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REVIEW

Androgen regulation of host defenses and response to inflammatory stimuli in the prostate gland

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Abstract

The prostate gland is a strictly androgen-dependent organ which is also the main target of infectious and inflammatory diseases in the male reproductive tract. Host defenses and immunity of the gland have unique features to maintain a constant balance between response and tolerance to diverse antigens. In this context, the effects of reproductive hormones on the male tract are thus complex and have just started to be defined. From the classical description of "the prostatic antibacterial factor," many host defense proteins with potent microbicidal and anti-tumoral activities have been described in the organ. Indeed, it has been proposed a central role for resident cells, that is, epithelial and smooth muscle cells, in the prostatic response against injuries. However, these cells also represent the target of the inflammatory damage, leading to the development of a Proliferative Inflammatory Atrophy-like process in the epithelium and a myofibroblastic-like reactive stroma. Available data on androgen regulation of inflammation led to a model of the complex control, in which the final effect will depend on the tissue microenvironment, the cause of inflammation, and the levels of androgens among other factors. In this paper, we review the current scientific literature about the inflammatory process in the gland, the modulation of host defense proteins, and the influence of testosterone on the resolution of prostatitis.

Keywords: host defense; inflammation; innate immunity; prostate; testosterone

Introduction

Prostatic inflammation represents a significant health issue worldwide. Moreover, a strong relationship between inflammation of the gland and other conditions with a high impact on human health such as male infertility (Motrich et al., 2009), benign prostatic hyperplasia (Kramer et al., 2007) or prostate cancer (De Marzo et al., 2007a) has been reported. However, research on basic aspects of the gland, including the molecular mechanisms controlling prostatic inflammation or the tissue response against inflammation, is still scarce. The prostate is a strictly androgen-dependent organ which is the main target of infectious and inflammatory diseases in the male reproductive tract. In this paper, we review the current scientific literature about the inflammatory process in the gland, the modulation of host defense proteins, and the influence of testosterone on the resolution of prostatitis.

Host defense comprises a group of body protective systems, such as physical barriers and the innate immune response (including pathogen receptors, cytokines, chemokines, and antimicrobial peptides), which normally guards

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Abbreviations: CFA, Freund's Complete Adjuvant; DAMPs, Danger-associated molecular patterns; ErbB1, Avian Erythroblastic Leukemia Viral Oncogene Homolog 1; ErbB2, Avian Erythroblastic Leukemia Viral Oncogene Homolog 2; hBD-1, Human beta defensin-1; LPS, lipopolysaccharide; MD-2, Myeloid Differentiation Protein-2; MyD88, Myeloid Differentiation Factor 88; NALP1, Nod-like receptor family, pryin domain containing-1; NALP3, Nod-like receptor family, pryin domain containing-3; TLRs, Toll-like receptors; NF-κB, Nuclear factor kappa-light-chain-enhancer of activated B cells; PAMPs, Pathogen-associated molecular patterns; PBP, Prostatic Binding Protein; PIA, Proliferative Inflammatory Atrophy; SP-D, Surfactant Protein D

against injuries (Hall et al., 2002). Once inflammation cascades are initiated, a set of mechanisms modulates the resolution of the inflammation leading to the re-establishing of tissue homeostasis. Hence, anti-inflammatory and immunoregulatory molecules secreted by local cells also play a critical role in protecting the body against the damage of uncontrolled and/or unnecessary inflammation.

