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Review

Viral etiology of prostate cancer: Genetic alterations and immune response. A literature review

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ABSTRACT

Prostate cancer is one of the most common cancers in men. Recent estimates suggest that over a million men are diagnosed with the disease annually. Prostate cancer pathogenesis involves both heritable and environmental factors. The molecular events involved in the development or progression of prostate cancer are still unclear. Recent body of literature highlights the role of viral infections in initiation or progression of prostate cancer. In this regard, certain viruses have been reported to interact with host proteins and bring about changes in genetic, immunological and inflammatory events that lead to initiation or progression of prostate cancer.

We conducted a comprehensive PubMed database search to identify publications relevant to viruses associated with prostate cancer. In this review, we discuss the possible viral etiology of prostate cancer and evidence of viral-mediated genetic changes, and immune dysregulation involved in initiation or progression of prostate cancer.

1. Introduction

Prostate cancer (PCa) is the second most common cancer in men. According to recent estimates, over a million men are diagnosed with the disease annually, with the greatest incidence in more developed regions such as Australia, New Zealand, North America, and Western and Northern Europe. Incidence rates are also relatively high in the Caribbean and sub-Saharan Africa, which also has the highest prostate cancer mortality rates [1].

PCa pathogenesis involves both heritable and environmental factors. The latter have been implicated from studies in immigrant Asian populations to the West that exhibits a higher incidence of PCa than their counterparts still living in Asia. As in cancers of the stomach, intestine, and liver, chronic inflammation secondary to infection and other environmental factors such as diet, may also play a role in the development of prostate cancer [2].

Mechanisms of prostate carcinogenesis and role of inflammation have been reviewed in detail previously [2,3]. Here we focus specifically on possible viral etiology of prostate cancer and evidence of viral-mediated genetic changes and associated immune dysregulation.

2. Methods

The PubMed, Medline, Google Scholars, and Cochrane databases were searched for publications relevant to viruses associated with PCa (Fig. 1). An initial broad search was conducted using the terms “Prostate cancer”, “prostate cancer, virus and immune system”, “prostate cancer, virus and genetic changes” and “virus-mediated genetic changes in prostate cancer”. The 1176 articles identified were further limited to 561 after only selecting studies on humans and those published in English. After additionally excluding unrelated publications, such as those involving bacterial etiology, infectious diseases, cancer therapy, case reports, methodology papers, etc., 48 full-text articles were reviewed. This includes four articles identified by reference hand-searches.

3. Viruses associated with prostate cancer

A number of pathogens can infect the prostate, including viruses. Several studies have documented the presence of viruses such as human papillomavirus (HPV), herpesviruses including cytomegalovirus (CMV), human herpes simplex virus type 2 (HSV2), human herpesvirus type 8 (HHV8) and Epstein-Barr virus (EBV), polyomavirus BKV and xenotropic murine leukemia virus-related virus (XMRV), in the prostate.

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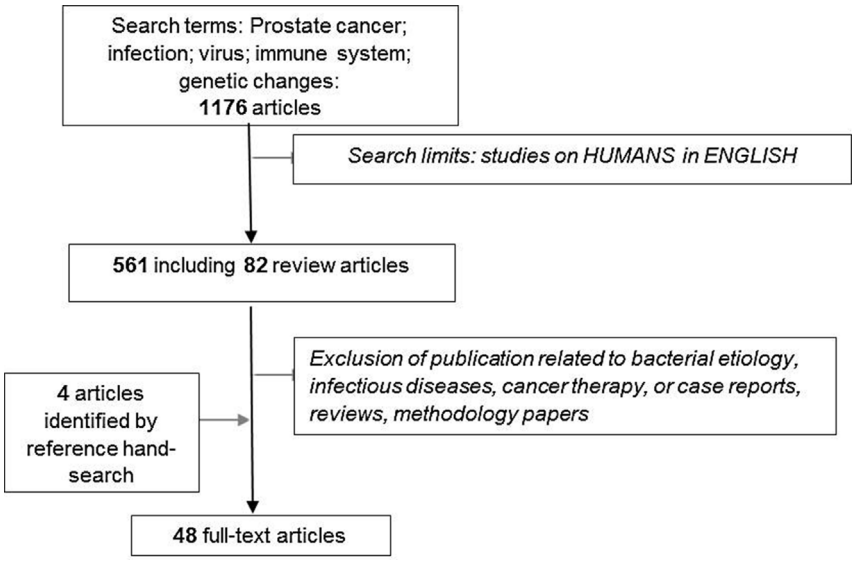

Fig. 1. Flowchart outlining the search strategy employed to identify the relevant studies.

