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## Inflammatory Signaling Involved in High-Fat Diet Induced Prostate Diseases

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### Abstract

High-Fat Diet (HFD) has emerged as an important risk factor not only for obesity and diabetes but also for urological disorders. Recent research provides ample evidence that HFD is a putative cause for prostatic diseases including prostate cancer. The mechanisms whereby these diseases develop in the prostate have not been fully elucidated. In this review we discuss signaling pathways intricately involved in HFD-induced prostate disease. We performed a search through PUBMED using key words “high fat diet” and “prostate”. Our data and perspectives are included in this review along with research performed by various other groups. HFD is positively associated with an increased risk of benign prostatic hyperplasia (BPH) and prostate cancer. HFD induces oxidative stress and inflammation in the prostate gland, and these adverse influences transform it from a normal to a diseased state. Studies demonstrate that HFD accelerates the generation of reactive oxygen species by driving the NADPH oxidase system, exacerbating oxidative stress in the prostate. HFD also causes a significant increase in the levels of pro-inflammatory cytokines and gene products through activation of two important signaling pathways: the Signal Transducer and Activator of Transcription (STAT)-3 and Nuclear Factor-kappa B (NF- $\kappa$ B). Both these pathways function as transcription factors required for regulating genes involved in proliferation, survival, angiogenesis, invasion and inflammation. The crosstalk between these two pathways enhances their regulatory function. Through its influences on the NF- $\kappa$ B and Stat-3 signaling pathways, it appears likely that HFD increases the risk of development of BPH and prostate cancer.

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## Keywords

Signal transducer and activator of transcription; Nuclear factor-kappa B; Benign prostatic hyperplasia; NADPH oxidase; prostate cancer

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## Introduction

The current trend towards an increasingly sedentary lifestyle and increasing consumption of high-caloric 'Western style' high-fat diet (HFD) has contributed to the sharply increasing prevalence of metabolic disorders such as obesity and type 2 diabetes in the United States [1]. Presently, obesity is a major health concern, and according to the Center for Disease Control & Prevention, approximately 40% of the adults in the United States are obese and ~20% of children and adolescents are overweight [2]. A closer examination of obesity has revealed that a preferential accumulation of fat in the abdominal region of men is associated with increased risk of urologic complications including urinary incontinence, erectile dysfunction, benign prostatic hyperplasia (BPH) and perhaps cancer [3]. A strong association between fatty acids and prostate diseases has been reported with several intriguing hypothesis. These include mechanisms involving inflammation, oxidative stress, peroxidation of lipids and accumulation of 8-hydroxy-2'-deoxyguanosine and increased androgen synthesis driving the growth of the prostate. High-fat diet induces a low-grade chronic inflammatory response, a phenomenon designated as 'metabolically triggered inflammation' or meta-inflammation [4,5]. The direct effects of HFD on the prostate are still unclear, though it is considered to cause inflammation and oxidative stress through alteration in various signaling pathways that increases the vulnerability of the prostate to numerous diseases [4–6]. In this review we focused on the role of HFD in the genesis of oxidative stress and intraprostatic inflammation and their influences on signaling pathways that orchestrate various prostate diseases, including cancer.

## High-fat diet induced intraprostatic inflammation

Prostate inflammation is frequently observed in histological specimens from aging men [7]. Mounting data suggest that intraprostatic inflammation plays a pivotal role in the development of BPH, lower urinary tract symptoms (LUTS) and cancer [5–7]. Accumulating evidence suggests that other than aging, androgens and genetic predisposition, modifiable factors such as obesity, diet, dyslipidemia, hormonal imbalance, hypertension, metabolic syndrome, alcohol and smoking also contribute to the development of BPH and/or LUTS [4,5,6,8]. A previous study from our group reported an association between chronic intraprostatic inflammation and carcinogenesis. In this 5 year follow-up study, initial biopsies from patients with chronic inflammation had a 20% higher incidence of the development of prostate cancer with a significant association between serum prostate specific antigen (PSA) and the degree of inflammation [9]. Clinically, a number of cross sectional studies reveal the association between the presence of inflammatory infiltrates and increased prostate volume. A recent study on Prostate Cancer Prevention Trial patients with inflammation and BPH has higher incidence towards the development of prostate cancer [10]. In another study, Giovannucci *et al.* observed that consumption of animal fat is a risk