Host defense mechanisms have extensively been studied in macrophages and dendritic cells owing to their professional function in activating the immune response (Kaisho and Akira, 2003; Takeda et al., 2003). Epithelial roles in innate immunity have been known since Fleming's (1922) finding on lysozyme and other mucosal substances preventing bacterial growth in 1922. However, only in the last decades have the molecular mechanisms of host defense at epithelial surfaces begun to be elucidated, especially in epithelial cells from the airways and the digestive system (Diamond et al., 2000; Hall et al., 2002; Bartlett et al., 2008). In the urogenital tract, several contributions have revealed the importance of host defense proteins during inflammatory conditions (Hall et al., 2002; Rao et al., 2003; Samuelsson et al., 2004; Sun et al., 2004; Jalkanen et al., 2005; Wira et al., 2005), with male tract research being mainly focused on the epididymis (Rao et al., 2003; Jalkanen et al., 2005) and testis (Grandjean et al., 1997; Dettin et al., 2003). As an example, the epididymis secretes antimicrobial peptides including lysozyme, lactoferrin, and members of the defensin family (Hall et al., 2002; von Horsten et al., 2002; Com et al., 2003; Palladino et al., 2003; Jalkanen et al., 2005). In the testis, the presence of immunomodulatory proteins such as galectin-1 plays a critical role in protecting the male gametes (Dettin et al., 2003).

At the frontline of defense, the innate immune system has evolved several molecules such as Toll-like receptors (TLRs) to sense infections and other injuries (Takeda et al., 2003; Kawai and Akira, 2007, 2010). These receptors recognize and are activated by Pathogen-associated molecular patterns (PAMPs) and Danger-associated molecular patterns (DAMPs), which trigger multiple signaling pathways that finally lead to nuclear translocation of NF-κB and the subsequent activation of antimicrobial and proinflammatory genes (Takeda et al., 2003; Kawai and Akira, 2007). Typically, the innate immune response to Gram-negative bacteria implies the recognition of the lipopolysaccharide (LPS) by TLR4, while CD14 and MD-2 serve as the ligand-binding part of the LPS receptor complex (Kawai and Akira, 2010). Triggering of TLR4 results in the activation of the common intracellular TLR adaptor MyD88 or in an alternative pathway that relies on the Toll/IL-1R domain-containing adaptor-inducing IFNβ (TRIF) (Takeda et al., 2003; Kawai and Akira, 2007, 2010). With the male urogenital tract representing an entry point for micro-organisms from the environment, it is not surprising that TLRs, as well as CD14 and MyD88 and other essential host defense molecules, have been found to be expressed in the testis, epididymis, vas deferens, and accessory sex glands of different species (Hall et al., 2002; Girling and Hedger, 2007; Palladino et al., 2007; Pudney and Anderson, 2010). In addition, LPS-binding protein has been described throughout the male tract (Malm et al., 2005; Palladino et al., 2007) and, characteristically, the testis expresses defensins (Grandjean et al., 1997; Sang et al., 2005) among others.

Host defense molecules in the prostate gland

TLR4, which was termed hToll at the time, was the first human homologue of TLR, cloned and studied by Ruslan Medzhitov and Charles Janeway in 1997 (Medzhitov et al., 1997), instigating a new era in innate immunity research that culminated in the 2011 Nobel Prize. TLR4 recognizes and is activated by the lipopolysaccharide (LPS) present in Gram-negative bacteria and DAMPs; upon activation, TLR4 triggers the inflammatory response by inducing nuclear translocation of NF-κB (Takeda et al., 2003). TLR4 is widely expressed in epithelia in permanent contact with external injuries like those in cornea (Song et al., 2001), oral cavity (Uehara et al., 2002), respiratory tract (MacRedmond et al., 2005), intestine (Hornef et al., 2003), and urinary tract (Samuelsson et al., 2004), as well as in immune cells (Takeda et al., 2003; Akira and Takeda, 2004). Our research group and others have described TLR4 in the prostate gland of rodents and humans, with the expression being localized in both epithelial and stromal cells (Gatti et al., 2006, 2009; Quintar et al., 2006). Strikingly, in steady state conditions, TLR4 localizes mainly at the intracellular compartment of the prostatic cells in vivo (Quintar et al., 2006) as well as in vitro (Mackern-Oberti et al., 2006), contrasting with the classical membrane expression in macrophage and other immune cells (Akashi et al., 2000). This localization seems to be related to cellular function: while immune cells must be ready to quickly respond to pathogens, epithelial cells exposed to normal microbiota must have their pathogen sensors strictly regulated. Inasmuch as the occurrence of normal microflora in the prostate has been suggested (Willen et al., 1996), how it is controlled and how it interacts with the epithelial cells become emerging concerns. In addition, some DAMPs are normally present in the seminal plasma (Laudat et al., 1997; Park et al., 1997; Fung et al., 2004) and could incite unwanted inflammatory reactions since semen is often in contact with the surface of the prostate epithelium (Nelson et al., 1988). Consequently, the intracellular distribution of TLR4 could serve to prevent a permanent triggering of TLR4 cascades in prostatic epithelial cells. Different TLRs have also been reported to be expressed by prostate epithelial cell lines in vitro (Gatti

