

IMPLICATIONS FOR THE RETROVIRUS XMRV IN HUMAN DISEASE

Robert H. Silverman

Department of Cancer Biology, Lerner Research Institute, Cleveland Clinic, Cleveland, Ohio

XMRV is a human retrovirus discovered in prostate tumor tissue from patients homozygous for a reduced activity variant of the antiviral gene, RNase L. While the distribution of the virus in the human population and its risks to human health remain largely unexplored, XMRV is in the *Retroviridae* family, genus gammaretrovirus, members of which cause leukemia, lymphoma and neurologic diseases in animals. Therefore, XMRV should be considered as a potential threat to human health unless proven otherwise. Virus-host interaction studies could provide insight on the pathogenic consequences of XMRV infections as well as a means for controlling infections. Our findings show that XMRV is susceptible to inhibition by type I interferon through its effector pathway mediated by RNase L. In contrast, amyloid fibrils in semen, known as semen-derived enhancer of virus infection (SEVI), greatly increase XMRV infections of primary prostatic epithelial and stromal cells. The fact that the precursor of SEVI, prostatic acid phosphatase, is produced in abundance by the prostate indicates that XMRV replication occurs in an environment that provides a natural enhancer of viral infection, and this may play a role in spread of this virus between infected individuals. Because androgens stimulate prostate tumors and some retroviruses, we investigated effects of dihydrotestosterone (DHT) on XMRV transcription and replication. Transcription from the XMRV U3 region was stimulated by DHT, but only in cells containing a functional androgen receptor. Mutations in the glucocorticoid response element (GRE) of XMRV impaired basal transcription and androgen responsiveness. Furthermore, DHT stimulated XMRV replication, whereas androgen inhibitors (casodex and flutamide) suppressed viral growth. Findings suggest that integration of the XMRV LTR into host DNA could impart androgen stimulation on cellular genes. The occurrence of XMRV infections in the human population, in particular in prostate cancer, has implications for pathogenesis, assessing risk, and for novel therapeutic options.