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REVIEW

Is XMRV a causal virus for prostate cancer?

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The potential association between xenotropic murine leukaemia virus-related gammaretrovirus (XMRV) and prostate cancer (PCa) has been documented since 2006. It is important for furthering our understanding of the biological mechanisms of PCa to ascertain whether this association is causal. To summarize the available information on the epidemiological and laboratory findings of the association, we conducted a literature search of the PubMed electronic database (from March 2006 to February 2011) to identify relevant published studies that examined the association between XMRV and PCa. Although several studies showed the positive association between XMRV and PCa, more recent studies did not support this conclusion. The positive findings might be due to contamination of human samples. Further studies are needed to clarify this association.
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INTRODUCTION

Prostate cancer (PCa) is the most commonly diagnosed cancer among men in the United States (US). PCa alone accounted for 28% (217 730 new PCa cases out of 789 620 total cancer cases) of cancer incidence and 11% (32 050 PCa deaths out of 299 200 total cancer deaths) of the estimated cancer deaths among men in the US in 2010.[1] On the basis of PCa cases diagnosed between 1999 and 2005, an estimated 92% of these new cases are expected to be diagnosed at local or regional stages.[1] In the US, African-American men have a relatively higher incidence of PCa and are twice as likely to die from PCa as Caucasian-American men. The 5-year relative survival rate is 100% for Caucasian-Americans, 98% for African-Americans and 100% for Asian/Pacific Islanders.[1]

The aetiology of PCa is complex. The cancer has been associated with a range of socioeconomic,[2] cultural,[2] genetic and familial factors.[3] A meta-analysis pooling 11 case–control studies from 1971 to 1996 reported an increased risk of PCa among men with a history of prostatitis (odds ratio=1.57; 95% confidence interval: 1.01–2.45).[4] This meta-analysis also reported that the odds ratio increased to 1.77 (95% confidence interval 1.05–2.98) if analysis was restricted to the six population-based case–control studies.[4] The prevalence of prostatitis is in the range of 2%–10% among various populations in Asia, North America and Europe.[5]

Viral infections may cause chronic inflammation and tumourigenesis of the prostate.[6–8] To date, viruses such as those of the human herpes virus family (HHP-2, HHV-8, human cytomegalovirus (HCMV or HHV-5) and Epstein–Barr virus (HHV-4)), polyomaviruses (BKV, JCV and SV40) and human papillomaviruses have been detected in association with PCa.[9,10] More recently, in 2006, xenotropic murine leukaemia virus-related gammaretrovirus (XMRV), a member of the gammaretrovirus family, was isolated from human PCa tissue.[11] This review will focus on summarizing the epidemiological and laboratory research progress in examining the association of XMRV and PCa, according to reports available in the PubMed electronic database (from March 2006 to February 2011).

BACKGROUND OF XMRV

XMRV was first identified to be associated with PCa by the US investigators Urisman *et al.*[11] in their investigation of the role of viruses in the carcinogenesis of PCa in 2006. The sequence of the virus was closely related to that of the xenotropic murine leukaemia viruses (MLVs or MuLVs), and hence it was referred to as a xenotropic murine leukaemia virus-related retrovirus (XMRV).[11] More specifically, it was identified as a novel gammaretrovirus.[11]

Mice have been hosts to retroviruses for millions of years, and there are contributions from perhaps hundreds of retroviruses in the mouse genome, with a number of phylogenetic groups identified.[12,13] In contrast to MLVs, XMRV rarely infects mouse cells; indeed, it more often infects human cells, similar to other xenotropic MLVs.[14] As with other retroviruses, XMRV is a simple RNA-containing virus that can convert RNA to DNA by reverse transcription. This DNA copy can be integrated with infected host cells' DNA and can replicate within the host. Thus, the retrovirus' genetic information can persist in the infected host cells and their descendants for an indefinite number of generations.[14] Urisman *et al.*[11] also reported that XMRV was different from other MLVs in some parts of the viral genome, such as a 24-nucleotide deletion in the *gag* leader, a stop codon 53 amino acid residues downstream from the alternative gag start codon, and several single-nucleotide substitutions in the long terminal repeat. However, Hue *et al.*[15] disputed whether the 24-nucleotide deletion signature was specific to XMRV. In their studies, primers targeting the 24-nucleotide deletion were able to amplify MLV sequences in inbred and wild-derived inbred mouse strains.