et al., 2006; Mackern-Oberti et al., 2006). Furthermore, other receptors for PAMPs such as inflammasome components NALP1 and NALP3 are present in prostatic cells (Chen et al., 2013).

The prostate gland is an important site for secretion of antimicrobial substances accompanying the sperm. Since the classical description of "the prostatic antibacterial factor," then identified as a zinc salt (Fair et al., 1976), many peptides and proteins with a potent microbicidal activity have been demonstrated in the gland. Such molecules include semenogelins (Edstrom et al., 2008), defensins (Quintar et al., 2012), and collectins (Oberley et al., 2007). Surfactant Protein D (SP-D) is a collectin normally expressed in the prostate epithelium of rats and mice as well as in different organs of the male tract as the epididymis, deferent ducts, seminal vesicles, and testis (Oberley et al., 2007). When comparing all those sites, the highest expression of SP-D occurs in the prostate (Oberley et al., 2007), supporting the idea that the gland is a main source of host defenses in the male genital tract.

Our studies have found that not only the epithelial but also stromal cells of the prostate express TLR4 both in vivo (Quintar et al., 2006; Gatti et al., 2009) and in vitro (Leimgruber et al., 2011, 2013). Additional works have documented that all TLRs are expressed in prostatic stromal cells (Penna et al., 2009). However, the implications of those findings have just started to be defined. For instance, studies in human samples have proposed a role for TLR4 in prostate cancer progression (Gatti et al., 2009), with stromal cells being also able to actively contribute to the TLR-mediated inflammatory process by acting as antigen-presenting cells in the gland (Penna et al., 2009).

Prostatic inflammation and its impact on prostatic tissues

The renewed interest in the pathogenesis, diagnosis, and treatment of the prostatitis syndromes have brought new basic research activity in animal models (Vykhovanets et al., 2007; Zeng et al., 2014) and immunological analysis (Motrich et al., 2007; Rivero et al., 2007). Although these investigations have mainly focused on the nature and extent of inflammatory cell infiltrates, a possible role for both resident stromal and epithelial cells in the prostatic reaction to infection or injuries has emerged. In this sense, prostatic cells and their secretory products have been shown to locally modulate the early response to bacteria (Ceri et al., 1999; Oberley et al., 2005). Takeyama et al. (2006) and Gatti et al. (2006) have demonstrated that prostatic cell lines secrete proinflammatory cytokines in response to *M. hominis* and LPS, acting through TLR2 and TLR4, indicating that epithelial cells could function as a first line in prostatic host defenses. Our research group has demonstrated that in vivo TLR4 expression increases in both epithelial and stromal cells after acute bacterial infection of the prostate (Quintar et al., 2006); besides, bacterial infection induces NF-κB translocation to the nucleus in the prostatic epithelium (Quintar et al., 2012). Ultrastructural analysis revealed a translocation of TLR4 from the cytoplasm to the apical plasma membrane of epithelial cells after acute inflammation (Quintar et al., 2006). However, in vitro LPS stimulation failed to translocate TLR4 from the cytoplasm to the plasma membrane in the murine Mat-Lu cell line, suggesting that LPS recognition and TLR4 activation would be performed intracellularly in prostatic tumoral epithelial cells (Mackern-Oberti et al., 2006). In contrast, human PC3 cells express TLR4 at the plasma membrane and TLR4 levels increase after LPS treatment (Pei et al., 2008). In any case, prostate cells are able to react to bacterial compounds regardless the localization of TLR4.