However, the frequency of infection and whether an inflammatory response is elicited or has a direct association with prostate carcinogenesis has not yet been established [2]. A systematic review of three decades of research on infection and prostate cancer published in 2013 also found no conclusive evidence of the role of infection in the etiology of PCa [4]. This may be because many reported studies investigating viral infections in PCa have been limited by small sample size, inability to test previous or non-persistent infections, and inadequate tissue sampling or viral detection methods [2]. In the past 5 years (January 2012–January 2017), further studies have continued to explore the viral etiology of PCa, which are summarized below.

3.1. HPV

HPV infection is an established etiologic factor for cancers of the cervix, uterus, vulva, vagina, penis, and anus [5]. Given its anatomic proximity to anogenital and urinary sites, the prostate has been extensively investigated for HPV infection. Studies reported in the literature, mostly in Western populations, have varied considerably in terms of study design and methodology. Consequently, conclusions have also not been homogenous, with only some studies showing statistically significant differences in HPV infection between prostate cancer patients and controls [4]. More recently, studies from Mediterranean and Asian populations have suggested a link between HPV, particularly high-risk sub-types 16 and 18, and prostate cancer [6–9]. The strength of association varies with geographic distribution [10–13]. Moreover, studies have found significant positive associations of PCa with sexual activities and sexually transmitted diseases [14–16], including HPV, suggesting further that an infectious etiology may be involved in prostate carcinogenesis. HPV warrants a more rigorous investigation, particularly to reconcile the diversity in reported results within the same populations [17–20].

3.2. Herpesviruses

Herpesviruses can be transmitted through both sexual and non-sexual routes, and are highly prevalent in some populations [21]. Herpesviruses, such as EBV and HHV-8, have been associated with human malignancies [22]. In prostate cancer, CMV, HSV-1, HSV-2, HHV-8 and EBV infections have been investigated [4]. A recent study in men from Tobago, a region with one of the highest incidence and mortality rates from PCa, showed that HHV-8 establishes a latent infection in the prostate that is associated with macrophage infiltration and inflammation [23]. However, a meta-analysis to explore the association between infections caused by several sexually transmitted pathogens, including HSV-1, HSV-2, HHV-8, and CMV, revealed no significant association with increased risk of PCa [24].

3.3. BKV

Polyomavirus BK is usually acquired in early childhood, has a long latency period with the urinary tract as the primary site of latency and possibly oncogenic potential as demonstrated in animal models. Theoretically, it is an attractive candidate for viral etiology of PCa and has been detected in PCa [4]. In a recent study from Iran, some of the highest BK infection rates were reported, with 28% in PCa, mainly in patients with lower Gleason scores, and 15% in benign prostatic hyperplasia samples [25]. Further research is needed to identify how BK may exert oncogenic activity over the clinical course of the disease, particularly in early stages of PCa development [26].

3.4. XMRV

Since its discovery in 2006, the role of the gammaretrovirus XMRV in PCa has been highly debated. XMRV has been detected in PCa, but high false positive rates in most published studies due to contamination of samples and/or laboratory reagents have brought its role as a human pathogen in prostate carcinogenesis into question [4,27]. Recent studies have not found any conclusive biologic evidence of XMRV infection in PCa in different populations [28–32]. Work in human cell lines has also shown XMRV is not a human pathogen [33], although it infects prostate cancer cell lines preferentially [34]. Further studies are required to determine whether XMRV has any clinical association with the onset or progression of PCa.