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factor for prostate cancer [11]. HFD intake has been shown to cause a remarkable downregulation in the gene expression of glutathione peroxidase 3 (GPx3) in the prostate, which is considered to modulate carcinogenesis [12]. Tumor progression is accelerated in genetically-engineered transgenic adenocarcinoma of the mouse prostate (TRAMP) mice that progresses through multiple stages and exhibits both histological and molecular features similar to that of human prostate cancer, upon HFD feeding [13]. In another study, Vykhovanets *et al.* showed that NF- $\kappa$ B reporter mice consuming HFD with a composition similar to a Western-style diet developed increased intraprostatic inflammation as well as increased cellular proliferation and increased size of the prostate gland [14]. A study by Cai *et al.* demonstrated increased ventral prostate weight in mice fed with HFD, without any changes in serum or intraprostatic androgen levels [15]. Consumption of a diet rich in animal fat not only causes obesity, impaired glucose tolerance, and insulin resistance, but also elevates ataxin levels in the adipose tissue, causing increased production of lysophosphatidic acid. This chemical in turn has been shown to act directly on the prostate to induce hyperplastic and neoplastic growth contributing to prostate cancer progression and BPH by creating a pro-inflammatory environment [16]. Another recent report has shown that in a HFD setting, prostate cancer cell proliferation is increased through activation of MCP-1/CCR2 signaling [17].

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While inflammation of the prostate is believed to cause tissue damage and growth, there is no clear understanding of the mechanisms involved. It has been suggested that inflammation leads to activation of lymphocytes and macrophages which are attracted to the prostate tissue, leading to the secretion of pro-inflammatory cytokines directly affecting prostate growth [18]. Our previous studies revealed that activation of cytokine IL-1 $\beta$  initiates a time-dependent wave of signals that initiates early phase of intraprostatic inflammation and signal inflammatory pathways [19,20]. In adipose tissue, HFD-induced inflammation leads to the production of various pro-inflammatory cytokines such as IL-1, IL-6 and TNF $\alpha$  [21,22]. Reports indicate that pro-inflammatory cytokine TNF $\alpha$  mediates insulin resistance as a result of obesity [23,24]. Feeding HFD to mice caused a macrophage inflammatory response in white adipose tissue that was associated with morbid fat mass expansion and TNF $\alpha$  release that triggered pre-adipocytes to enhance the expression of inflammatory genes [25,26]. This is consistent with studies in obese patients demonstrating an increase in the plasma levels of TNF $\alpha$  that is associated with weight gain [27,28]. Our studies have shown that HFD not only caused a significant increase in the plasma levels of IL-6, IL-17, IL-1 $\beta$  and TNF $\alpha$  but also a marked elevation of intraprostatic IL-6 expression [29]. These pro-inflammatory cytokines affect peripheral tissues, causing inflammation *via* activation of transcription factors that result in the recruitment and activation of macrophages and lymphocyte infiltration [30].

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Pro-inflammatory cytokines induce inflammatory mediators such as cyclooxygenase -2 (COX-2) and inducible nitric oxide (iNOS) that contribute to prostate growth [7]. It has been shown that IL-17 can exert a direct influence on COX-2, thus stabilizing and preventing its degradation, increasing its enzymatic activity [31]. Vykhovanets *et al.* have demonstrated increased production of IL-17 by macrophages and neutrophils in proliferative inflammatory atrophy (PIA) lesions [32]. Levels of IL-17 producing cells were similar in zones of benign

prostate tissue and areas of prostate cancer. Increased COX-2 expression has been reported in BPH with moderate to severe T lymphocyte and macrophage infiltration. The increased COX-2 expression was noted in areas where the epithelium was highly proliferative [33]. The presence of COX-2 has been reported in inflammatory cells in the epithelium and interstitial spaces in proliferative inflammatory atrophy lesions, generating pro-inflammatory prostaglandins [34,35]. Inflammation is reported to induce expression and enzyme activity of iNOS and COX-2, which produces pro-inflammatory mediators such as prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) and nitric oxide [36–39]. We reported that HFD intake by C57BL/6 mice caused a significant increase in the levels of COX-2 and iNOS in the prostate [14]. The levels of iNOS increases in epithelial cells identified with conditions of BPH, high-grade prostatic intraepithelial neoplasia (PIN) and prostate cancer [40]. Long term HFD intake has been shown to decrease excretion of nitrite in the urine as a result of oxidative stress [41].

