Inflammation, Apoptosis, and BPH: What is the Evidence?

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Abstract

Background: Benign prostatic hyperplasia (BPH) is one of the most common diseases of aging men but its aetiology is far from being completely understood.

Methods: Data were identified by searching MEDLINE from which 134 records were identified. Full texts were reviewed by to select the most relevant studies. In addition, other significant texts cited in the reference lists of the selected papers were considered.

Results: Based on the role played in several models of human pathology, inflammation and apoptosis have been extensively investigated in the last decade. Inflammation is the basic process whereby tissues of the body respond to injury. Detection of injury or the presence of invaders in the tissue leads to a relatively circumscribed set of responses that removes the damaged structures and cells, kills and clears the invaders, and promotes cell and matrix replacement and repair. The role of inflammation in prostate pathologies is suggested by the presence of several kinds of inflammatory cells within the normal gland, as well as in patients with BPH and prostate cancer. Apoptosis (or programmed cell death) refers to the death of cells, which occurs as a normal and controlled part of the growth of an organism. Apoptosis is currently considered a genetically encoded, ubiquitous pathway, enabling cells to undergo highly regulated cell death in response to specific signalling, which have been largely investigated, as well as its intracellular effectors. Both inflammation and apoptosis are of major interest in understanding the aetiology of BPH, as well as the action mechanism of the drugs currently used and, most importantly, the development of new, more efficacious molecules.

Conclusion: This review summarises the available evidence concerning the role of inflammation and apoptosis in BPH pathogenesis and treatment.

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1. Introduction

Benign prostatic hyperplasia (BPH) is one of the most common diseases of aging men [1]. Lower urinary tract symptoms (LUTS) possibly related to benign prostatic enlargement (BPE) and benign prostatic obstruction (BPO) due to BPH interfere significantly with normal daily activities. The prevalence of histologic marks of BPH is age-related, rising up to 88% in the ninth decade of life [2]. According to Bostwick's description, those findings include the presence of enlarged, hypertrophic basal cells; the increase in stromal mass (due mostly to the amount of smooth muscle cells); an enhanced extracellular matrix deposition, with reduced elastic tissue; and an increase in the number of infiltrating lymphocytes [3]. Moreover, McNeal pointed out that the landmarks of BPH were the budding and branching of epithelium glandular tissue from pre-existing ducts [4]. Clinical signs and symptoms due to BPE are also highly prevalent. By the age of 60 yr, nearly 60% of the cohort of the Baltimore Longitudinal Study of Aging had some degree of LUTS [5], whereas moderate-to-severe symptoms can occur among 13% of men aged 40–49 yr and among 28% of those >70 yr of age [6].

Nonetheless, the aetiology of BPH is far from being completely understood, despite the great efforts made by molecular and clinical researchers. Most of the initial research studies focused on hormonal factors, thinking that advanced age and the presence of functioning testes were the two best-established conditions for the development of BPH. Based on the role played in several models of human pathology, inflammation and apoptosis have been investigated extensively in the last decade, achieving significant improvements in our knowledge of both physiologic prostate growth and BPH pathogenesis.

Inflammation is the basic process whereby tissues of the body respond to injury. Detection of injury or the presence of invaders in the tissue leads to a relatively circumscribed set of responses that removes the damaged structures and cells, kills and clears the invaders, and promotes cell and matrix replacement and repair. In normal conditions, the original cells and tissue function are restored [7]. The role of inflammation in prostate pathologies is suggested by the presence of several kinds of inflammatory cells within the normal gland, as well as in patients with BPH and prostate cancer. Apoptosis (or programmed cell death) refers to the death of cells that occurs as a normal and controlled part of the growth of an organism. Although this phenomenon was observed for the first time in 1842, it was extensively studied in the last decades of the 20th century, when Kerr, Wyllie, and Currier introduced the term “apoptosis” [8]. Apoptosis is currently considered a genetically encoded, ubiquitous pathway, enabling cells to undergo highly regulated cell death in response to specific signaling, which, along with its intracellular effectors, have been largely investigated [8].

Both inflammation and apoptosis may be of major interest in understanding the aetiology of BPH, as well as the action mechanism of the drugs currently used and, most importantly, the development of new, more efficacious molecules. The present review focuses on the role of both inflammation and apoptosis in the pathogenesis and treatment of BPH.