4. Prostate carcinogenesis: interplay of host genetics and viral infection

The molecular events involved in the development of PCa are still unclear. As discussed earlier, in addition to heredity causes, prostate cancer can be initiated or progressed by viral infections (Fig. 2). Many viruses are known to interact with host proteins and bring about changes in genetic, immunological and inflammatory events that lead to initiation or progression of tumors [35]. Viral products, for example, large T antigen of polyomaviruses, or E6/E7 proteins of HPV, can transform prostate cells and interfere with the interferon (IFN)

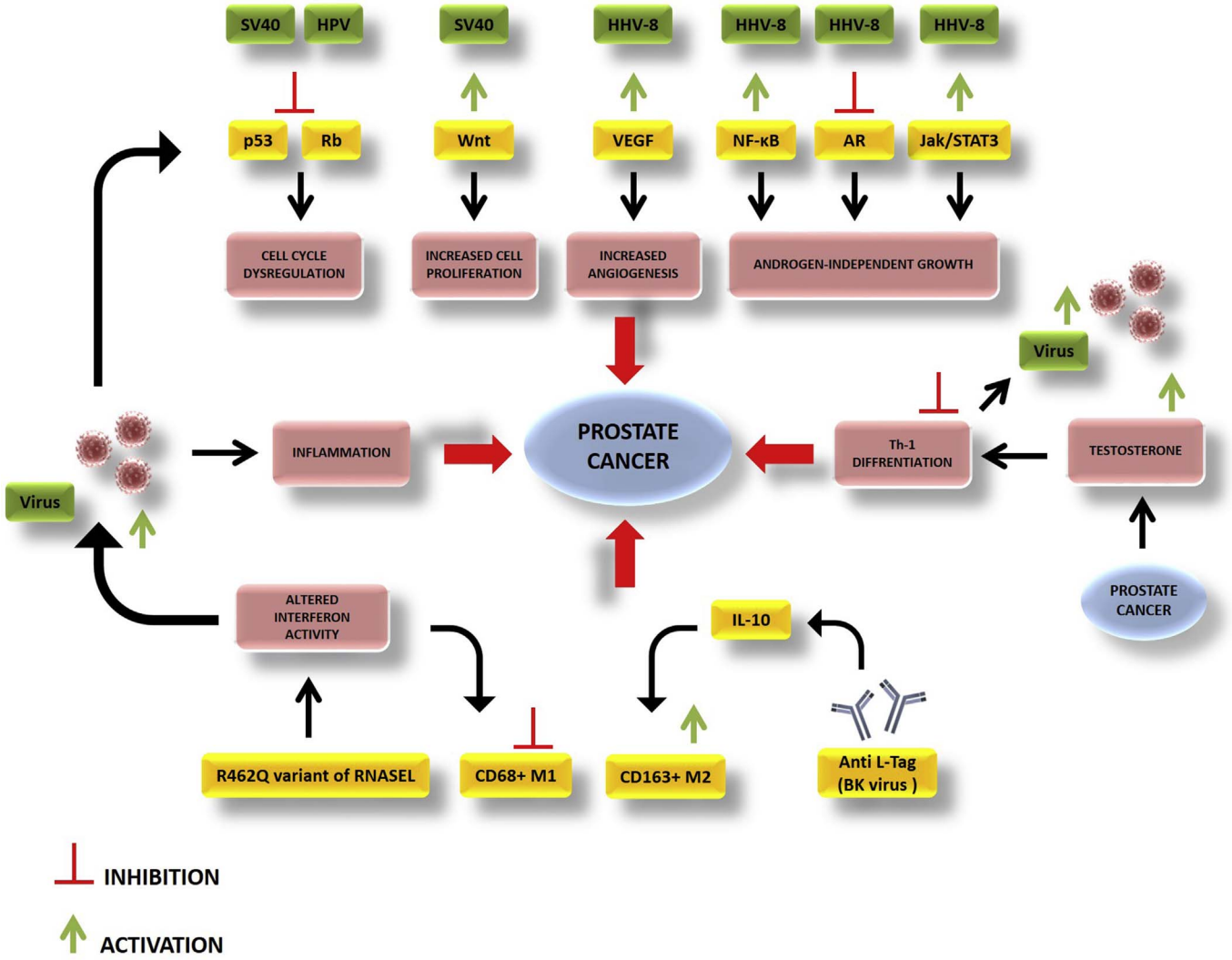

Fig. 2. The interplay between host genetics, host immunity and viral infection that lead to initiation or promotion of prostate cancer. The complex interplay between host genetics, host immunity, and viral infection can initiate and promote PCa. Key viral factors, for example, leads to inhibition of cell cycle proteins, such as p53 and RB by SV40 and HPV, inhibition of antigen receptor (AR) signaling by HHV-8, and conversely, activation of Wnt by SV40, and activation of VEGF, Jak/STAT3 and NF-κ B by HHV-8 that overall favors uncontrolled androgen-independent cell growth along with angiogenesis, etc. Viruses also mediate chronic inflammation that can directly result in PCa. Host factor includes variations in cancer susceptibility genes, such as R462Q variation of RNASEL gene that has altered interferon activity, resulting in poor viral control. Similarly, antibody titer against the viral protein (BK virus large T-antigen) is shown to increase IL-10 levels that promotes differentiation of immunosuppressive M2 macrophages. Prostate cancer cells also upregulate testosterone levels that suppress Th1 diffraction resulting in decreased clearance of viral particles and cancer cells due to compromised cytotoxic T cell response. *Original artwork by the authors.*

signaling pathways [36]. Host genetics add an additional layer of complexity to the molecular pathways involved in PCa initiation or progression, where polymorphisms in certain genes can favor viral progression or poor control of viral infections, eventually enabling the virus to exert its cytopathic effects or transform normal prostate cells.