### High-fat diet induced oxidative stress in the prostate

It is hypothesized that inflammation of the prostate, through the generation of reactive oxygen species (ROS), causes repeated tissue damage and post-translational DNA modifications, thereby inducing neoplasia in the prostate [42]. The major sources of ROS are the mitochondrial respiratory chain, an uncontrolled arachidonic acid cascade, and NADPH oxidase. These processes make use of molecular oxygen and produce ROS which include superoxide anion and hydrogen peroxide [43]. Elevated ROS production has a deleterious effect and is associated with tissue injury, DNA damage, neoplastic transformation and aberrant growth and proliferation. Thus, disproportionate formation of ROS can result in oxidative stress and might play an important role in the pathogenesis of several prostatic diseases including cancer [44]. The NADPH oxidase system has been reported as a contributor to the genesis of prostate diseases, including prostate cancer [45]. Several recent studies have shown a substantial generation of ROS and NADPH oxidase activity, which are thought to play a critical role in the growth and maintenance of prostate cancer [45–50]. We found that HFD feeding to NF- $\kappa$ B reporter mice caused an increase in the expression of NADPH oxidase subunits such as gp91phox, p47phox and p22phox in the prostate [14]. We hypothesize that HFD accelerates the generation of ROS by driving the NADPH oxidase system, thereby enhancing several signaling pathways that are involved in inflammation. This is in concurrence with the findings of other investigators who have shown that generation of ROS either through the NADPH oxidase system or arachidonic acid pathway leads to the activation of inflammatory signaling pathways, primarily the NF- $\kappa$ B pathway, that orchestrate the gene expression of several pro-inflammatory mediators [43]. Sustained oxidative stress and inflammatory mediators activate two important signaling pathways that have a role as core transcription factors in diverse immune responses; specifically, the signal transducer and activator of transcription (STAT)-3 and nuclear factor-kappa B (NF- $\kappa$ B) pathways. Both these pathways are activated by external stimuli through cytosolic signals and function as transcription factors required for regulating genes involved in proliferation, survival, angiogenesis, invasion and inflammation. Pro-inflammatory cytokines have been shown to activate both Stat-3 and NF- $\kappa$ B and their transcriptional targets establishes a feedback loop [51].

## Nuclear factor-*kappa*-B (NF- $\kappa$ B)

NF- $\kappa$ B encompass a family of pleiotropic transcription factors that integrate a complex network of extracellular perturbations and signaling pathways, resulting in the transcriptional regulation of hundreds of genes related to inflammation, immunity, apoptosis, cell proliferation, and differentiation [52,53]. NF- $\kappa$ B activation is orchestrated either through classical/canonical or alternative/non-canonical pathways resulting in its nuclear translocation. Activating stimuli involve phosphorylation and engagement of the inhibitor of the  $\kappa$ B kinase (IKK) signalosome, which is composed of two catalytic subunits, IKK $\alpha$  (IKK1) and IKK $\beta$  (IKK2), and a regulatory subunit, IKK $\gamma$  (NF- $\kappa$ B essential modulator) and inhibitors of  $\kappa$ B (I $\kappa$ B) proteins, I $\kappa$ B $\alpha$ , I $\kappa$ B $\beta$ , I $\kappa$ B $\epsilon$  that regulate nuclear translocation and DNA binding of NF- $\kappa$ B. Normally NF- $\kappa$ B dimers are either bound to I $\kappa$ B $\alpha$ , I $\kappa$ B $\beta$ , I $\kappa$ B $\epsilon$ , or the precursor proteins p100 and p105 that maintain these dimers in the cytoplasm in an inactive state. The activation of canonical pathway occurs as a result of interaction of ligands to their corresponding receptors that result in activation of the  $\beta$  subunit of I $\kappa$ B kinase (IKK) complex IKK $\beta$  that phosphorylates and degrades I $\kappa$ B $\alpha$ . This causes the NF- $\kappa$ B heterodimers (comprising of p65, p50 and c-Rel) to translocate into the nucleus and induce or repress genes by binding to discrete DNA sequences known as  $\kappa$ B elements in promoter and enhancer elements of target genes [52–54]. In the case of the alternative pathway activation results from the transformation of NF- $\kappa$ B2/p100 to p52 that is activated by phosphorylation of NF- $\kappa$ B2/p100 by IKK $\alpha$ , allowing the translocation of p52 along with RelB into the nucleus.

