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Review

Epstein Barr Virus and Cytomegalovirus in Prostate - A Controversial Subject

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REZUMAT

Prezența virusului Epstein Barr și a citomegalovirusului în prostată - un subiect de controversă

Virusul Ebstein-Barr a fost încadrat de IARC drept carcinogen de grupul I având capacitatea de a imortaliza limfocitele B cât și celulele de carcinom epitelial. Citomegalovirusul are de asemenea capacitatea de a imortaliza celule umane în vitro, în special la nivel tegumentar unde este prezent frecvent. Dată fiind implicarea certă a acestor 2 virursuri în diverse neoplazii s-a ridicat întrebarea dacă nu cumva există o posibilă implicare a acestora în neoplazia prostatică. Am căutat in literatura de specialitate date privind prezența Ebstein Barr Virus și citomegalovirus in patologia prostatică, căutând metode specifice de determinare a prezenței acestor tipuri de virusuri în țesutul prostatic. Asocierea celor 2 virusuri cu țesutul prostatic este un fapt dovedit. Ceea ce ridică semne de întrebare este rolul acestor 2 virusuri în apariția neoplaziei prostatice, fie că este vorba de adenomul prostatic, PIN sau adenocarcinomul prostatic. Implicarea celor 2 virusuri ca promotori ai neoplaziei prostatice a fost deja dovedită.

Cuvinte cheie: Ebstein Barr Virus, citomegalovirus, prostată, oncomodulare

ABSTRACT

Epstein Barr virus was encoded by IARC as a Group I carcinogen and it has the ability to immortalize in vitro B cells as well as the epithelial carcinoma cells. Cytomegalovirus, a Herpesviridae family member can also immortalize various human cells in vitro, especially in the skin where it its presence was noticed. The oncogenic capacity of these two viruses was demonstrated rising to questions related to a possible involvement in neoplastic prostate pathology. We extensively searched and studied in the specialized literature data which refer to these two viruses and their presence in the prostate, looking for specific methods used to detect them

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in the prostate tissue. The presence of these two viruses in prostate is a verified fact. What raises questions is their role in various forms of prostatic neoplasia whether it is prostatic adenoma, PIN or prostatic adenocarcinoma. Their role as promoter and oncogenic modulator has already been proved.

Key words: Epstein Barr virus, cytomegalovirus, prostate, oncomodulation

INTRODUCTION

Epstein-Barr virus (EBV) is a member of the Herpes Virus family and is also known as Human Herpes Virus 4. The virus was first isolated in 1964 by the British virologists Michael Anthony Epstein and Yvonne Barr, on a cell line derived from a Burkitt lymphoma. EBV infection is especially common in young individuals with low hygiene standards and also low social and economic status. Thereby it is considered that until the third decade of life, around 80 – 100% individuals have become carriers of infection [1,2]. Although EBV is considered to be a lymphotropic B virus, it can also infect T and NK lymphocytes or some epithelial cells, as it has been found in T cell lymphomas, stomach, nose, and throat carcinomas [2]. The most common host cell for EBV is B lymphocyte, although in some cases the virus can also be detected in epithelial cells. The role of epithelial cells is likely to permit the replication and amplification of EBV persistence than that of the latent infection [3].

Human Cytomegalovirus (HCMV) is a member of Betaherpesvirinae, a subfamily of Herpesviridae and it is a highly prevalent pathogen that infects the majority of young adults [4,5]. The percent of people infected with HCMV until the age of 40, is considered to range between 50 to 85% [6]. It has been demonstrated that HCMV has an important role to play in many inflammatory and proliferative diseases, like cardiovascular diseases or some types of cancers [5] and is also responsible for about 8% of mononucleosis cases [7]. Human Cytomegalovirus is also the most important cause of birth defects, which determines most often deafness and mental retardation to the newborn, if the mother is exposed to the virus during pregnancy [8].