To date, at least nine candidate genes have been discovered that increases susceptibility to prostate carcinogenesis. These include *RNASEL/HPC1, SR-A/MSR1, ELAC2/HPC2, PON1, CHEK2, BRCA2, OGG1, MIC-1,* and *TLR4*. Majority of these genes play a crucial role in cellular defenses against inflammation and oxidative stress [37]. Variations/mutations in these genes can either modulate inflammatory processes or hinder the control of infections. *RNASEL/HPC*, a candidate gene for hereditary PCa, for example, is involved in antiviral and antiproliferative roles of IFNs (Fig. 2) [35]. The R462Q variant of *RNASEL* gene is reported in many of the sporadic prostate cancers, and this variant has lesser enzymatic activity than the wild type, which may also affect the control/suppression of viral infection, such as one reported for XMRV in prostate cancer patients [35].

As mentioned earlier, prostate serves a possible target for infection with HPV due to anatomical reasons especially because for the ease of access of the virus to prostate directly via urethra [38]. HPV high-risk types, such as type 16 and 18, exert their carcinogenic potential through their E6 and E7 proteins. E6 protein of HPV interacts with tumor suppressor protein p53 and targets it for proteasomal degradation, while E7 binds and inactivates the retinoblastoma protein pRb (Fig. 2) [38]. A polymorphism (either proline or arginine) at position 72 of p53 gene is known to modulate the E6 mediated degradation of the p53 protein, where p53 with arginine at position 72 is more susceptible to E6-mediated proteasomal degradation, as compared to proline at the same position. Studies both in support or opposition of this observation have been published for cervical cancer, however, a single study on PCa supports the observation that proline at position 72 is associated with a reduced risk of PCa [38].

In addition to HPV, Simian Virus 40 (SV40) is also known to bring about epithelial tumor transformation of the prostate cells in transgenic models, although, a direct role of SV40 infection and PCa development has not been proven in clinical studies [39]. SV40 proteins Large-T and small-T antigens have been extensively studied because of their role in tumorigenesis. The principal function of Large T-antigen is to bind and target p53 and Rb proteins for degradation, which promotes viral

replication and cellular transformation [36] (Fig. 2). Small T-antigen itself does not cause transformation but provides necessary mitogenic signals that facilitate cellular transformation [40]. Small T-antigen, for example, interacts with and inhibits PP21, a serine-threonine protein phosphatase. Inhibition of PP2A constitutively activates Wnt pathway which promotes cell proliferation (Fig. 2). Additionally, inhibiting PP2A also induces changes in the actin cytoskeleton and tight junctions, which leads to loss of cell polarity and promotes tumor invasiveness [40].