Prostatic cells also upregulate the expression of SP-D and defensins after prostatic inflammation (Oberley et al., 2007; Kim et al., 2011). SP-D has been reported in human prostate mainly associated to inflammatory foci, where it inhibits *C. trachomatis* invasion into prostatic cells (Oberley et al, 2005). Interestingly, some of these elements of the innate immune system, as the case of Human Beta Defensin-1 (hBD-1), have also shown anti-tumor activity in the prostate (Donald et al., 2003; Bullard et al., 2008). Therefore, epithelial- and stromal-derived host defense proteins play a fundamental role in protecting the gland not only against foreign agents but also defending it from malignant transformation.

As mentioned before, the inflammatory response is a complex mechanism addressed to protect the body against cellular damage induced by external or internal injuries. However, uncontrolled reactions could lead to chronic conditions with multiple tissue alterations and loss of cellular functions (Balkwill and Mantovani, 2001; Coussens and Werb, 2002; De Marzo et al., 2003, 2007a). Consequently, the mechanisms controlling or modulating inflammation are pivotal elements in organ and cellular homeostasis, with immunomodulatory actions being initiated simultaneously with pro-inflammatory pathways (Serhan and Savill, 2005). A wide range of immunomodulatory/anti-inflammatory proteins has been described to be induced in prostatic resident cells under inflammatory conditions. For instance, members of the secretoglobins superfamily of proteins are present in both rat (Aumuller et al., 1982; Quintar et al., 2010) and human prostate (Manyak et al., 1988), where they appear also to hold antitumoral properties (Patierno et al., 2002). These proteins have potent anti-inflammatory functions (Maccioni et al., 2001) and are widely expressed in respiratory (Roth et al., 2007) and reproductive tracts (Quintar et al., 2008). During acute infection of the rat prostate, Prostatic Binding Protein

(PBP, a secretoglobin member produced only by the prostatic epithelium) increases very early with the infection, but decreases after 72 h post-infection when the epithelium is completely atrophic (Quintar et al., 2010).

The fact that prostatic resident cells can be activated in response to bacterial infection might represent a beneficial mechanism for eliminating microorganisms at first glance. However, the consequence of chronic inflammatory signals on epithelial cells could also constitute a pivotal component in the pathophysiology of many human diseases. In fact, prostatic inflammation has recently been considered a key factor in the development and maintenance of hyperplasia (Kramer et al., 2007) and prostate cancer (De Marzo et al., 2007b), with an inflammatory environment possibly modifying the balance between cellular growth and turnover, thus leading to an uncontrolled proliferation. Accordingly, Elkahwaji et al. (2007) have reported that chronic bacterial inflammation induces reactive hyperplasia associated with oxidative stress injury. Furthermore, the administration of *M. tuberculosis*-containing Freund's Complete Adjuvant (CFA) for 30 days promoted prostatic epithelial hyperplasia (Kessler et al., 1998), thereby supporting the proposed link among inflammation, oxidative DNA damage, and prostate carcinogenesis. Results from our group and others revealed that cellular activation in the prostate is initiated very early after bacterial infection (Fulmer and Turner, 1999; Quintar et al., 2010), including the induction of the oncogenes ErbB1 and ErbB2 and nuclear translocation of NF-κB. NF-κB regulates the expression of many genes involved in immunity and cell growth and differentiation, acting as a master switch of intracellular signally pathways (Ghosh et al., 1998; Ghosh and Hayden, 2008) and a possible player in inflammation promoting cancer (Haverkamp et al., 2008). In this context, what occurs in prostatic tissues after bacterial prostatitis, that is, hyperproliferation along with cell atrophy (Elkahwaji et al., 2007; Quintar et al., 2010) would be clearly related to the term "Proliferative Inflammatory Atrophy (PIA)," assumed to be a preneoplastic lesion for prostate cancer by De Marzo et al. (2007b).

