

## A New Virus for Old Diseases?

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### **A retrovirus associated with cancer is linked to chronic fatigue syndrome.**

There is little consensus in the medical community on whether chronic fatigue syndrome is a distinct disease. As its name implies, the condition is characterized by debilitating fatigue persisting for many years, and it affects as much as 1% of the world's population. Although chronic inflammation is often found in these patients, no infectious or toxic agent has been clearly implicated in this disease, which is diagnosed largely by excluding other conditions that cause similar symptoms (1). In this week's *Science Express*, Lombardi *et al.* (2) describe the detection of xenotropic murine leukemia virus-related virus (XMRV) in about two-thirds of patients diagnosed with chronic fatigue syndrome. Both laboratory and epidemiological studies are now needed to determine whether this virus has a causative role, not only in this disease, but perhaps in others as well.

Chronic fatigue syndrome is not the first human disease to which XMRV has been linked. The virus first was described about 3 years ago in a few prostate cancer patients (3), and recently detected in nearly a quarter of all prostate cancer biopsies (4). It has been isolated from both prostate cancer and chronic fatigue syndrome patients, and is similar to a group of endogenous murine leukemia viruses (MLVs) found in the genomes of inbred and related wild mice. Although a half century of studies on MLVs and other gammaretroviruses have led to important discoveries on which much of our current understanding of cancer rests, there has been no clear evidence demonstrating human infection with gammaretroviruses, or associating these agents with any human disease.

Endogenous viruses, such as xenotropic MLV, arise when retroviruses infect germline cells. The integrated viral DNA, or provirus, is passed on to offspring as part of the host genome (see the figure). Endogenous proviruses form a large part of the genetic complement of modern mammals—about 8% of the human genome, for example. Xenotropic proviruses first entered the mouse germ line about a million years ago, but cannot infect cells of the mice that carry them because of a mutation in the cellular receptor for the virus presumed to have arisen after viral entry into the germ line. The propensity of xenotropic MLVs to infect rapidly dividing human cells has made it a common contaminant in cultured cells, particularly in certain human tumor cell lines (5).

There is more than 90% DNA sequence identity between XMRV and xenotropic MLV, and their biological properties are virtually indistinguishable (6–9), leaving little doubt that the former is derived from the latter by one or more cross-species transmission events. There are several lines of evidence that transmission happened in the outside world and was not a laboratory contaminant. One is that XMRVs from disparate locations and from both chronic fatigue syndrome and prostate cancer patients are nearly identical: The viral genomes differ by only a few nucleotides, whereas there are hundreds of sequence differences between XMRVs and xenotropic murine leukemia proviruses of laboratory mice. Other evidence includes the presence of XMRV and high amounts of antibodies to XMRV and other MLVs in chronic fatigue syndrome and prostate cancer patients.

There is still much that we do not understand. Whether the virus plays a causative role in either chronic fatigue syndrome or prostate cancer is unknown. For example, XMRV infection might, coincidentally, be more frequent in the same geographical region as a cluster of patients with chronic fatigue syndrome. And individuals with either disease might be more readily infected due to immune activation. XMRV might prefer to grow in rapidly dividing prostate cancer cells (10), and the presence of rapidly dividing cells in either condition might make infection more readily detectable. We do not know how the virus is transmitted, and the suggestion, based on indirect evidence, that there is sexual transmission (8) is premature. Given that infectious virus is present in plasma and in blood cells, blood-borne transmission is a possibility. Furthermore, we do not know the prevalence or distribution of this virus in either human or animal populations, and animal models for infection and pathogenesis are badly needed.

Two characteristics of XMRV are particularly noteworthy. One is the near genetic identity of isolates from different diseases and from individuals in different parts of the United States. The two most distantly related genomes sequenced to date differ by fewer than 30 out of about 8000 nucleotides. Thus, all of the XMRV isolates are more similar to each other than are the genomes isolated from any one individual infected with the human immunodeficiency virus. In this respect, XMRV more closely resembles human T cell lymphotropic viruses (HTLVs) isolated from the same geographic region (11). As in the case with HTLV, the lack of diversity implies that XMRV recently descended from a

common ancestor, and that the number of replication cycles within one infected individual is limited.

Another notable feature of XMRV is that the frequency of infection in nondiseased controls is remarkably high—about 4% in both normal individuals from the same geographic region as infected patients with chronic fatigue syndrome, and in nonmalignant prostates. If these figures are borne out in larger studies, it would mean that perhaps 10 million people in the United States and hundreds of millions worldwide are infected with a virus whose pathogenic potential for humans is still unknown. However, it is clear that closely related viruses cause a variety of major diseases, including cancer, in many other mammals. Further study may reveal XMRV as a cause of more than one well-known “old” disease, with potentially important implications for diagnosis, prevention, and therapy.

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**Path to human infection.** Although xenotropic murine leukemia virus (MLV)—derived from exogenous MLVs that became established as proviruses in the mouse germ line—can no longer infect mice, it can infect humans, apparently leading to one or more cross-species infection events to become XMRV.

## Exogenous MLV



## Germ line infection

## Endogenous MLV



## Loss of receptor