Constitutive activation of NF- $\kappa$ B has been implicated not only in prostate cancer but also in a wide range of human diseases like rheumatoid arthritis, inflammatory bowel diseases, neurodegenerative conditions, asthma and chronic obstructive pulmonary disease [55–60]. Since NF- $\kappa$ B is the key mediator of inflammation, we and others have investigated whether or not HFD can cause its activation. Carlson *et al.* reported that HFD caused elevated NF- $\kappa$ B activation in mice and there was a regional difference between males and females: in females the activity was localized to the thoracic region, whereas in males the activity was observed in the abdominal region. We reported that HFD feeding to NF- $\kappa$ B reporter mice caused increased activation of NF- $\kappa$ B in the whole body and remarkably extended activation was observed in the prostate [61]. A notable elevation in the levels of Rel A/p65, phosphorylation of IKK $\alpha$ / $\beta$  and I $\kappa$ B $\alpha$  in the prostate suggested that HFD activates NF- $\kappa$ B. Overexpression of NF- $\kappa$ B and its association with increased presence of ROS and NADPH oxidase activity has been reported in various inflammatory diseases [62]. Upregulation of NF- $\kappa$ B during inflammation also results in the recruitment of inflammatory cells leading to the production of various pro-inflammatory cytokines, such as IL-1, IL-6, IL-8 at the site of inflammation [63,64]. Earlier reports from our group suggest that NF- $\kappa$ B is constitutively activated in prostate adenocarcinoma [59]. Constitutive activation of NF- $\kappa$ B is associated with upregulation of pro-survival molecules including Bcl-2 family members such as Bcl-2, Bcl-X<sub>L</sub>, and Mcl-1 that helps evade apoptosis. Transcriptional regulation of Bcl-2 by NF- $\kappa$ B as well as strong association between NF- $\kappa$ B activation and Bcl-X<sub>L</sub>/Mcl-1 expression has been documented in prostate cancer [65]; but not in HFD environment. Detailed studies are required to establish the role of Bcl-2 family members in the etiology of BPH/LUTS and

HFD environment. In the kidney, consequence of HFD caused a contemporaneous increase in the levels of TNF $\alpha$ , resulting in increased phosphorylation of p-IKK/ $\beta$  and NF- $\kappa$ B activation, causing oxidative stress [66]. In the mouse intestine, HFD-induced increase in TNF $\alpha$  and NF- $\kappa$ B activation promotes inflammation through interaction with enteric bacteria which precedes obesity and insulin resistance [67]. In our study with HFD we observed increased plasma levels of TNF $\alpha$  and IL-6, suggesting that HFD feeding may cause sustained activation of NF- $\kappa$ B in the prostate [29]. Previously we had reported that cytokines such as TNF $\alpha$ , IL-6 and IL-1 $\beta$  could activate NF- $\kappa$ B, and that IL-1 $\beta$  initiates a time depended wave of signals that could induce the initial phase of intraprostatic inflammation [19,20].

### Signal transducer and activator of transcription (STAT-3)

STAT-3 is a transcription factor located in the cytosol during inactive state. Several types of receptor tyrosine kinases activate STAT-3. They are epidermal growth factor receptor (EGFR), fibroblast growth factor receptor (FGFR), platelet-derived growth factor receptor and Janus kinase (JAK) family members that are constitutively bound to the cytoplasmic tails of cytokine receptors, or non-receptor-associated tyrosine kinases. Growth factors like EGF and FGF, initiate STAT-3 signal transduction when they bind to their receptors and activate intracellular kinases. JAK proteins or receptor tyrosine kinases recruit inactive STAT-3 monomers and phosphorylate them on tyrosine-705, leading to homo- or heterodimer formation. STAT-3 dimers then translocate to the cell nucleus, where they act as transcription activators [68,69]. Discovered as an acute-phase response protein, STAT-3 has been implicated in driving inflammation. Several pro-inflammatory cytokines have been shown to activate STAT-3 especially IL-6. Activation by IL-6 has been shown to be dependent on COX-2 [68,70,71]. It has been shown that IL-11 and its glycoprotein 130 (gp130) receptor activation in inflammation-associated gastric epithelial cell oncogenic transformation is mediated by and dependent on increased activation of STAT-3 [72].

