positively correlated to tumor load [40]. In other study Shariat *et al.* showed that LNCaP cells continuously exposed to IL-6 develop increased invasiveness as assessed by chamber-based migration assay [41]. Moreover, it has been demonstrated that PC cells develop neuroendocrine features when exposed to IL-6 [42].

In addition to the clinical observations, *in vitro* studies have provided evidence that IL-6 modulates prostate cancer cell growth of hormone-refractory cells, but had no effect on the growth of hormone-dependent cell lines [43].

IL-6 has also been implicated in other aspects of prostate cancer pathophysiology such as tumorigenesis in the prostate microenvironment. IL-6 foremost effect is the activation of Janus kinase (JAK) signaling and of signal transducers and activators of transcription (STAT) proteins, especially STAT3 [44]. Through this signaling pathway, IL-6 stimulates autocrine activation of insulin-like type I growth factor receptor (IGF-IR) to confer tumorigenesis [44]-[46]. Depending on the cellular context, IL-6 can also signal through MAPK and phosphatidylinositol-3 kinase (PI3K) pathways [47] [48].

The other cytokines like IL-8 and IL-17 are also involved in human prostate epithelial cells, growth and survival. It has been shown that Human IL-8, an inflammatory chemokine, promotes tumor cell growth and the progression of human solid tumors; this includes PCa, due largely to its ability to regulate the expression of matrix metalloproteinases (MMPs) [49]. Numerous studies have demonstrated a correlation between MMPs, IL-8, and CaP. Increased levels of IL-8, MMP-2, and MMP-9 were associated with high Gleason scores and metastatic disease. Also, a high level of IL-8 leads to an increase in MMP-9 expression, which in turn may directly increase the tumor grade and metastasis in PCa patients [49] [50].

Steiner *et al.* have shown that 58% of human malignant prostate tissues have an increased level of IL-17 messenger ribonucleic acid and both prostate tumor cells and prostate stromal cells treated with IL-17 *in vitro* have an increase in messenger ribonucleic acid and protein expression of both IL-6 and IL-8. These data suggest that IL-17 acts directly on the prostate tumor cells and promotes their growth and metastasis, or indirectly by increasing the level of inflammatory cytokines and growth factors released locally in the prostate.

Together above, experimental studies have validated the crucial role of various pro/anti-inflammatory cytokines in prostate cancer progression and development.

4. Conclusion and Future Direction

The evidence presented in this review provides a strong association between inflammation and prostate cancer but the whole story between inflammation and prostate cancer is still far from being completely understood. The question regarding the intriguing feedback loop between cytokines and NF-κB is which activation is the initial event during the prostate cancer. In addition, animal models for inflammation-derived cancers and combination to molecular approaches, such as specific gene knockout mouse, will be helpful and necessary to address the questions in this field. We believe that the better clarification of mechanisms linking inflammation and prostate cancer will be beneficial to the development of efficacious prevention and therapies of inflammation-associated cancers.

References

[1] Albini, A. and Sporn, M. (2007) The Tumour Microenvironment as a Target for Chemoprevention. *Nature Reviews Cancer*, **7**, 139-147. http://dx.doi.org/10.1038/nrc2067

[2] Abate, S. and Shen, M. (2000) Molecular Genetics of Prostate Cancer. *Genes Development*, **14**, 2410-2434. http://dx.doi.org/10.1101/gad.819500

[3] Ferlay, J., Autier, P., Boniol, M., Heanue, M., Colombet, M. and Boyle, P. (2007) Estimates of the Cancer Incidence and Mortality in Europe. *Annals of Oncology*, **18**, 581-592. http://dx.doi.org/10.1093/annonc/mdl498

[4] Pisani, P., Parkin, M., Munoz, N. and Ferlay, J. (1997) Cancer and Infection: Estimates of the Attributable Fraction in 1990. *Cancer Epidemiology, Biomarkers Prevention*, **6**, 387-400.

[5] Klein, E. and Silverman, R. (2008) Inflammation, Infection, and Prostate Cancer. *Current Opinion in Urology*, **18**, 315-319. http://dx.doi.org/10.1097/MOU.0b013e3282f9b3b7

[6] Balkwill, F. and Mantovani, A. (2001) Inflammation and Cancer: Back to Virchow? *Lancet*, **357**, 539-545. http://dx.doi.org/10.1016/S0140-6736(00)04046-0

[7] Nelson, W, Sfanos, K., DeMarzo, A. and Yegnasubramanian, S. (2013) Prostate Inflammation and Prostate Cancer. *Management of Prostate Cancer*, **4**, 103-115.