It has been reported that the stromal compartment critically influences the initiation and/or maintenance of proliferative pathologies in the prostate gland (Tuxhorn et al., 2002; Antonioli et al., 2004; Penna et al., 2009). Indeed, we described a rapid stromal response to bacterial infection, characterized mainly by hypertrophy and the acquisition of a secretory phenotype in smooth muscle cells (Quintar et al., 2006) which was then reproduced in vitro (Leimgruber et al., 2011, 2013, 2016). Related to this, much evidence suggests that smooth muscle cells are metabolically dynamic cells with the potential to express and secrete numerous highly active signaling proteins (Singer et al., 2004). In addition (or as a consequence), these cells can originate myofibroblasts with a potent secretory activity, which are considered to be an important component of the reactive stroma supporting prostate cancer (Tuxhorn et al., 2002). Penna et al. (2009) reported that prostatic stromal cells from patients secrete IL-8, CXCL10, and IL-6 in a TLR-mediated manner. These authors propose that stromal cells represent nonprofessional antigen-presenting cells, being able to induce and sustain inflammatory processes within the prostate (Penna et al., 2009). Accordingly, we demonstrated that smooth muscle cells respond to bacterial compounds by switching their phenotype from a contractile to a myofibroblast-like secretory profile in vivo (Quintar et al., 2006) as well as in vitro (Leimgruber et al., 2011, 2013, 2016) indicating that prostatic smooth muscle cells may play a role in host defenses. However, the phenotypic switch could alter the tissue microenvironment leading to chronic proliferative conditions. In this scenario, TGFβ1 is strongly implicated by activating metalloproteinases and promoting a reactive stroma response in the prostate gland (Tuxhorn et al., 2002; Danielpour, 2005). TGFβ1 increases in a time-dependent manner after acute bacterial prostatitis, with its levels probably being responsible for the hypertrophy of smooth muscle observed at 24 h postinfection (Quintar et al., 2010). Afterwards, the presence of potent proinflammatory signals, along with TGFβ1, may have acted as dedifferentiator factors on the prostatic smooth muscle cells. In agreement with this hypothesis, it has been previously shown that the cytokine IL-8 induces phenotypical changes on prostatic stromal cells in vitro, leading to the development of myofibroblastic cells (Schauer et al., 2008).

Taken together, these data suggest a central role for resident cells, that is, epithelial and smooth muscle cells, in the prostatic response against injuries. However, these cells also represent the target of the inflammatory damage, leading to the development of a PIA-like process in the epithelium and a myofibroblastic-like reactive stroma.

Androgen modulation of host defense molecules

Unlike many organs in the body, the prostate is under the strict control by testicular male hormones. Orchiectomy causes a rapid involution of the prostate due to epithelial apoptosis leading to a complete cessation of the secretory functions. Strikingly, smooth muscle cells and fibroblasts of the prostatic stromal compartment change their phenotypes after androgen deprivation, augmenting their cellular activity (Antonioli et al., 2004). In this context, it is not surprising that testosterone may influence the expression of host defenses as well as the outcome of infectious and inflammatory diseases of the prostate (Quintar et al., 2012). Moreover, the hormonal regulation of innate immunity gains special importance in the male reproductive tract as a

putative preventer of sperm damage as well as of venereal diseases.

Little is known about the specific effects of androgens on host defenses. What we know derives mainly from straightforward approaches by adding testosterone to culture media of monocytes/macrophages and other professional immune cells. Testosterone regulates negatively the TLR4 expression and macrophage sensitivity to a TLR4-specific ligand (Rettew et al., 2008). Additionally, androgens exert anti-inflammatory effects by inhibiting IL-6, TNFα, iNOS, and NO synthesis and inducing IL10 production by LPS-stimulated macrophages (Ahmed and Talal, 1990; Kanda et al., 1996; D'Agostino et al., 1999; Friedl et al., 2000). In vivo removal of endogenous testosterone results in a more susceptible phenotype to endotoxic shock, with macrophages isolated from these animals having significantly higher TLR4 cell surface expression than those derived from sham gonadectomized mice (Rettew et al., 2008).