Several infectious and non-infectious agents are known to cause inflammation and involve STAT-3 activation by various distinct mechanisms [70,73,74]. Case control studies draw a link between STAT-3 polymorphism and metabolic syndrome and these studies demonstrate that common genetic variants in the locus of STAT-3 is associated with abdominal obesity, a key factor of metabolic syndrome [75]. In fact, dietary saturated fat has been reported to activate STAT-3, which is involved in body weight regulation. Park *et al.* demonstrate that dietary and genetic obesity promote liver inflammation and tumorigenesis by enhancing IL-6 and TNF $\alpha$  expression [76]. In the prostate, HFD feeding resulted in increased STAT-3 activation and DNA binding that might be IL-6 mediated, as there was a significant increase in the plasma levels [29]. HFD may create an environment that potentiates the IL-6-STAT-3 axis, thereby sustaining persistent chronic inflammation.

### Crosstalk between NF- $\kappa$ B and STAT3

NF- $\kappa$ B and STAT3 are ubiquitously expressed transcription factors that are thought to play critical roles in inflammation and tumorigenesis, and their association occurs in a direct and an indirect manner [51,69,77]. These proteins interact directly with one another via a

physical interaction; indirectly, these pathways activate one another to sustain inflammation and tumor progression. Although these pathways transcribe their own sets of genes, induction of certain gene subsets requires cooperation between the STAT-3 and NF- $\kappa$ B pathways [51]. The crosstalk between these two pathways has become a hallmark during inflammation driven carcinogenesis [51,78,79]. The persistently activated STAT-3 retains NF- $\kappa$ B activity in the nucleus by causing its acetylation at Lysine 310 [77]. The association or crosstalk requires cytokines or other signaling pathways such as the release of IL-6 by NF- $\kappa$ B that causes the stimulation of STAT-3 by an autocrine/paracrine mechanism [79]. In colitis associated cancer, IL-6 not only bridges NF- $\kappa$ B and Stat-3 but also is responsible for tumor growth and tumor initiation [51]. NF- $\kappa$ B and STAT-3 are interconnected and require phosphoinositide 3-kinase (PI3K) and Myc expression, and the physical association between NF- $\kappa$ B and STAT-3 is important in the development of Myc-driven B-cell neoplasia [80].

The functions of NF- $\kappa$ B and STAT-3 broaden beyond carcinogenesis, as both of these transcriptional factors play a pivotal role in immune and inflammatory responses [52,81]. STAT-3 creates a pro-inflammatory condition and simultaneously suppresses anti-tumor immune response [82]. In intestinal epithelial cells, STAT-3 and NF- $\kappa$ B have been reported to be required in tumor promotion and NF- $\kappa$ B is reported to control STAT-3 activation in a dual manner by recruiting myeloid cells that secrete STAT-3 induced cytokines, and transcribing these cytokines that activate STAT-3 [73]. Other notable feature of STAT-3-NF- $\kappa$ B interaction is the induction of inflammatory mediators like IL-6, COX-2, IL-17 and IL-23, which require STAT-3 as a co-transcription factor with RelA for potentiating their expression and thus causing immune suppression [71,81]. We have recently demonstrated a physical association between STAT-3 and NF- $\kappa$ B and their binding to the promoter regions of inflammatory genes in C57BL/6 mouse fed with high-fat diet [29]. Together, these two transcription factors require association for persistent induction of their activators. It is unclear whether this association is only present in tumor microenvironment. Could potential risk factors such as HFD drive the association between STAT-3 and NF- $\kappa$ B in cells that are in a state of inflammation? In our studies we observed that HFD not only activated STAT-3 and NF- $\kappa$ B but also their association caused persistent chronic inflammation in the mouse prostate. The uniqueness of this association is that it happens in a non-cancerous environment induced by HFD that drives a wide range of pro-survival, proliferative and inflammatory genes [29]. Another function of STAT-3 is to suppress immune response as it inhibits the expression of NF- $\kappa$ B target genes involved in T<sub>H</sub>1 innate immunity and adaptive immune responses that is required for controlling microbial infections and tumor growth [81]. Thus, interaction of STAT-3 with NF- $\kappa$ B occurs at multiple levels and the outcome of this interaction depends on the cellular environment. In the prostate, HFD driven STAT-3/NF- $\kappa$ B interaction may be one of the underlying causes of chronic prostatic inflammation which could be the initiator for the development of common prostatic diseases, such as BPH and prostate cancer. Theoretically, HFD initiated STAT-3/NF- $\kappa$ B association should cease once the dietary pattern changes and normalcy could be restored. Unremitting HFD consumption may set the stage for persistent activation of STAT-3 and NF- $\kappa$ B, leading to their association, which may exacerbate prostate inflammation, leading to prostate diseases including cancer.