In order to make a comprehensive assessment of the implications of EBV and HCMV infection, we extensively searched the specialized literature data which refer to these two viruses and their presence in the prostate. Therefore, we have found a series of articles published mainly in the last 10 years in which we have looked for specific methods used to detect this virus in the prostate tissue. Microscopy, PCR (polymerase chain reaction) and ELISA (Enzyme-Linked Immunosorbent Assay) are methods used to detect the presence of HCMV. Acute infection with EBV is demonstrated by the presence of heterophile antibodies in sera like VCA (viral capsid antigen) and early diffuse antigen (EAD). The presence of VCA IgM antibodies is essential for acute infection diagnosis. PCR and ELISA are also used for the detection of EBV.

The role of Epstein-Barr virus and cytomegalovirus in prostatic pathology

Epstein Barr virus is known for its oncogenic role involved in the pathogenesis of lymphomas and various epithelial tumors like breast cancer.

Grinstein published a study in which he tried to isolate Epstein Barr virus in malignant tumors and tried to demonstrate its presence in various sites, including prostate with adenocarcinoma [9]. The control group for this study was represented by 10 patients with normal prostates who tested negative for EBV [9]. The presence of viral infection in regions with PIN and prostate adenoma was the most important aspect to this work [9]. The methods used to detect the expression of EBNA-1 in tissue fragments obtained from the Rush-Presbyterian-St. Luke's Medical Center in Chicago, were based on immunohistochemistry [9]. The tissue fragments were also analyzed using PCR for gene amplification and in situ hybridization [9]. The authors were unable to identify the CD21 receptor fragments in either normal or dysplastic lesions of target organs [9]. Therefore, they raised the hypothesis that these viral strains did not presented this type of receiver, based on the fact that either the host cell had a different mechanism of penetration that does not require a receiver or other viral envelope has a glycoprotein as a ligand [9].

The work of Sfanos et al included a group of 30 patients with prostatic neoplasia and other 200 patients in the control group for the presence of

various pathogens [10]. They found in 16 of them the presence of a viral stain based on the IS-PCR and PCR to increase the specificity and sensitivity of the determination [10].

In his study, Dr. Saad Mohammed Hassan Ali concentrates its efforts to demonstrate a determinant relationship between EBV infection and the presence of benign or malignant prostate tumors [11]. For this reason he showed that 10% of the patients (2 of 20) diagnosed with benign prostate hyperplasia (BPH) presented EBV infection, while in 47.5% of the patients (19 of 40) diagnosed with prostate adenocarcinoma have also been diagnosed with EBV infection [11]. These results indicated that EBV infection may be among the causes that gave rise to a benign or malignant tumor of the prostate [11]. A discouraging result for the causal relationship between BPH and the development of adenocarcinoma by the EBV pro-oncogenic activity is the study of J. Bergh [12]. Prostate fragments were studied and the EBV was detected in 29 of them; 9.4% [12] were cases that have progressed from BPH to ADK-P, and 8.8% [13] of the fragments were patients in the control group who suffered from ADK-P [12].

The results of this study showed that this virus is not responsible for the progression of HBP to ADK-P in these patients and there were no statistically significant differences between positive and negative test samples, in chronic inflammation [12,13]. Recently they found strains of EBV using both classical and in situ PCR in 4 of 10 patients with ADK - P and in 2 of 10 patients with BPH [14]. The paper aimed to demonstrate the strains of HPV in parallel with EBV and their co-existence and the presence of koilocytes (a classic marker of HPV infection) were also studied in parallel [14]. The authors emphasized the presence of HPV strain 18 and its implications in cervical cancer, raising the hypothesis of a relationship between the pro-oncogenic effect of this viral stain and prostate cancer [14].

Since the mid 70's was demonstrated the oncogenic role of this ubiquitous virus, sustained recently in many studies by the oncomodulatory role, demonstrated on immortalized human cells.

Stapleton's study attempted to prove the involvement of CMV in prostate adenoma using alternative methods for its detection by PCR and immunohistochemistry, but only two positive results have been reported: one in the control group which had normal prostate tissue and one from the group of cases diagnosed with BPH [15]. The results of this study cannot support the idea that CMV may play the role of promoter for the progression of BPH [15]. Usually a rich history in STDs is also closely related to CMV seropositivity rate and there is recent evidence which point out that CMV has oncogenic potential [13]. The results of this study show that patients diagnosed with prostate adenocarcinoma have a lower level of CMV antibodies than patients with BPH [13,15].