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GENETIC FACTORS RELATED TO THE HOST SUSCEPTIBILITY TO XMRV

XMRV infection of human tissue cells also depends on the specific host's genetic characteristics that affect the immune response. One of the important genetic mutations involves the *RNASEL* gene, which encodes the protein ribonuclease L (RNase L), an endoribonuclease that is essential for anti-viral defence of the host.[11] R462Q polymorphisms in the *RNASEL* gene have been reported to result in a reduced-activity variant of the innate anti-viral factor RNase L.[11] *RNASEL* plays a role in anti-viral activity mediated through interferon.[16,17] Although it was initially proposed that the homozygous QQ genotype of *RNASEL* R462Q was associated with XMRV,[11] these results were not reproduced in later studies.[18,19]

Groom *et al.*[20] found that two of the three major classes of retroviral restriction factors identified to date were associated with restricting XMRV replication. These two factors include apolipoprotein B mRNA editing complex 3 (APOBEC3) and tetherin proteins, which may act to inhibit viral DNA synthesis[21–23] and restrict the release of newly generated retroviral particles,[24] respectively.[20] Paprotka *et al.*[25] found that XMRV preferentially infected cells such as PCa cells expressing low or nearly undetectable mRNA levels of APOBEC3F and APOBEC3G.

METHODS FOR DETECTING XMRV IN PCA IN LABORATORIES

Several laboratory methods can be used to detect XMRV, e.g., polymerase chain reaction (PCR), reverse transcriptase-polymerase chain reaction, immunohistochemistry, fluorescence *in situ* hybridisation,[14,26] serum assay[27] and virus neutralisation and culture.[28] DNA sequence analysis has been used to detect the *RNASEL* G1385A (R462Q) mutation.[19,29] Sensitivity analysis of the PCR assay can be performed using a PCR calibrator.[29] Danielson *et al.*[19] suggested that the detection of XMRV required specific PCR conditions. Their study showed that *env* primers were a more sensitive choice for XMRV detection than *gag* and *pol* primers; they also recommended using at least 600 ng (1×10^5 cells) prostatic tissue DNA for reliable PCR detection of XMRV. However, Aloia *et al.*[14] suggested that the extraordinary sensitivity of the PCR technique increased the risk of finding false positives. More recently, Sakakibara *et al.*[30] reported that factors that could lead to NF-κB activation would enhance XMRV transcription and replication.

EPIDEMIOLOGICAL STUDIES IN HUMANS

XMRV was first discovered in 2006 by Urisman *et al.*[11] at the University of California, San Francisco. Among 11 PCa patients with the homozygous R462Q (QQ) genotype, seven were found to be positive for XMRV, as detected by DNA microarray analysis. Further detection of 20 R462Q (QQ) cases by reverse transcriptase-polymerase chain reaction found that 40% of them were positive for XMRV.[11] A case–control study of 334 PCa tissues (233 cases *vs.* 101 benign controls) at Columbia University Medical Center demonstrated that XMRV protein was detected in 23% of PCa cases and 4% of controls, independent of *RNASEL* gene mutation.[18] The study also found that the higher the grade of tumour (as measured by the Gleason score), the higher the prevalence of XMRV protein positivity ($P=0.06$ for trend analysis).[18] Another study using a novel serum assay at Emory University found serological evidence of XMRV in 11 out of 40 patients (27.5%). The prevalence of XMRV was higher among those patients with the *RNASEL* R462Q (QQ) genotype than among those with other genotypes (40% *vs.* 15%).[27] A retrospective study in the southern US (Baylor College of Medicine), which enrolled 114 postprostatectomy PCa patients with a family history of PCa in at least one first- or second-degree relative, demonstrated that XMRV was present in 22% (32 out of 144) of PCa patients; however, XMRV infection did not correlate with *RNASEL* R462Q genotype.[19] The proportion of XMRV positivity in this southern US study was similar to that obtained in the previous two studies of PCa patients in the US.[18,27]