2. Search strategy

We performed a nonsystematic review of the literature. Data were identified by searching MEDLINE using a “MeSH” (Medical Subject Heading) search. Specifically, the MeSH search was conducted using the terms “Prostatic Hyperplasia,” “Inflammation,” and “Apoptosis” retrieved from the MeSH browser provided by MEDLINE. The MEDLINE search findings were pooled, with languages (“English”) being the only search limit used. A total of 134 records were finally identified, whose full texts were reviewed by two of the authors (G.N., A.G.) to select the most relevant studies. In addition, other significant texts cited in the reference lists of the selected papers were considered.

3. Prostate growth

Prostate growth is regulated by complex interactions between epithelium and prostatic stroma [9]. Human prostatic epithelium consists of three major cell types: basal cells, luminal cells, and neuroendocrine cells. Basal cells form a layer of flattened, small cells on the basement membrane. Basal cells do not show androgen receptors and are considered the stem cell population of the prostatic epithelium. Independently of androgen stimulation, these cells give rise to intermediate cells, which proliferate and translocate towards the luminal compartment, where terminal differentiation gives origin to a cohort of androgen-sensitive luminal cells. Luminal cells produce part of the seminal plasma, including prostatic-specific antigen (PSA) and prostatic acid phosphatase [10–12]. Among epithelial cells are scattered neuroendocrine cells, which are thought
to play a regulatory role through the secretion of several peptides, such as somatostatin, calcitonin, and neurotensin [10,11]. Prostatic stroma consists of several kinds of cells entrapped in an extracellular matrix, made of several types of collagens and glycoproteins. Fibroblasts and smooth muscle cells are the predominant cellular types, although androgen-sensitive endothelial cells, nerve cells, and, above all, blood-borne cells (mostly T lymphocytes) are amply represented [10].

The prostate is an androgen-dependent organ, but studies on cultures of prostatic epithelial cells established clearly that androgens had no direct mitogenic effects on the prostatic epithelium [10]. Androgen effects are thought to be mediated by interactions between epithelial and stromal compartments, through a complex network of paracrine and autocrine factors. Basic fibroblast growth factor (bFGF) was the first growth factor to be isolated in the prostate in the late 1980s and was followed by almost 20 different proteins of the same family, with mitogenic effect on epithelial or stromal cells [10]. Similarly, other factors recognized to stimulate prostate growth are insulin-like growth factors (IGFs) I and II, several epidermal growth factors (EGFs), and transforming growth factor α (TGF-α) [10]. On the other hand, a few inhibitory growth factors have been discovered, whose prototype is transforming growth factor β (TGF-β), the first identified member of a super-family of growth factors including >25 proteins. TGF-β is a ubiquitous multifunctional polypeptide, acting through an androgen-independent pathway, which regulates epithelial cell proliferation and differentiation, apoptosis, extracellular matrix formation, and degradation [13]. Specifically, in the prostate, TGF-β1, -β2, and -β3 are produced by smooth muscle cells, and their receptors have been identified in both epithelial and stromal cells. Acting on epithelial cells, TGF-β is able to inhibit proliferation and facilitate differentiation of the basal cells to luminal cells. Acting on stromal cells, TGF-β is able to induce the smooth muscle phenotype, resulting in aggregation of smooth muscle cells. In addition, TGF-β is thought to be a key factor in stimulating programmed cell death, a process in which a major role is played by a family of proteases, called caspases, which were discovered in 1993 and extensively studied thereafter, also in BPH [14]. To date, 12 different caspases have been identified, allowing a clear comprehension of the pathways controlling their regulation. Two major activation mechanisms have been found: the first is mediated by the activation of cell surface receptors (the so-called death receptors), and the second is activated by their release of cytochrome c from mitochondria, due to cell damage, following administration, for example, of cytotoxic drugs [8]. In both cases, the signals activate the caspase cascades, where initiator (caspases 2, 8, 9, 10, and 12) and effector (caspases 3, 6, and 7) proteins have been identified, whose final targets are different kinds of proteins of major relevance in cell life (proteins regulating the cell cycle, proteins repairing cell damage, proteins involved in the regulation of apoptosis or structural proteins) [8].

