XMRV in prostate cancer

The question of whether xenotropic murine leukemia virus-related virus (XMRV) contributes to the development of prostate cancer remains unanswered. The first evidence of XMRV infection in humans was reported in 2006, with a prevalence of 40% in a group of US men with prostate cancer who also harbored the R462Q mutation in the antiviral *RNASEL* gene. It has been suggested that the lack of functional RNase L makes cells susceptible to infection by XMRV, which might be involved in the pathogenesis of prostate cancer. Three new studies provide further data regarding this issue.

A recent report from the US has found no correlation between XMRV infection and R462Q status. Using polymerase chain reaction (PCR) and immunohistochemistry, the researchers analyzed 233 prostate cancer specimens and 101 benign prostatic hyperplasia controls. XMRV protein was detected in 23% of prostate cancers and 4% of controls. However, the allelic distribution of R462Q was similar in patients with and without the virus; 7% of men with evidence of XMRV harbored the homozygous R462Q mutation, compared to 10% of XMRV-negative patients. If XMRV susceptibility is indeed independent of *RNASEL* mutations, the population at risk of infection might be much larger than originally thought. The investigators also found a statistically significant association between XMRV and high-grade tumors; 44% of Gleason grade 9 tumors were XMRV-positive. The authors conclude that although these results are consistent with a causal role for XMRV in prostate cancer pathogenesis, more studies are required to determine whether this is the case.

By contrast, a research team from Berlin led by Norbert Bannert investigated the prevalence of XMRV in a cohort of German men, and found no evidence of viral infection. They examined biopsy specimens from 589 men with histologically proven prostate cancer, 76 of whom were homozygous for the R462Q mutation. All samples were found to be XMRV-negative by PCR. In addition, ELISA and western blotting failed to detect virus proteins in 146 specimens. "If no correlation between prevalence and disease is found, this would argue against a major role in prostate cancer for this virus," states Bannert.

Finally, researchers from Cleveland, USA, have demonstrated that XMRV transcription and replication can be stimulated by androgens. A glucocorticoid response element, very similar to the androgen response element, has previously been identified in the promoter region of XMRV. Accordingly, the investigators found that transcription of XMRV was enhanced twofold in cells treated with androgens, and mutations in the glucocorticoid response element prevented this effect. Similarly, the androgen inhibitors bicalutamide and flutamide were found to suppress viral growth by threefold. These effects were observed only in prostate cancer cells that express the androgen receptor. "Our findings could help explain why XMRV is found in the prostate," says Robert Silverman, co-author of the study.

Sarah Payton

Original articles Schlager, R. *et al.* XMRV is present in malignant prostatic epithelium and is associated with prostate cancer, especially high-grade tumors. *Proc. Natl Acad. Sci. USA* **106**, 16351–16356 (2009) | Hohn, O. *et al.* Lack of evidence for xenotropic murine leukemia virus-related virus (XMRV) in German prostate cancer patients. *Retrovirology* **6**, 92 (2009) | Dong, B. & Silverman, R. H. Androgen stimulates transcription and replication of XMRV (Xenotropic Murine Leukemia Virus-Related Virus). *J. Virol.* doi:10.1128/JVI.01763-09