[8] Lee, J., Demissie, K., Lu, S. and Rhoads, G. (2007) Cancer Incidence among Korean-American Immigrants in the United States and Native Koreans in South Korea. *Cancer Control*, **14**, 78-85.

[9] Sfanos, K. and Marzo, M. (2012) Prostate Cancer and Inflammation: The Evidence. *Histopathology*, **60**, 199-215. http://dx.doi.org/10.1111/j.1365-2559.2011.04033.x

[10] Mantovani, A., Allavena, P., Sica, A. and Balkwill, F. (2008) Cancer-Related Inflammation. *Nature*, **454**, 436-444. http://dx.doi.org/10.1038/nature07205

[11] Chughtai, B., Lee, R., Te, A. and Kaplan, S. (2011) Role of Inflammation in Benign Prostatic Hyperplasia. *Reviews in Urology*, **13**, 147-150.

[12] Fibbi, B., Penna, G., Morelli, A., Adorini, L. and Maggi, M. (2010) Chronic Inflammation in the Pathogenesis of Benign Prostatic Hyperplasia. *International Journal of Andrology*, **33**, 475-488. http://dx.doi.org/10.1111/j.1365-2605.2009.00972.x

[13] Koopmann, W. and Krangel, M. (1997) Identification of a Glycosaminoglycan-Binding Site in Chemokine Macrophage Inflammatory Protein-1α. *The Journal of Biological Chemistry*, **272**, 10103-10109. http://dx.doi.org/10.1074/jbc.272.15.10103

[14] Coussens, L.M. and Werb, Z. (2002) Inflammation and Cancer. *Nature*, **420**, 860-867. http://dx.doi.org/10.1038/nature01322

[15] Shacter, E. and Weitzman, S. (2002) Chronic Inflammation and Cancer. *Oncology*, **16**, 217-226.

[16] Jackson, R., Seed, M., Kircher, C., Willoughby, D. and Winkler, J. (1997) The Codependence of Angiogenesis and Chronic Inflammation. *FASEB Journal*, **11**, 457-465.

[17] Federico, A., Morgillo, F., Tuccillo, C., Ciardiello, F. and Loguercio, C. (2007) Chronic Inflammation and Oxidative Stress in Human Carcinogenesis. *International Journal of Cancer*, **121**, 2381-2386. http://dx.doi.org/10.1002/ijc.23192

[18] Sies, H. (1997) Oxidative Stress: Oxidants and Antioxidants. *Experimental Physiology*, **82**, 291-295.

[19] Finkel, T. and Holbrook, N. (2000) Oxidants, Oxidative Stress and the Biology of Ageing. *Nature*, **408**, 239-247. http://dx.doi.org/10.1038/35041687

[20] Naber, K. and Weidner, W. (2000) Chronic Prostatitis—An Infectious Disease? *Journal of Antimicrobial Chemotherapy*, **46**, 157-161. http://dx.doi.org/10.1093/jac/46.2.157

[21] Sugar, L. (2006) Inflammation and Prostate Cancer. *Canadian Journal of Urology*, **13**, 46-47.

[22] Josson, S., Matsuoka, Y., Chung, L., Zhau, H. and Wang, R. (2010) Tumor-Stroma Co-Evolution in Prostate Cancer Progression and Metastasis. *Seminars in Cell & Developmental Biology*, **21**, 26-32. http://dx.doi.org/10.1016/j.semcdb.2009.11.016

[23] Sun, S., Sprenger, C., Vessella, R., Haugk, K., Soriano, K., Mostaghel, E., Page, S., Coleman, I., Nguyen, H., Sun, H., Nelson, P. and Plymate, S. (2010) Castration Resistance in Human Prostate Cancer Is Conferred by a Frequently Occurring Androgen Receptor Splice Variant. *Journal of Clinical Investigation*, **120**, 2715-2730. http://dx.doi.org/10.1172/JCI41824

[24] Nguyen, D., Li, J., Yadav, S. and Tewari, A. (2013) Recent Insights into NF-κB Signalling Pathways and the Link between Inflammation and Prostate Cancer. *BJU International*, **4**, 23-28.