4. Possible roles of inflammation and apoptosis in the development of BPH

After physiologic growth to adult size, the prostate enters a maintenance phase, where prostatic cell proliferation occurs at a daily rate of 1–2% counterbalanced by an equal rate of programmed cell death [13,15]. A lack of this balancing has been advocated as causative in BPH.

Several studies highlighted possible alterations at different stages of prostate growth regulation that might lead to BPH. Several in vitro studies supported the role of inflammation. Stromal nodules of BPH present infiltrates of B lymphocytes, T lymphocytes, and macrophages [16]. Those cells accumulate around the epithelial ducts and can disrupt glandular epithelium [17]. To date, the factors that trigger the infiltration are unknown, although Kakehi et al. recently reported that patients with “symptomatic” BPH had down-regulation of the gene for macrophage inhibitory cytokine-1 (MIC-1), a cytokine with inhibitory effects on macrophage activity [18]. Several groups investigated the cytokine production of those cells, with the aim of showing how that production might alter the networks of intraprostatic growth factors. The role of interleukin 17 (IL-17), a cytokine with a key proinflammatory role, was analysed by Steiner et al. [19]. IL-17 is secreted by the activated CD4+ T cells and is able to stimulate epithelial, endothelial, and fibroblastic cells to produce several proinflammatory molecules, such as IL-1β, TNF-α, IL-8, and cyclooxygenase 2 (COX-2). The authors showed that healthy prostate tissue did not express IL-17, which, on the other hand, was evident in smooth muscle cells and in the apical part of the epithelial ducts in BPH. Moreover, the authors demonstrated that IL-17 up-regulated the secretion of other proinflammatory cytokines, such as IL-8 and IL-6 by stromal cells, as well as of TGF-β. IL-8 and IL-6 are recognised 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 [19]. Those data suggested that IL-17 played a pivotal role in the inflammatory process present in patients with BPH, being the principal proinflammatory cytokine and promoting a cascade of other proinflammatory molecules. Important data on the role of IL-8 were provided by Castro et al., who found that senescent prostatic epithelial cells secrete IL-8, whose levels were significantly related to prostate volume [20]. The same group provided similar data for IL-1α, suggesting that senescent cells could contribute to BPH by the secretion of FGF, mediated by IL-8 and IL-1α [21]. Proinflammatory cytokines, moreover, are able to induce expression of COX-2, the inducible isof orm of the enzyme responsible for the production of prostaglandins from arachidonic acid. Using immunohistochemistry, Wang et al. investigated the expression of COX-2 in BPH, showing a significant expression of the isoenzyme in the luminal epithelial cells within ducts adjacent to foci of chronic inflammation. In addition, the authors showed that cells expressing COX-2 had a higher proliferation rate and up-regulated the antiapoptotic gene Bcl2 [22], providing further correlations between inflammation, apoptosis, and prostate growth imbalance.

A few clinical studies support the role of inflammation in BPH. Di Silverio et al., analyzing retrospectively the clinical and pathologic data of approximately 4000 patients who had undergone transurethral resection of the prostate (TURP) or open prostatectomy for BPH, found evidence of acute or chronic inflammation in 1700 patients (43.1%). The authors demonstrated a statistically significant correlation between prostate volume and both acute and chronic inflammation, with neutrophic or mononuclear infiltrates present in 29.9%, 37.3%, and 50% of the prostates with a size of 40–49, 50–59, and 60–69 cc, respectively [23]. These data might suggest that the more serious the inflammation, the larger the prostate growth.