Similarly, the persistence of HHV-8 in the prostate gland can alter the outcome of disease toward an androgen-independent phenotype in high-risk individuals [41]. HHV-8 contains several open reading frames, and at least 17 mature microRNAs that can alter the growth properties of infected cells by inhibiting crucial processes such as immune surveillance, and apoptosis, and promotion of pathways such as cellular transformation and activation of signaling pathways pertaining to cancer histogenesis [41]. For example, HHV-8 encoded interleukin-6 homolog activates Jak/STAT3 pathway that possibly enables trophic shift and aiding in the androgen-independent growth of prostate cells. Another viral G protein-coupled receptor stimulates VEGF that promotes angiogenesis. Additionally, the same receptor also stimulates viral FLICE-inhibitory protein that activates NF-κB pathway and promotes progression to androgen-independent growth. In the androgen-deprived environment, HHV-8 suppresses androgen receptor (AR) signaling pathway that promotes androgen-independent growth phenotype (Fig. 2) [41].

5. Viral-mediated immune dysregulation and role in prostate cancer

Presence of chronic inflammatory microenvironment is well-established in human PCa. The site of inflammation has shown to be a precursor to prostate intraepithelial neoplastic (PIN) lesion [42,43]. Since viruses (as mentioned above) are shown to play a significant role in the etiology of prostate cancer; therefore, their role in promoting pro-inflammatory microenvironment cannot be undermined. Inflammatory microenvironment has been shown to be immunosuppressive and support cancer progression [44]. As mentioned above, a variant of an endonuclease *RNASEL* gene (which is crucial for anti-viral response) could possibly lead to defect in immunity. In addition, the presence of immunosuppressive molecules such IL-6, TGF-β and nitric oxide synthase (NOS) in PCa microenvironment has also been reported [45].

Both cells of the innate and adaptive immune contribute to immune dysfunction. With regards to the innate immune system, the association of *TLR10-TLR-6-TLR1* gene cluster and PCa has been under investigation [46]. As mentioned previously, TLR4 has been associated with an increased susceptibility to prostate carcinogenesis. In addition, a shift in the paradigm of macrophages has also been reported with disease progression. $CD68^+$ M1 macrophages, for example, which is mainly stimulated by interferon-γ (IFN-γ), have been found in confined disease, while $CD163^+$ M2 macrophages (which are mainly stimulated by immunosuppressive IL-10) have been found in advanced disease [43]. *Lanciotti* et al., has attempted to correlate aggressiveness of prostate cancer with the presence of M1 and M2 macrophages in biopsy specimens [47]. M1 macrophages were found to be present frequently in biopsy specimens of patients with the confined disease, while, in contrast, M2 macrophages were found in biopsy specimens with extracapsular extension [47]. In addition, the authors also found a high biochemical recurrence (BCR) free survival in patients whose biopsy showed the prevalence of M1 macrophages compared to M2 macrophages [47]. It is possible that hosts with the susceptible genetic background, such as the presence of R462Q variant of RNASEL/HPC gene, have decreased $CD68^+$ M1 macrophages activation due to suppressed IFN-γ activity, resulting in widespread dissemination of prostate cancer. The suppressed antiviral activity of IFN coupled with decreased in $CD68^+$ M1 macrophage activation might favor viruses to replicate in the prostate milieu and bring about genetic and immunogenic changes that lead to progression of PCa (Fig. 2). Similarly, increase titer of antibody to large T-antigen (L-Tag) of polyoma BK virus has been found to be associated with an increase in expression of IL-10 compared to IFN-γ [42]. It is possible that L-Tag of SV40 also mediates similar changes. These reports point towards the possible contribution of viruses in promoting an altered differentiation of macrophages. Macrophages, in general, have also been found to produce arginase which can potentially induce anergy in lymphocytes. Changes in other cells of the innate immune system have also been reported. Natural killer (NK) cell dysfunction has also been shown [48]. This could possibly be due to the presence of TGF-β in the PCa tumor microenvironment. Increase in the absolute neutrophil count has found to be associated with high tumor grade [43].

Like many tumors, cells of PCa also mediate immune escape by down-regulating expression of HLA-class I antigen [49]. In addition, the link between innate and adaptive immune system is also compromised due to decrease number of dendritic cells (DCs) in PCa tissue [50]. However, functional DCs are present in the periphery of the tumor which could be an incentive to develop immunotherapy for PCa.