## Protein kinase C epsilon (PKC $\epsilon$ ) and Akt

In our recent studies we observed that HFD caused increased activation of upstream kinases such as Protein Kinase C epsilon (PKC $\epsilon$ ) and Akt which orchestrates signaling via STAT-3 and NF- $\kappa$ B in the prostate [29]. While PKC $\epsilon$  has been reported to activate STAT-3, Akt activates NF- $\kappa$ B and increases pro-survival signals through upregulation of Bcl-2, Bcl-X<sub>L</sub> and Mcl-1 [65,83,84]. In a HFD environment, PKC $\epsilon$  is reported to play a critical role in the liver by mediating fat-induced hepatic insulin resistance [85]. Leptin has also been associated with PKC $\epsilon$  and PI3K/Akt, while it has been shown to cause inhibition of lysophosphatidic acid-induced intracellular calcium rise in a PKC $\epsilon$  dependent manner, its resistance has been reported to cause impairment in the PI3K pathway [86,87]. We reported that HFD feeding could induce a repertoire of pathways which could lead to the activation of the inflammatory signals [29]. The scenario seems to be complex as these upstream kinases also activate pro-inflammatory cytokines. In adipocytes PKC $\epsilon$  has been implicated in the activation of IL-6 via a MAPK pathway thereby contributing to the pathogenesis of type 2 diabetes [88]. In a HFD prone milieu we reported that PKC $\epsilon$  activation in the prostate could serve as an impetus not only for STAT-3 activation but also IL-6. More systematic studies are needed to evaluate this mechanism.

## High-fat diet induced increase in leptin

Accumulation of fat occurs primarily in the adipose tissue and previous studies delineate a clear link between obesity, insulin resistance, and inflammation as a result of inflammatory cytokines, adipokines and leptin [89–91]. The end result of HFD intake is an increase in the amount of adipose tissue which is a large repository of cholesterol serving as precursor for testosterone, androstenedione and triglycerides that may stimulate prostate epithelial cell growth through upregulation of androgen receptor [92]. Leptin is a pivotal hormone of the adipose tissue that regulates appetite and body weight and transduces the signaling of STAT-3 by activating the JAK-STAT pathway [93]. HFD induces resistance to the effect of leptin causing impairment in the PI3K pathway precedes that of the STAT-3 pathway [87]. High expression of leptin receptor has been observed in the prostate and circulating leptin levels increase in parallel with prostate growth at puberty in rats [94,95]. Elevated immunoreactivity for leptin receptors in prostatic cancer specimens, with a strong expression in high-grade PIN lesion has been reported [96]. Stattin *et al.* observed that moderately increased leptin levels are associated with the development of prostate cancer [97]. HFD feeding has been shown to increase circulating levels of leptin in normal mice and mice with transgene-induced ablation of brown adipose tissue making them obese without increasing their caloric intake [98]. We have observed that intake of HFD to C57BL/6 male mice in a time-dependent manner caused increased levels of inflammatory molecules related to leptin and estrogen signaling in the prostate [99]. Thus, excessive leptin may be a possible key link between Western lifestyle and prostate diseases.

## Immune cell response

As mediators of low-grade chronic inflammation associated with obesity, several reports implicate the involvement of immune cells [100,101]. HFD feeding has been shown to cause



depletion of hepatic Natural Killer T (NKT) cells resulting in obesity and insulin resistance [102]. This study demonstrate that NKT cells are the key mediators of HFD-induced metabolic abnormalities. HFD feeding of C57BL6 mice has also shown to elevate CD4, CD8 and macrophages levels in the inguinal adipose tissue suspected to be a cause for low-grade inflammation [103]. Significant recruitment of peripheral immune cells was observed in the central nervous system of obese mice fed with HFD contributing to inflammatory response during obesity [104]. In clinical studies, nodules of BPH patients contain infiltrates of T-lymphocytes, macrophages and B-lymphocytes that are chronically activated [105]. These infiltrating cells produce cytokines viz. IL-2, IFN- $\gamma$  and TGF- $\beta$  which may support fibromuscular growth in BPH. Other *in situ* studies have demonstrated that elevated expression of pro-inflammatory cytokines in BPH, IL-6, IL-8 and IL-17, may perpetuate chronic immune response in BPH and induce persistent intraprostatic inflammation and fibromuscular growth by an autocrine or paracrine loop [106,107]. Further studies are needed to establish association between obesity and the role of invading immune cells in causing BPH/LUTS symptoms in the prostate.