At the 2005 meeting of the American Urological Association (AUA), Roehrborn et al. reported interesting findings concerning inflammation in a subset of patients from the Medical Therapy of Prostatic Symptoms (MTOPS) trial [24]. The authors studied 544 patients who had shown acute (only 31) or chronic inflammation at the baseline prostate biopsy. Compared to those without inflammation, the patients with evidence of inflammation were older (64 vs. 62.8 yr, \( p = 0.001 \)), had larger glands (41.1 vs. 36.8 ml; \( p = 0.0002 \)), and had higher serum PSA level (3.3 vs. 2.5 ng/ml; \( p < 0.0001 \)). On the other hand, the International Prostate Symptom Score (IPSS), Qmax, and quality of life scores were overlapping. Those patients showed higher risk of acute urinary retention across all the treatment groups and a non-statistically significant trend for increased rate of overall clinical progression (21.0 vs. 13.2%; \( p = 0.083 \)). Furthermore, the authors found that a greater percentage of the patients presenting inflammation who were randomised to placebo experienced a rise in the AUA-Symptom Index (13.7% vs. 11.2%) and crossover to invasive therapy (7.3% vs. 3.9%), compared to those without evidence of inflammation [24]. To date, such data have not been extensively published, which complicates their interpretation. The authors’ conclusions were that inflammation made patients “more prone to progress clinically in terms of symptoms and crossing over to invasive therapy” [24].

Another clinical study addressed the correlation between prostatic hyperplasia and C-reactive protein, a nonspecific marker of inflammation. Rohrman et al. performed a cross-sectional study on a sample of the US civilian, noninstitutionalised population, collecting structured interviews concerning LUTS, a physical examination, and C-reactive protein measurements in 2337 men. Once adjusted for body mass index, smoking status, alcohol intake, and having excluded men with active acute infections, the authors showed that patients with C-reactive protein above the limit of detection (0.3 mg/dl) had odds of 1.47 (95% confidence interval, 0.87–2.5) of complaining of three or more urinary symptoms [25]. Although the data were not statistically significant, they might suggest a trend for a correlation between LUTS and C-reactive protein and support further research in the era of serum biomarkers inflammation in BPH.

Several in vitro studies suggested that a reduction of apoptosis might occur in BPH. Kiprianu et al. reported that basal and luminal epithelial cells in BPH overexpress Bcl-2, compared to healthy prostate tissue [26]. In the authors’ opinion, enhanced expression of Bcl-2 might be involved in the deregulation of the normal apoptotic cell death mechanisms in the human prostate, resulting in a growth imbalance in favour of cell proliferation, which might ultimately promote prostatic hyperplasia. Similar data were proposed by Colombel et al., who found that Bcl-2 was strongly expressed in the basal cells within mature glandular nodules and in most cells of young small nodules [27]. Subsequently, Claus et al., using Ki-67 and terminal transferase-mediated dUTP-biotin nick-end labeling (TUNEL) to label proliferative and apoptotic cells, showed that the prostate outgrowth was compartmentalised in the stroma, where cell death was absent [28]. These data were further reconfirmed by Tunn et al., who studied the average life span of
epithelial and stromal cells of human prostate by superoxide dismutase activity, estimating that the average life span of stromal cells was longer than 30 years [29].

Further insights were recently provided by Shariff et al., who studied immunohistochemically specimens of radical prostatectomy, open prostatectomy, and radical cystectomy [15]. The authors showed that caspase-3 was highly expressed in the epithelial cells of patients with BPH, whereas survivin, an inhibitor of apoptosis that counteracts cell death and controls mitotic progression, was overexpressed in the stromal compartment. Moreover, the levels of survivin turned out to be related to the IPSS, quality of life score, and postvoid residual urine volume [15]. The loss of the cell’s ability to undergo apoptosis is typical of cell senescence, a process whereby cells are metabolically active in a growth-arrested state, which could contribute to the cell accumulation present in BPH [11]. Choi et al. studied this phenomenon, evaluating the expression of a specific biomarker, the senescence-associated (SA)-β-galactosidase, in BPH. The authors found that galactosidase expression was closely related to prostate weight, with prostates larger than 55 g having the highest levels [30]. Surprisingly, SA-β-galactosidase was identified only in epithelial cells. To sum it up, the available experimental data suggest that one of the main issues in BPH is the inhibition of the apoptosis, which is due to the activation of the Bcl-2 pathway, which up- and down-regulates the actions of several effector proteins.

5. Anti-inflammatory and proapoptotic actions of the drugs available for LUTS

The drugs currently available for the treatment of LUTS due to BPE are α-blockers, 5-α-reductase inhibitors, and phytotherapeutic agents. Several studies investigated and demonstrated the possible mechanisms of action of those drugs, suggesting possible interactions with inflammation and apoptotic mechanisms.