Aberrant function of the adaptive immune system has been reported in PCa. B cell function seems to be compromised in PCa by testosterone since increased levels of testosterone levels are correlated with a decrease in antibody response to vaccination [51]. Testosterone has also been postulated to maintain T cell tolerance to virus and tumor antigen by inhibiting Th1 differentiation which is a critical step in virus clearance and T cell response to tumor antigen (Fig. 2). Th1 $CD4^+$ cells have been found to be biased towards differentiation to T-regulatory- (T-reg) or Th17-cells [43]. Numbers of Th17 cells have been found to be directly proportional to Gleason score [52]. It has been shown that altered Th1 differentiation of $CD4^+$ T cells is mediated via inhibition of IL-12-induced Stat4 phosphorylation by testosterone [53]. Androgens also negatively alter IFN-γ signaling along with Th17 differentiation [53]. Furthermore, androgen deprivation therapy (ADT) in humans has reported to improve $CD4^+$ T cell differentiation and promote infiltration of T cell in PCa microenvironment [53]. In mice models, castration has been shown to improve $CD8^+$ T cell response [53]. Interestingly, the presence of polyoma BK has been shown to be associated with increased expression of $CD4^+CD25^+FoxP^+$ cells which in turn produce immunosuppressive cytokines IL-10 and TGF-β [42].

6. Conclusion

Taken together, these observations highlight the complex interplay between host genetics, host immunity and viral infection that leads to initiation or promotion of prostate cancer. These data warrant the need for the development of antiviral and immune modulating therapeutic agents for the treatment of PCa, indeed, immune therapy has been found to increase the overall survival in patients diagnosed with PCa [44]. These treatment modalities can specifically be of benefit in patients with resistance to androgen deprivation therapy due to a mutation in androgen receptor gene. However, this can be further tailored to address the issue of virus-mediated immune dysfunction.

Ethical approval

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Author contribution

All authors contributed equally to the study design, data collections, data analysis, and writing.

Conflicts of interest

None.

Trial registry number

Not applicable.

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Disclosure

None.