In contrast, several studies in the US reported the absence, or extremely low prevalence, of XMRV in PCa. For instance, Sfanos *et al.*[31] did not detect any XMRV DNA in 338 samples representing tumour, normal and benign prostate hyperplasia (BPH) tissues from 200 PCa patients. In contrast to the previous report that the virus was most frequent in patients homozygous for the R462Q variant QQ,[11] PCa patients in this study were less likely to have the *RNASEL* QQ variant.[31] Another research study conducted by Aloia *et al.*[14] did not find any signs of XMRV infection using two assays (real-time PCR and immunohistochemistry with two rabbit polyclonal antisera) and surveying nearly 800 prostate tumours prepared as full tumour tissue sections or tumour tissue microarrays, including microdissected prostate tumour, metastatic prostate tumour and intermediate as well as high-grade primary prostate tumour tissues.

Investigators conducting studies on the associations between XMRV and PCa in Europe have reported either rare detection of XMRV or negative findings. One case–control study by Fischer *et al.*[32] reported that 0.95% (1 out of 105) of PCa patients were positive for XMRV compared to 1.42% (1 out of 70) of healthy controls. In addition, the prevalences of the homozygous mutation R462Q (QQ), as determined by *RNASEL* genotyping of SNP R462Q, were 8.04% for PCa cases and 5.71% for controls.[32] Two years later, the same research group reported finding XMRV sequences in respiratory tract secretions among 329 immunocompetent and immunocompromised patients, indicating the possible transmission of XMRV through the respiratory system.[33] Another study examined 500 PCa tissue samples and did not find evidence of XMRV infection.[34] One study reported that 4% (3 out of 74) of PCa patients were positive for XMRV in their prostatic tissue, and two of the three XMRV-positive patients displayed a homozygous *RNASEL* G1385A genotype (G/G).[29] This result may be due to either a low prevalence of XMRV in the area where the study was performed or the unnatural presence of XMRV in seminal plasma, as suggested by a study investigating the presence of XMRV in seminal plasma samples from HIV-1-infected men in this population.[35] One study did not find any evidence of XMRV infection in the tissue samples of nine PCa patients selected from 139 patients after genotyping for R462Q mutations.[36]

In addition, in contrast to the original finding by Urisman *et al.*,[11] a case–control study on Mexican PCa patients failed to find any XMRV infection among 52 PCa cases and found only one XMRV-positive sample, with an R462 R/R genotype, out of 75 control samples.[9] The prevalence of XMRV among these subjects was much lower than that reported in the study by Urisman *et al.*[11]

XMRV-RELATED FINDINGS AND CLINICAL CHARACTERISTICS OF PCA

Cell types

In terms of cell types infected by XMRV in the prostate, the original study discovered the presence of infection exclusively in non-malignant stromal and haematopoietic cells adjacent to carcinoma.[11] In contrast, another study found that XMRV was primarily located in prostate carcinoma cells.[18] A more recent study in the southern US

reported that XMRV was detectable in both normal and tumour prostate tissues from PCa patients, independent of R462Q genotype, which suggested that XMRV infection might precede cancer onset.[19] Therefore, the role of XMRV infection in prostate carcinogenesis remains to be clarified.[10]

Clinical pathological parameters

To date, current studies reporting the association of XMRV and various clinical pathological parameters of PCa are limited. Only two studies report the correlation of XMRV with Gleason score: Schlaberg *et al.*[18] found a correlation of XMRV infection with high Gleason scores; Danielson *et al.*[19] also found a slight trend in favour of an increasing Gleason score, but the result was not statistically significant. Additional studies will need to include larger numbers of patients to evaluate the correlation between XMRV infection and clinical pathological parameters, including Gleason scores, seminal vesicle invasion, extracapsular extension, surgical margin invasion and lymph node involvement. These parameters are important factors to determine the stage of PCa,[37] which is critical information for clinicians who wish to prescribe appropriate treatments and enhance survival rate.[38]