Increasing the number of patients it was hoped that the "statistical relevance" will also increase. Bergh and collaborators did not identify CMV virus on a sample of 402 patients of whom 201 with prostatic adenoma, in both the control group and in the group with prostate cancer [12].

Serological studies made on smaller lots have found a small number of patients with cytomegalovirus active infection. In an attempt to increase the spectrum they tried to identify as many strains as possible. Isolated case presentations involving the virus in the prostate in acute diseases have appeared in medical literature over time; so there are described cases of acute prostatitis with CMV [16,17].

A representative study in this sense is that of Hrbacek et al which focused on BPH progression to adenocarcinoma [18]. The control group of this study included patients diagnosed with BPH from which 86.7% (91 patients) were found positive for CMV [18].

One of the largest studies published which concerns this topic focuses on serological methods to detect the virus on a large number of patients (614 cases of prostate cancer cases and 616 controls) [19]. Although the study included a large number of patients, the results were disappointing because they found no statistically significant association between viral infection and prostate infliction [19]. An important aspect of this study is the window of opportunity, specifically if the infection and oncology changes coincided serological detection methods cannot be used unless serum harvesting is done when infection is present [19]. Thus, it is pointed out one of the drawbacks of this method of detection [19]. There is also the possibility of reactivation of dormant viral strains and infection with another strain. In such cases it is impossible to distinguish

between infection with the role of promoter and other events [19]. Unfortunately no methods that rely on tissue sampling (DNA, RNA) may be useful in such cases [19].

Older papers using immunofluorescence methods or in situ hybridization, found in higher proportions the viral presence [20]. To increase the sensitivity and specificity more recent studies used a real battery of investigations like immunohistochemistry, in situ hybridization and polymerase chain reaction [13]. These methods are used by Samanta et al in a study in 2003 to investigate the presence of viral proteins in prostate PIN lesions [13]. Like in a small sample of 22 patients with prostate adenocarcinoma and PIN they found 100% viral presence [13]. The viral presence was less expressed in cancerous lesions as much in PIN and hyperplasia [13].

Leskinen MJ et al in a paper in 2003 used PCR on a small group of prostate cancer patients and an equivalent control group with benign prostatic hyperplasia to detect strains of CMV in radical prostatectomy tissue [21]. None of the investigated patients had infection with CMV or HPV and HSV [21]. Yet in recent years the meta-analysis made on this subject could not give a reliable result of this type of virus implication in prostate pathology [21]. A very recent review of Caini studying the involvement of various sexually transmitted microorganisms in prostatic neoplastic pathology cannot find a statistically significant association than for gonorrhea [22].

DISCUSSION

These results showed that EBV may be involved in cell proliferation but not necessarily in the development of premalignant or malignant lesions. However, the presence of EBV in dysplastic or precancerous lesions stresses that EBV may have additional involvement in the development of carcinomas in this organ. There are numerous plausible assumptions that indicate the role of Epstein Barr virus as a neoplastic promoter interfering with various defense mechanisms of the body and facilitating the process of alteration and deletion at the cellular level.

The role of neoplastic promoter of cytomegalovirus is and has been the subject of many debates. We know now that it is at least an enhancer of other neoplastic processes facilitating the penetration and oncogenic role of other pathogens [23]. The term used lately for the activities of this virus is oncomodulation. The oncomodulation, is a relatively new term in the definition of CMV virus is the ability of this virus to alter the antitumor defense mechanisms of the host organism and to facilitate and / or accelerate the development of a neoplastic process already present. Until now it could not be demonstrated the direct oncogenic role of this virus. It is interesting and important to determine if it can have a role in the transition from hyperplasia to benign prostatic adenocarcinoma. On the other hand, there are studies which raise the suspicion of a sexually transmitted pathogen that could play a role in the progression of prostatic neoplasia [24,25].

CONCLUSIONS

The presence of both viruses in the prostate tissue is a fact. There are still a lot of questions about what role are these two viruses playing in the neoplastic process either benign hyperplasia or adenocarcinoma of the prostate. New immunological methods are now approaching their oncogenic properties. The key to mutations seems to reside in the presence of these organisms and the changes that they produce in the cellular life cycle.

Conflict of interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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