Several authors have reported that prostatic PBP levels notably decrease in the epithelium of castrated animals (Heyns et al., 1978; Aumuller et al., 1982; Janulis et al., 2000). Unpublished observations indicate that galectin-1, another potent inmmunosuppresive factor, is positively regulated by androgens in the prostate gland. It is interesting to note that galectin-1 is also expressed in female genital tract, where it could play an important strongly progesterone-regulated role in embryo implantation and immune tolerance (Choe et al., 1997; Gray et al., 2004; Blois et al., 2007; Than et al., 2008). In this way, testosterone maintains high levels of immunomodulatory factors in the prostate in accordance with its immunosuppressive and anti-inflammatory effects on immune responses (Olsen and Kovacs, 1996).

The hypothesis of androgens dampening host defenses in the prostate is also supported by our own results which clearly indicated that testosterone negatively modulates the TLR4 pathway, including the expressions of TLR4, CD14, and MyD88 in prostatic cells (Quintar et al., 2012). In line with this, androgens can inhibit the expression of TLR4 mRNA in human endothelial cells (Norata et al., 2006) and can reduce TLR4 expression in the cell surface of isolated macrophages in mice (Rettew et al., 2008). Furthermore, these results could explain, in part, the ability of testosterone to increase susceptibility to bacterial infection in both males and females (Rettew et al., 2010), with castration being efficient to eliminate pathogens and to dampen infection-related inflammation within the prostate gland.

This immunosuppressive function of androgens in the prostate is understandable as a means of avoiding uncontrolled immune responses against the haploid male gamete in the reproductive tract. In fact, the seminal plasma possess strong anti-inflammatory and immunosuppressive properties (Dostal et al., 1995; Kelly and Critchley, 1997) that would be controlled by androgens. Moreover, the immunity of the gland has unique features (the presence of a hemato-prostatic barrier among others) which allowed to consider the prostate as a site of immune privilege where responses are rather suppressed (Whitmore and Gittes, 1977; Fulmer and Turner, 2000).

Effects of androgens on prostatic inflammation

Sexual hormones influence strongly the immune response, resulting in a clear dimorphism in immune dysregulation-driven diseases. Female produce a vigorous humoral and cellular immunity, being more resistant to bacterial infection than males (Blazkovec et al., 1973; Ahmed and Talal, 1990; Druckmann, 2001). Moreover, women have higher incidence than men of autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, Hashimoto thyroiditis, and multiple sclerosis (Cutolo et al., 2004; Bouman et al., 2005). In general, androgens exert a suppressive effect on the adaptive immune response through diverse mechanism including apoptosis of T and B cells and the induction of T regulatory cells and CD8+ suppressive cells. As described in the previous section testosterone would also play an immunosuppressive role on innate immunity.

In the prostate gland, most of studies have used castration models to analyze the effects of male hormones on the inflammatory environment. For instance, androgen deprivation has been successfully employed as a therapeutic modality in rat (Kaplan et al., 1983; Seo et al., 2003) and canine (Cowan et al., 1991) models of chronic bacterial prostatitis. In the same line of evidence, the administration of testosterone can induce severe prostatitis in young adult Wistar rats treated neonatally with beta-estradiol (Naslund et al., 1988). We have demonstrated that androgen withdrawal results in an increase of the proinflammatory TLR4 system and upregulation of prostate antimicrobial host defenses, correlating finally with an improved inhibition of bacterial growth in vivo as well as in vitro (Quintar et al., 2012). The same work revealed that acute bacterial prostatitis developed in testosterone-treated rats is associated to a higher infiltration of neutrophils compared to castrated animals. In this sense, androgens have been also shown to modulate neutrophil activation (Razmara et al., 2005; Deitch et al., 2006), resulting in a worst prognosis for men in endotoxin shock. Exaggerated recruitment and activation of neutrophils by testosterone during acute prostatitis could explain the high occurrence of these cells (Figure 1), but at the same time, this animals exhibited a higher amount of *E. coli* suggesting a malfunction of neutrophils related to testosterone administration (Quintar et al., 2012). Nevertheless, the improvement in antimicrobial capacity of the prostatic cells after androgen deprivation