XMRV ASSOCIATED WITH PCA AND CHRONIC FATIGUE SYNDROME

In addition to PCa, XMRV has been associated with a second human disease: chronic fatigue syndrome (CFS). Impaired regulation of the 2-5A synthetase/RNase L anti-viral pathway was reported to be associated with individuals with CFS.[39] In 2009, Lombardi *et al.*[28] found 68 XMRV-positive subjects out of 101 patients (67%) with severe CFS compared to 8 out of 218 healthy controls (3.7%), suggesting a causal role for XMRV in the pathogenesis of CFS. These two human disorders (PCa and CFS) are the only two human diseases that have been found to be associated with XMRV. At present, studies have detected XMRV at widely different rates in patients with PCa (0%–27%) and in patients with CFS (0%–67%).[26] Two studies conducted in the United Kingdom after 2009 failed to show evidence of association between XMRV and CFS.[40,41] A matched case–control study also failed to demonstrate the presence of XMRV in mononuclear cells from peripheral blood of CFS patients.[42] These three studies all cast doubt on the association between XMRV and CFS, similar to the findings for PCa. Furthermore, a cross-sectional study did not find any positive XMRV cases among enrolled patients with CFS, with other immunomodulatory diseases, such as HIV infection or rheumatoid arthritis, with haematopoietic stem-cell transplantation or solid organ transplantation, or among general patients seeking medical care.[43] To date, there are no laboratory data demonstrating the effects of XMRV on PCa and CFS.

CONTAMINATION IS A POTENTIAL PROBLEM

The factors responsible for the broad, inconsistent associations between XMRV prevalence and PCa/CFS are not well understood. However, there are concerns that human samples might have been contaminated with mouse DNA. Smith[44] reviewed four recent articles about mouse DNA contamination in XMRV-related research[15,45–47] and summarized three potential sources of contamination in studies of XMRV utilizing PCR-based techniques. The author reported that MLV-encoding nucleic acids have been detected in commercial PCR reagents and that mouse genomic DNA has been detected in human blood and tissue samples. In addition, nucleic acids of human tumour cell lines have been infected by XMRV or other gammaretroviruses.[44]

CONCLUSIONS

The role of infectious agents and chronic inflammation in carcinogenesis is increasingly being recognized. Given that viruses have been found in some cancerous tissues from PCa patients, the possibility that exposure to viral infection may contribute to PCa incidence has been considered. Since 2006, the role of XMRV in human disease has been intensively investigated, but its prevalence, geographical distribution and disease associations are still not clear.[48] The patients included in all of the past studies were not randomly selected, and both internal and external validity issues need to be investigated. There is no convincing evidence that exposure to XMRV plays a causal role in the pathogenesis of PCa. Many factors, including geographical location, study design, detection approaches in the laboratory, patient selection, analytical methods and control of confounding factors, have contributed to the inconsistent detection of XMRV among different human populations.[48] In addition, it is suggested that potential contamination of human samples with mouse DNA can lead to the false positive detection of XMRV.[15,44–47]

More research is needed to overcome the deficiencies in the data available to date. First, standardized and generally accepted assays for XMRV need to be developed. More sensitive assays for XMRV detection and isolation of infectious XMRV from PCa patients are also warranted. Second, large-scale epidemiological examination of the incidence and prevalence of XMRV among PCa patients may further help to explain the potential association. Given the higher incidence and lower survival rates of African-Americans with PCa compared to Caucasian-Americans and Asians, specific ethnic groups especially African-Americans should be targeted in future research to determine whether there are any racial differences in the association between XMRV infection and PCa. The investigation and resolution of these issues will improve our understanding of PCa and facilitate its prevention, diagnosis and treatment.

COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

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