References

[1] J. Ferlay, et al., GLOBOCAN 2012 v1.0, *cancer Incidence and mortality worldwide*, IARC CancerBase No. 11 [Internet] International Agency for Research on Cancer, Lyon, France, 2013.
[2] A.M. De Marzo, et al., Inflammation in prostate carcinogenesis, Nat. Rev. Canc. 7 (4) (2007) 256–269.
[3] G.S. Palapattu, et al., Prostate carcinogenesis and inflammation: emerging insights, Carcinogenesis 26 (7) (2005) 1170–1181.
[4] J. Hrbacek, et al., Thirty years of research on infection and prostate cancer: no conclusive evidence for a link. A systematic review, Urol. Oncol. 31 (7) (2013) 951–965.
[5] S. de Sanjose, L. Bruni, L. Alemany, HPV in genital cancers (at the exception of cervical cancer) and anal cancers, Presse Med. 43 (12 Pt 2) (2014) e423-8.
[6] F. Atashafrooz, F. Rokhbakhsh-Zamin, Frequency and type distribution of human papilloma virus in patients with prostate cancer, kerman, southeast of Iran, Asian Pac. J. Cancer Prev. APJCP 17 (8) (2016) 3953–3958.
[7] V. Michopoulou, et al., Detection of human papillomavirus (HPV) DNA prevalence and p53 codon 72 (Arg72Pro) polymorphism in prostate cancer in a Greek group of patients, Tumour Biol 35 (12) (2014) 12765–12773.
[8] N. Singh, et al., Implication of high risk human papillomavirus HR-HPV infection in prostate cancer in Indian population–a pioneering case-control analysis, Sci. Rep. 5 (2015) 7822.
[9] N.J. Whitaker, et al., Human papillomavirus and Epstein Barr virus in prostate cancer: koilocytes indicate potential oncogenic influences of human papillomavirus in prostate cancer, Prostate 73 (3) (2013) 236–241.
[10] S. Lumme, et al., Longitudinal biobanks-based study on the joint effects of infections, nutrition and hormones on risk of prostate cancer, Acta Oncol. 55 (7) (2016) 839–845.
[11] I. Meredith, et al., Cancer in pacific people in New Zealand, Cancer Causes Control 23 (7) (2012) 1173–1184.
[12] R. Tachezy, et al., HPV persistence and its oncogenic role in prostate tumors, J. Med. Virol. 84 (10) (2012) 1636–1645.
[13] L. Yang, et al., Worldwide prevalence of human papillomavirus and relative risk of prostate cancer: a meta-analysis, Sci. Rep. 5 (2015) 14667.
[14] S.D. Chung, et al., Increased risk of prostate cancer following sexually transmitted infection in an Asian population, Epidemiol. Infect. 141 (12) (2013) 2663–2670.
[15] W.Y. Huang, et al., Sexually transmissible infections and prostate cancer risk, Cancer Epidemiol. Biomark. Prev. 17 (9) (2008) 2374–2381.
[16] A.R. Spence, M.C. Rousseau, M.E. Parent, Sexual partners, sexually transmitted infections, and prostate cancer risk, Cancer Epidemiol 38 (6) (2014) 700–707.
[17] E. Ghasemian, et al., Evaluation of human papillomavirus infections in prostatic disease: a cross-sectional study in Iran, Asian Pac. J. Cancer Prev. APJCP 14 (5) (2013) 3305–3308.
[18] Z. Salehi, M. Hadavi, Analysis of the codon 72 polymorphism of TP53 and human papillomavirus infection in Iranian patients with prostate cancer, J. Med. Virol. 84 (9) (2012) 1423–1427.
[19] Y. Tolstov, et al., Human papillomaviruses in urological malignancies: a critical assessment, Urol. Oncol. 32 (1) (2014) 46 e19-27.
[20] M.A. Yow, et al., Detection of infectious organisms in archival prostate cancer tissues, BMC Canc. 14 (2014) 579.
[21] J.S. Pagano, Is epstein-barr virus transmitted sexually? J. Infect. Dis. 195 (4) (2007) 469–470.
[22] M. Sunil, E. Reid, M.J. Lechowicz, Update on HHV-8-associated malignancies, Curr. Infect. Dis. Rep. 12 (2) (2010) 147–154.
[23] J.D. Henning, et al., Human herpesvirus 8 establishes a latent infection in prostates of Tobago men resulting in increased macrophage infiltration, Prostate 76 (8) (2016) 735–743.
[24] S. Caini, et al., Sexually transmitted infections and prostate cancer risk: a systematic review and meta-analysis, Cancer Epidemiol 38 (4) (2014) 329–338.
[25] A. Taghavi, et al., Polyomavirus hominis 1(BK virus) Infection in prostatic tissues: Cancer versus hyperplasia, Urol. J. 12 (4) (2015) 2240–2244.
[26] E.X. Keller, et al., Polyomavirus BK and prostate cancer: a complex interaction of potential clinical relevance, Rev. Med. Virol. 25 (6) (2015) 366–378.
[27] P. Hong, J. Li, Lack of evidence for a role of xenotropic murine leukemia virus-related virus in the pathogenesis of prostate cancer and/or chronic fatigue syndrome, Virus Res. 167 (1) (2012) 1–7.