[25] Karin, M. and Lin, A. (2009) NF-κB at the Crossroads of Life and Death. *Nature Immunology*, **3**, 221-227. http://dx.doi.org/10.1038/ni0302-221

[26] Stock, D., Groome, A. and Siemens, R. (2008) Inflammation and Prostate Cancer. A Future Target for Prevention and therapy? *Urologic Clinics of North America*, **35**, 117-130. http://dx.doi.org/10.1016/j.ucl.2007.09.006

[27] Shukla, S., MacLennan, G., Marengo, R., Resnick, M. and Gupta, S. (2004) Nuclear Factor κB/p65 (Rel A) Is Constitutively Activated in Human Prostate Adenocarcinoma and Correlates with Disease Progression. *Neoplasia*, **6**, 390-400. http://dx.doi.org/10.1593/neo.04112

[28] Suh, J., Payvandi, F., Edelstein, L., Amenta, P., Zong, W., Gélinas, C. and Rabson, A. (2002) Mechanisms of Constitutive NF-κB Activation in Human Prostate Cancer Cells. *The Prostate*, **52**, 183-200. http://dx.doi.org/10.1002/pros.10082

[29] Pahl, H. (1999) Activators and Target Genes of Rel/NF-κB Transcription Factors. *Oncogene*, **18**, 6853-6866. http://dx.doi.org/10.1038/sj.onc.1203239

[30] Mantovani, A. (2009) Cancer: Inflaming Metastasis. *Nature*, **457**, 36-37. http://dx.doi.org/10.1038/457036b

[31] Pollard, J. (2004) Tumour-Educated Macrophages Promote Tumour Progression and Metastasis. *Nature Reviews Cancer*, **4**, 71-78. http://dx.doi.org/10.1038/nrc1256

[32] Locksley, R., Killeen, N. and Lenardo, M. (2001) The TNF and TNF Receptor Superfamilies: Integrating Mammalian Biology. *Cell*, **104**, 487-501. http://dx.doi.org/10.1016/S0092-8674(01)00237-9

[33] Nakashima, J., Tachibana, M., Ueno, M., Miyajima, A., Baba, S. and Murai, M. (1998) Association between Tumor Necrosis Factor in Serum and Cachexia in Patients with Prostate Cancer. *Clinical Cancer Research*, **4**, 1743-1748.

[34] Irie, A., Lee, K., Kadowaki, K., Toda, K. and Yamada, Y. (1999) Elevation of Serum and Urine Tumor Necrosis Factor Levels after Transurethral Resection of the Prostate. *Nippon Hinyokika Gakkai Zasshi*, **90**, 502-508.

[35] Nakajima, Y., Dellipizzi, A., Mallouh, C. and Ferreri, N. (1996) TNF-Mediated Cytotoxicity and Resistance in Human Prostate Cancer Cell Lines. *The Prostate*, **6**, 296-302.

[36] Davis, J., Nastiuk, K. and Krolewski, J. (2012) TNF Is Necessary for Castration-Induced Prostate Regression, Whereas TRAIL and FasL Are Dispensable. *The Journal of Clinical Endocrinology and Metabolism*, **96**, 873. http://dx.doi.org/10.1210/jcem.96.3.zeg873a.

[37] Alcover, J., Filella, X., Luque, P., Molina, R., Izquierdo, L., Maria, J. and Alcaraz, A. (2010) Prognostic Value of IL-6 in Localized Prostatic Cancer. *Anticancer Research*, **30**, 4369-4372.

[38] Nguyen, D., Li, J. and Tewari, A. (2013) Inflammation and Prostate Cancer: The Role of Interleukin-6. *BJU International*, Published Online.