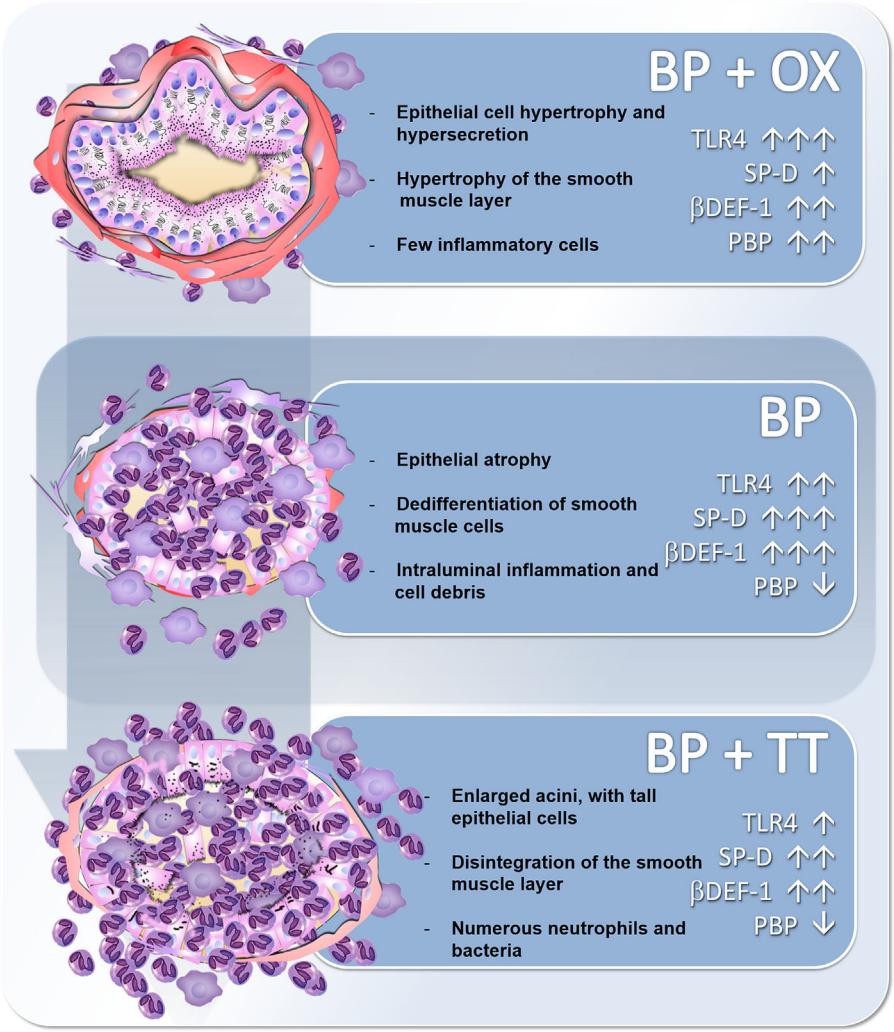

Figure 1 Schematic representation of prostatic morphofunctional alterations during acute bacterial prostatitis (BP) under different androgen status. Orchiectomized rats (BP + OX) have a better resolution of the inflammation after 3–5 days of *E. coli* inoculation compared to rats with normal (BP) or supraphysiological levels of testosterone (BP + TT). Based on (Quintar et al., 2006, 2010, 2012)and on unpublished observations. The amount of arrows indicates the grade of expression change. TLR4, Toll-like Receptor 4; SP-D, Surfactant Protein-D; bDEF-1, bDefensin-1; PBP, Prostatic Binding Protein.