[28] M. Arredondo, et al., Prevalence of xenotropic murine leukemia virus-related virus infection in different risk populations in Spain, AIDS Res. Hum. Retrovir. 28 (9) (2012) 1089–1094.
[29] F.A. Baig, et al., Detection of Xenotropic murine leukemia virus-related virus in prostate biopsy samples, J Coll Physicians Surg Pak 24 (9) (2014) 636–639.
[30] S.T. Gomes, et al., Lack of evidence for human infection with Xenotropic murine leukemia virus-related virus in the Brazilian Amazon basin, Rev. Soc. Bras. Med. Trop. 47 (3) (2014) 302–306.
[31] H.C. Groom, et al., No evidence for infection of UK prostate cancer patients with XMRV, BK virus, Trichomonas vaginalis or human papilloma viruses, PLoS One 7 (3) (2012) e34221.
[32] R. Mendoza, et al., No biological evidence of XMRV in blood or prostatic fluid from prostate cancer patients, PLoS One 7 (5) (2012) e36073.
[33] C.M. Sturzel, et al., Utilization of replication-competent XMRV reporter-viruses reveals severe viral restriction in primary human cells, PLoS One 8 (9) (2013) e74427.
[34] K. Kakoki, et al., Androgen-independent proliferation of LNCaP prostate cancer cells infected by xenotropic murine leukemia virus-related virus, Biochem. Biophys. Res. Commun. 447 (1) (2014) 216–222.
[35] M.L. Martinez-Fierro, et al., Identification of viral infections in the prostate and evaluation of their association with cancer, BMC Canc. 10 (2010) 326.
[36] Z.M. Zheng, Viral oncogenes, noncoding RNAs, and RNA splicing in human tumor viruses, Int. J. Biol. Sci. 6 (7) (2010) 730–755.
[37] E.A. Klein, R. Silverman, Inflammation, infection, and prostate cancer, Curr. Opin. Urol. 18 (3) (2008) 315–319.
[38] G.J. Leiros, et al., Detection of human papillomavirus DNA and p53 codon 72 polymorphism in prostate carcinomas of patients from Argentina, BMC Urol. 5 (2005) 15.
[39] K.K. Deeb, et al., Identification of an integrated SV40 T/t-antigen cancer signature in aggressive human breast, prostate, and lung carcinomas with poor prognosis, Canc. Res. 67 (17) (2007) 8065–8080.
[40] S. Kasper, J.A. Smith Jr., Genetically modified mice and their use in developing therapeutic strategies for prostate cancer, J. Urol. 172 (1) (2004) 12–19.
[41] J.G. Mygatt, et al., Oncogenic herpesvirus HHV-8 promotes androgen-independent prostate cancer growth, Canc. Res. 73 (18) (2013) 5695–5708.
[42] G. Sais, et al., Differential patterns of large tumor antigen-specific immune responsiveness in patients with BK polyomavirus-positive prostate cancer or benign prostatic hyperplasia, J. Virol. 86 (16) (2012) 8461–8471.
[43] A. Strasner, M. Karin, Immune infiltration and prostate cancer, Front Oncol 5 (2015) 128.
[44] M.C. Maia, A.R. Hansen, A comprehensive review of immunotherapies in prostate cancer, Crit. Rev. Oncol. Hematol. 113 (2017) 292–303.
[45] N. Rajarubendra, et al., Prostate cancer immunology - an update for Urologists, BJU Int. 107 (7) (2011) 1046–1051.
[46] V.L. Stevens, et al., Genetic variation in the toll-like receptor gene cluster (TLR10-TLR1-TLR6) and prostate cancer risk, Int. J. Canc. 123 (11) (2008) 2644–2650.
[47] M. Lanciotti, et al., The role of M1 and M2 macrophages in prostate cancer in relation to extracapsular tumor extension and biochemical recurrence after radical prostatectomy, BioMed Res. Int. 2014 (2014) 486798.
[48] C. Pasero, et al., Inherent and tumor-driven immune tolerance in the prostate microenvironment impairs natural killer cell antitumor activity, Canc. Res. 76 (8) (2016) 2153–2165.
[49] H. Zhang, et al., Concordant down-regulation of proto-oncogene PML and major histocompatibility antigen HLA class I expression in high-grade prostate cancer, Canc. Immun. 3 (2003) 2.
[50] A. Troy, et al., Phenotypic characterisation of the dendritic cell infiltrate in prostate cancer, J. Urol. 160 (1) (1998) 214–219.
[51] D. Furman, et al., Systems analysis of sex differences reveals an immunosuppressive role for testosterone in the response to influenza vaccination, Proc. Natl. Acad. Sci. U. S. A. 111 (2) (2014) 869–874.
[52] K.S. Sfanos, et al., Phenotypic analysis of prostate-infiltrating lymphocytes reveals TH17 and Treg skewing, Clin. Canc. Res. 14 (11) (2008) 3254–3261.
[53] H.T. Kissick, et al., Androgens alter T-cell immunity by inhibiting T-helper 1 differentiation, Proc. Natl. Acad. Sci. U. S. A. 111 (27) (2014) 9887–9892.