## Conclusions and future directions

Accumulated evidence suggests that HFD influences prostatic inflammation and plays a significant role in the development of prostatitis, BPH and prostate cancer. Though the precise molecular mechanisms potentiating prostate growth or inflammation mediated by HFD is unclear, current studies offer evidence supporting the involvement of the above described pathways in the development of these diseases. A schematic presentation of these pathways and disease development is shown in Figure 1. HFD-induced chronic inflammation plays a key role in the induction of prostate growth and BPH progression, while potentiation of oxidative stress may give rise to PIA lesions making the prostate vulnerable to cancer initiation. Our work in this area suggests that HFD-induced association between NF- $\kappa$ B and STAT-3 is possibly one such signaling mechanism that drives inflammation in the prostate. We speculate that HFD may also orchestrate other pathways that may trigger inflammation of the prostate leading to BPH or cancer. Dietary fat has been reported to affect the secretion and metabolism of androgens [108]. While HFD may deregulate androgen metabolism, future work may shed light on the signaling pathways that crosstalk or activate NF- $\kappa$ B, STAT-3 and AR, promoting the onset of BPH/LUTS or prostate cancer. The pro-survival members of Bcl-2 family of proteins including Bcl-2, Bcl-X<sub>L</sub> and Mcl-1 have been shown to play a definitive role during prostate cancer progression and resistance to apoptosis [65]; however the role of these proteins in HFD-induced intraprostatic inflammation and its association with BPH/LUTS is lacking. Although evidences in the literature reveals transcriptional regulation of Bcl-2 by NF- $\kappa$ B and synergy between Akt and Bcl-X<sub>L</sub>, but these associations are not demonstrated in BPH/LUTS or in the HFD setting. Other potential pathways that may drive inflammation or proliferation in the prostate leading to BPH include but are not limited to IGF-1, estrogen or aromatase signaling [99]. These signaling pathways may lead to BPH in many ways: i) induce proliferation or inflammation independently, or ii) induce proliferation that may be a consequence of inflammation, and iii) crosstalk between proliferation and inflammation. It

will be worthwhile to explore these pathways induced by HFD that may potentate BPH and other prostatic diseases.

In summary, substantial research has demonstrated that lifestyle factors, especially natural and fiber-rich diet provides an opportunity for prevention of prostate diseases. It becomes potentially beneficial and important to promote healthy diets that would lower the risk for various prostate diseases and help in reducing the costs of medical treatment.

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## Abbreviations

<b>BPH</b>	benign prostatic hyperplasia
<b>COX-2</b>	cyclooxygenase-2
<b>EGFR</b>	epidermal growth factor receptor
<b>FGFR</b>	fibroblast growth factor receptor
<b>gp130</b>	glycoprotein 130
<b>GPx3</b>	glutathione peroxidase 3
<b>HFD</b>	high-fat diet
<b>HGPIN</b>	high-grade prostatic intraepithelial neoplasia
<b>IL</b>	interleukin
<b>iNOS</b>	inducible nitric oxide synthase
<b>IKK</b>	inhibitor of the $\kappa$ B kinase
<b>JAK</b>	janus kinase
<b>LUTS</b>	lower urinary tract symptom
<b>NF-<math>\kappa</math>B</b>	nuclear factor-kappa B
<b>PIA</b>	proliferative inflammatory atrophy
<b>PI3K</b>	phosphoinositide 3-kinase
<b>PKC<math>\epsilon</math></b>	protein kinase C epsilon
<b>PGE2</b>	prostaglandin E2
<b>ROS</b>	reactive oxygen species
<b>STAT-3</b>	signal transducer and activator of transcription
<b>TRAMP</b>	transgenic adenocarcinoma of the mouse prostate