seems to be mainly independent of professional immune cells since the increase in host defense observed in vivo is reproduced, at least in part, in isolated prostatic cells in absence of testosterone (Quintar et al., 2012). This is a striking point because several effects of castration on prostatic cells do not represent direct effects of testosterone withdrawal but could be mediated by multiple cells infiltrating the gland after castration (Mercader et al., 2001; Halin et al., 2007). Interestingly, the effects of androgens on immunity could involve non-classical membrane androgen receptors which elicit rapid responses (Benten et al., 2002, 2004). Consequently, studies to gain insight into the basis of the molecular mechanisms of testosterone affecting immunity and inflammation are necessary.

There are several reports indicating that androgen ablation enhances prostate anti-tumor immunity (Roden et al., 2004; Drake et al., 2005; Koh et al., 2009), even in castration-resistant tumors (Akins et al., 2010). In addition, medical castration results in prominent T cell infiltration of the human prostate (Mercader et al., 2001) and removes tolerance to prostate cancer antigens in a transgenic mouse model (Drake et al., 2005). Such T cell-mediated inflammation after androgen deprivation could have significant implications for the development of immunotherapeutic strategies to treat prostate cancer.

On the other hand, this immunomodulatory effect of androgens could be beneficially used to treat prostate inflammation in cases of autoimmune prostatitis (Diserio and Nowotny, 2003; Meng et al., 2011) and other non-bacterial prostatitis where high levels of testosterone are associated to a decreased aggressiveness of the inflammation and the number of inflamed acini in the prostate (Bernoulli et al., 2008; Yatkin et al., 2009). One interesting local mechanism by which testosterone would control inflammation relies on the ability to regulate positively the tight junction proteins Claudin 4 and Claudin 8, with testosterone supplementation in castrated mice significantly reducing prostate inflammatory cell numbers (Meng et al., 2011). Testosterone also protects rabbit prostate from metabolic syndrome-induced prostatic hypoxia, fibrosis, and inflammation (Vignozzi et al., 2012). Moreover, androgen supplementation reduces the expression of inflammatory markers in estrogen-induced prostatitis (Jia et al., 2015). In vitro studies demonstrated that testosterone applied before or after pro-inflammatory stimuli to prostatic smooth muscle cells acts as an anti-inflammatory agent by reducing the expression of TLR4 and pro-inflammatory signaling pathways (Leimgruber et al., 2013, 2016).

The exact role of androgens along with their immunoregulatory mechanisms on prostatic inflammation are far to be clarified. Considering available published data, it is reasonable to propose a model for the complex regulation of prostate immunity where the final effect will depend on the tissular microenvironment, the cause of inflammation, and the androgenic level among other factors. However, it is clear that androgens would have a dual and contradictory effect, favoring non-bacterial (metabolic, hormonal imbalance, or autoimmune) prostatitis, whereas playing a pathogenic role in bacterial inflammation of the prostate gland.

Conclusion and perspectives

The male genital tract is an important entry point for microbial agents threatening the integrity of the tract itself and the whole body, with HIV being just one example. On the other hand, the main task of the tract is to deliver a full-functioning haploid gamete, which represents a foreign antigen for the immune system. The cellular effects of reproductive hormones on the male tract are thus complex and require a constant balance between response and tolerance to diverse antigens. Moreover, the extremely high incidence of both benign and malignant proliferative pathologies in the prostate suggests the existence of a special state (privilege?) for host defenses and the immune system in the gland. Therefore, it would be too simplistic to ascribe a specific suppressive or boosting role to androgens on prostatic host defenses. It is clear, however, that a better understanding of the inflammatory response and its regulation within the prostate gland may open new frontiers to develop efficient therapies for inflammatory and immune-related prostatic diseases based on homeostatic androgen functions. In this context, the promising discovery of differential actions by membrane androgen receptors (Benten et al., 2004; Levin, 2014) will direct alternative approaches to dissect the androgen effects on prostate inflammation and host defenses.

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