α-Blockers are traditionally thought to act in patients with LUTS, targeting the dynamic component of the bladder outlet obstruction, produced from the tone of the smooth muscle cells of prostate and bladder neck. The research on new mechanisms of actions of the α-blockers was pioneered by Kyprianou et al., who were the first to report the proapoptotic effects of doxazosin [31]. The authors studied the specimens of 22 patients with LUTS, before and after doxazosin therapy, assessing proliferation rate and apoptosis. The authors showed that therapy with doxazosin significantly increased the apoptotic activity in the stromal cells. The activity was minimal at baseline, reached the highest level after 3 mo of therapy, and remained significantly elevated for up to 12 mo. Similarly, apoptosis was identified in epithelial cells, where the highest rates were reached after 4–5 mo of therapy. Interestingly, the proapoptotic effects of doxazosin were not reconfirmed after long-term treatments [31], suggesting the onset of a sort of cell resistance to the apoptosis induced by the α-blocker. Subsequent studies from the same group showed that the proapoptotic action of doxazosin was shared by terazosin [32] but not tamsulosin [33], a uroselective α1-adrenoceptor antagonist with a different chemical structure. Moreover, further data indicated that irreversible inhibitors of α-adrenoceptors, such as phenoxybenzamine, did not interfere with doxazosin-induced apoptosis, suggesting an action independent of α-adrenoceptors [13]. The same group reported that the effects of the quinazoline α-blockers (terazosin and doxazosin) on apoptosis were mediated by an increased expression of TGF-β and caspase-3 [34], data reconfirmed by Illo et al. [35], even in prostate cancer cells [36]. Further studies suggested other potentially relevant mechanisms of action of quinazoline α-blockers, such as increased expression of vascular endothelial growth factor (VEGF) and anoikis, the induction of apoptosis by disruption of the interaction between cells and extracellular matrix [33].

Interesting data are available on inhibitors of the 5-α-reductase, the enzyme that converts testosterone in dihydriosterone in prostatic stromal and epithelial cells. Finasteride, which was the only drug available for years, has been more extensively studied, whereas few studies are available on dutasteride, the dual inhibitor of type I and II 5-α-reductases.

Preliminary data on the proapoptotic effects of finasteride in BPH were reported by Rittmaster et al. in 1996 [37]. Subsequently, major insights as well as explanations of the fine mechanisms of actions were provided. Studies on rat prostates showed that finasteride induced apoptosis in epithelial cells, inhibiting IGF-1 and IGF-1R expressions, as well as several other proteins mediating the effect of IGF (Akt-1, Mek1/2, mitogen-activated protein kinase, c-raf) [38]. The same group reported, in addition, a major role of finasteride on the proteins of the Bcl-2 family, which play a major antiapoptotic action. Specifically, the authors showed that finasteride down-regulated the expression of Bcl-xL and Bcl-2, making prostate cells more susceptible to apoptosis.
Similarly, up-regulation of the Bad protein was discovered, which, binding Bcl-x<sub>L</sub> and Bcl-2, ultimately caused a proapoptotic effect [39]. Other studies on patients with BPH treated by finasteride reconfirmed the proapoptotic effect of finasteride on the epithelial cells. Saez et al. suggested that the up-regulation of TGF-β may be one of the most important molecular pathways activated by finasteride [40]. In a recently published paper, Bozec et al. reported new data on the temporal framework and molecular bases of finasteride effects. The authors found that finasteride triggered apoptosis in the epithelial cells within the first week of treatment, but, surprisingly, its apoptotic efficacy dropped after 30 d. How those findings could be related to the clinical data suggesting the need of a minimum of 6-mo therapy with finasteride before detecting any improvement in LUTS is not clear. Moreover, the same authors reported that finasteride-induced apoptosis was mediated by the activation of caspases-3, -6, and -9, providing further original contributions to the discovery of the fine molecular mechanisms of its action [41].

Data on the proapoptotic effects of dutasteride were recently reported but were obtained only in prostate cancer models [42–44]. Interestingly, a paper by Glassman et al., who studied apoptosis in patients treated with a combination therapy of terazosin and finasteride [34], authors showed that combination therapy caused higher rates of apoptosis, compared to either terazosin or finasteride monotherapy, without any effect on proliferation rates. In addition, the authors reported that combination therapy determined a higher expression of TGF-β compared to monotherapy [34]. Although the trend was not statistically significant because of the low numbers of patients studied, that issue might be one of the molecular bases of the findings of the MTOPS study [45].