[39] Chung, Y. and Chang, Y. (2003) Serum Interleukin-6 Levels Reflect the Disease Status of Colorectal Cancer. *Journal of Surgical Oncology*, **83**, 222-226. http://dx.doi.org/10.1002/jso.10269

[40] Shariat, S., Chromecki, T., Hoefer, J., Barbieri, C., Scherr, D., Karakiewicz, P., Roehrborn, C., Montorsi, F., Culig, Z. and Cavarretta, T. (2011) Soluble gp130 Regulates Prostate Cancer Invasion and Progression in an Interleukin-6 Dependent and Independent Manner. *The Journal of Urology*, **186**, 2107-2114. http://dx.doi.org/10.1016/j.juro.2011.06.048

[41] Deeble, P., Murphy, D., Parsons, S. and Cox, M. (2001) Interleukin-6- and Cyclic AMP-Mediated Signaling Potentiates Neuroendocrine Differentiation of LNCaP Prostate Tumor Cells. *Molecular and Cellular Biology*, **21**, 8471-8482. http://dx.doi.org/10.1128/MCB.21.24.8471-8482.2001

[42] Joseph, L., Jian, Z., Jill, A. and Evan, T. (2011) The PCa Tumor Microenvironment. *Cancer Microenvironment*, **4**, 283-297. http://dx.doi.org/10.1007/s12307-011-0073-8

[43] Blaszczyk, N., Masri, B., Mawji, N., Ueda, T., McAlinden, G., Duncan, C., Bruchovsky, N., Schweikert, H., Schnabel, D., Jones, E. and Sadar, M. (2004) Osteoblast-Derived Factors Induce Androgen-Independent Proliferation and Expression of Prostate-Specific Antigen in Human Prostate Cancer Cells. *Clinical Cancer Research*, **10**, 1860-1869. http://dx.doi.org/10.1158/1078-0432.CCR-0974-3

[44] Kosaka, T., Miyata, A., Ihara, H., Hara, S., Sugimoto, T., Takeda, O., Takahashi, E. and Tanabe, T. (1994) Characterization of the Human Gene (PTGS2) Encoding Prostaglandin-Endoperoxide Synthase 2. *European Journal of Biochemistry*, **221**, 889-897. http://dx.doi.org/10.1111/j.1432-1033.1994.tb18804.x

[45] Van der Giet, M., Tölle, M. and Kleuser, B. (2008) Relevance and Potential of Sphingosine-1-Phosphate in Vascular Inflammatory Disease. *Biological Chemistry*, **389**, 1381-1390. http://dx.doi.org/10.1515/BC.2008.165

[46] McCarty, M. (2004) Targeting Multiple Signaling Pathways as a Strategy for Managing Prostate Cancer: Multifocal Signal Modulation Therapy. *Integrative & Complementary Medicine*, **3**, 349-380. http://dx.doi.org/10.1177/1534735404270757

[47] Mahmud, S., Franco, E. and Aprikian, A. (2004) Prostate Cancer and Use of Nonsteroidal Anti-Inflammatory Drugs: Systematic Review and Meta-Analysis**.** *British Journal of Cancer*, **90**, 93-99. http://dx.doi.org/10.1038/sj.bjc.6601416

[48] Inoue, K., Slaton, J., Eve, B., Kim, S., Perrotte, P., Balbay, M., Yano, S., Bar-Eli, M., Radinsky, R., Pettaway, C. and Dinney, C. (2000) Interleukin 8 Expression Regulates Tumorigenicity and Metastases in Androgen-Independent Prostate Cancer. *Clinical Cancer Research*, **6**, 2104-2119

[49] Uehara, H., Troncoso, P., Johnston, D., Bucana, C., Dinney, C., Dong, Z., Fidler, I. and Pettaway, C. (2005) Expression of Interleukin-8 Gene in Radical Prostatectomy Specimens Is Associated with Advanced Pathologic Stage. *The Prostate*, **64**, 40-49. http://dx.doi.org/10.1002/pros.20223

[50] Steiner, G., Newman, M., Paikl, D., Stix, U., Memaran-Dagda, N., Lee, C. and Marberger, M. (2003) Expression and Function of Pro-Inflammatory Interleukin IL-17 and IL-17 Receptor in Normal, Benign Hyperplastic, and Malignant Prostate. *The Prostate*, **56**, 171-182. http://dx.doi.org/10.1002/pros.10238

Scientific Research Publishing (SCIRP) is one of the largest Open Access journal publishers. It is currently publishing more than 200 open access, online, peer-reviewed journals covering a wide range of academic disciplines. SCIRP serves the worldwide academic communities and contributes to the progress and application of science with its publication.

Other selected journals from SCIRP are listed as below. Submit your manuscript to us via either submit@scirp.org or Online Submission Portal.