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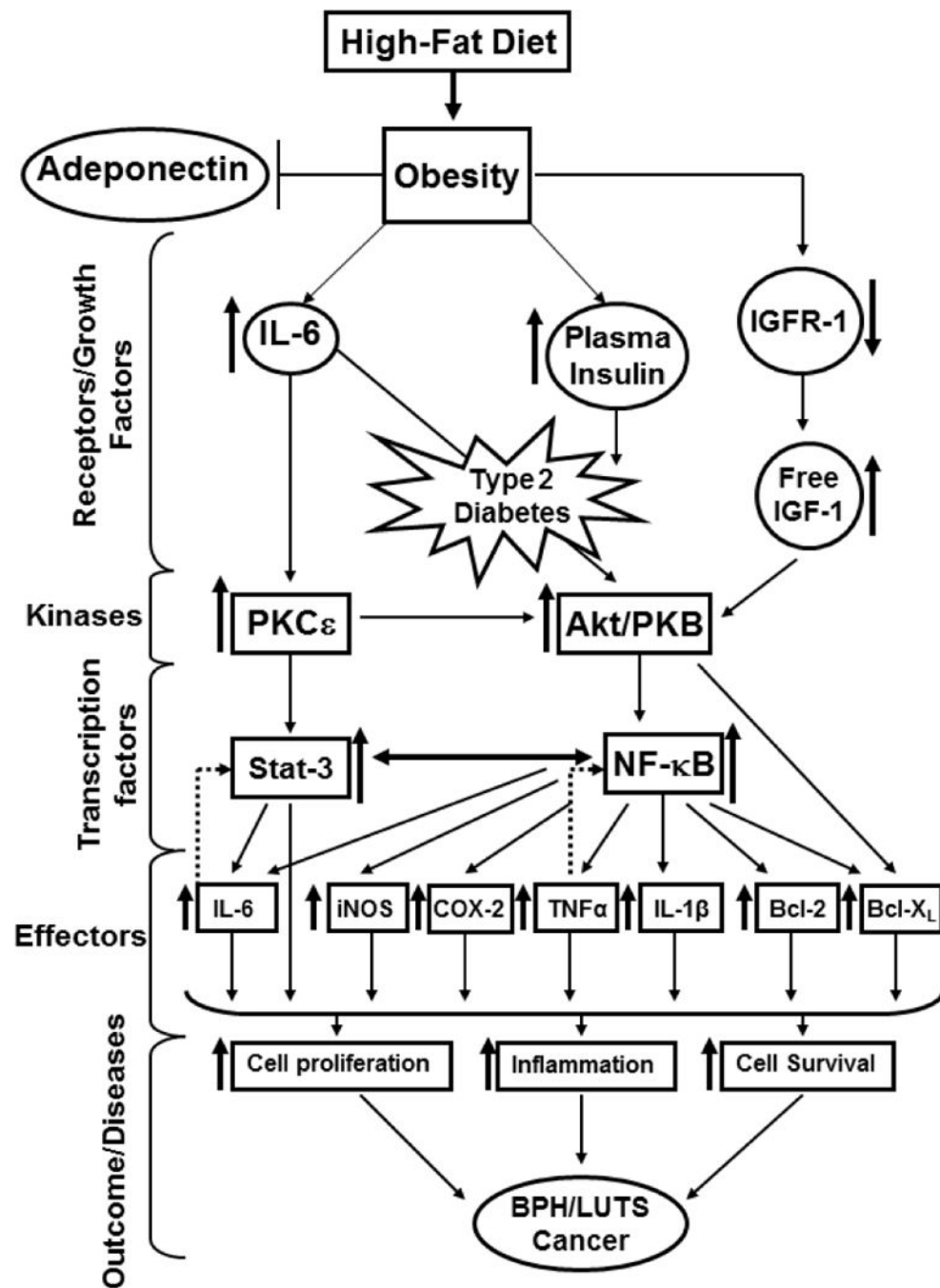
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**Figure 1.**

High-fat diet (HFD) is a key cause for benign prostatic hyperplasia, lower urinary tract symptom and cancer in men. The consequence of HFD-induced obesity leads to prostate diseases observed at various levels. 1) Adeponectin, involved in the regulation of glucose levels and fatty acid breakdown is deregulated by HFD contributing to obesity. 2) HFD causes alterations of receptors and growth factors such as IGFR-1, IL-6 and plasma insulin leading to type 2 diabetes. 3) Upstream kinases such as PKC $\epsilon$  and Akt/PKB are constitutively activated by these receptors and growth factors that in turn activate

transcription factors, Stat-3 and NF- $\kappa$ B initiating pro-inflammatory signaling pathways. 4) These transcription factors translocate into the nucleus and initiate transcription of several genes (iNOS, COX-2, TNF $\alpha$ , Bcl-X<sub>L</sub>, Bcl-2, IL-1 $\beta$ , IL-6) responsible for cell proliferation, inflammation and cell survival. The crosstalk between Stat-3 and NF- $\kappa$ B sustain pro-inflammatory signals and enhance disease progression.  $\uparrow$  denotes upregulation,  $\downarrow$  denotes downregulation,  $\leftrightarrow$  denotes crosstalk, and dotted arrow denotes feedback regulation.

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