Phytotherapy is another option available in the treatment of BPH. Extracts of the fruits of the American dwarf palm (saw palmetto), known as Serenoa repens, is the most commonly used drug in this category and formal meta-analyses showed its clinical efficacy [46,47], although phytotherapy is not currently recommended by the guidelines on male LUTS because of the lack of long-term studies. Several studies investigated the mechanisms of action of phytotherapeutic drugs, suggesting different possible molecular targets, such as the inhibition of 5-α-reductase, growth cell inhibition, and anti-inflammatory and proapoptotic effects. In vitro studies demonstrated that the free fatty acids present in the extracts can inhibit both type I and II 5-α-reductases, although it was shown that the PSA value was not affected [48]. With regard to the anti-inflammatory action, Serenoa repens was able to inhibit phospholipase A<sub>2</sub> and 5-lypoxxygenase, key enzymes in the metabolism of prostaglandins and leukotrienes, resulting in the inhibition of the production of proinflammatory chemokines [48]. Vela-Navarrete et al. studied a small group of patients undergoing TURP or open prostatectomy and randomised to receive placebo or a 3-wk therapy with Serenoa repens. The authors found that the specimens of patients in the treatment group contained a lower number of B lymphocytes as well as lower levels of TNF-α and IL-1β [49], which might be consistent with the described pathway of inhibition of prostaglandins and leukotrienes.

The action of phytotherapy has also been studied with regard to apoptosis. Vacherot et al. reported that 3 mo of therapy with Serenoa repens inhibited proliferation and induced programmed cell death in both epithelial and stromal cells [50]. The molecular basis of apoptosis after therapy with Serenoa repens was studied by Vela-Navarrete et al. The authors assessed the expression of Bax and Bcl-2, two proteins of the Bcl-2 family, with, respectively, proapoptotic and antiapoptotic actions, as well as the activity of caspase-3, one of the effector proteins in the caspase cascade [51]. After 3 wk of therapy with Serenoa repens, the Bax/Bcl-2 ratio and caspase-3 activity were increased compared to a control group of patients treated with a placebo [51]. These data clearly express a proapoptotic effect of Serenoa repens, which might, at least partially, be responsible for its clinical efficacy.

6. Inflammation, apoptosis, and prostate cancer

A huge number of studies addressed the correlations between inflammation, apoptosis, and the development of prostate cancer. Inflammation has been shown to be involved in several kinds of cancers, such as esophagus, stomach, liver, urinary bladder, and prostate [52,53]. Specifically, free radicals, predominantly oxygen and nitrogen species, key factors in immune defence system, are supposed to alter protein structure and function, causing lipid peroxidation and gene mutations [53]. Pathologic, experimental, and epidemiologic data support those relationships. Relevant pathologic evidence highlighted the role of proliferative inflammatory atrophy as a prostate cancer precursor [54]. Moreover, in the transgenic adenocarcinoma of the mouse (TRAMP) model of murine prostate cancer, the administration of a diet rich in
COX-2 inhibitors reduced the incidence of prostate cancer [55]. Similarly, a few epidemiologic studies tried to address the role of nonsteroidal anti-inflammatory drugs in human prostate cancer; reported results were controversial [56,57].

On the other hand, many papers investigated the role of apoptosis in prostate cancer, demonstrating the role of p53, TNF-α, TGF-β, caspases, and many other molecules [58–60].

Extensive insights on these topics are, however, beyond the scope of the present review, which focuses on BPH.

7. Conclusion

Clinical and experimental data suggest a possible role for inflammation and apoptosis in the development of BPH and prostate cancer. To date, the factors that trigger the imbalance in prostate growth leading to BPH are mostly unknown, but several details of the molecular pathways are well-known. Further research, however, is still needed to understand completely the aetiology of the disease. Most of the commonly used drugs seem to have pro-apoptotic actions, although the correlations between experimental studies and clinical data are not always clear and deserve further research. Anti-inflammatory actions were suggested for phytotherapy drugs, and especially for Serenoa repens. Further research is still needed to develop new molecules with higher efficacy in both prevention and therapy.

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