Mouse retroviruses and chronic fatigue syndrome: Does X (or P) mark the spot?

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Five years ago, a retrovirus resembling a murine leukemia virus (MLV) was found in patients with prostate cancer (1), and last year, a similar gammaretrovirus was identified in patients with chronic fatigue syndrome (CFS) (2). The agent was named xenotropic MLV-related virus (XMRV), because its env gene was nearly identical to that of xenotropic MLV, an infectious endogenous MLV that preferentially infects cells from foreign species, including humans (Fig. L4) (3). The two reports struck a common chord, because the viral sequences found in prostate cancer and CFS were nearly identical. A second common theme emerged in reports from Europe that XMRV was rarely found, if at all, in prostate-cancer samples or patients with CFS; however, other investigators confirmed the presence of XMRV in prostate-cancer samples from North America (4). Although a recent report from the Centers for Disease Control and Prevention (CDC) did not find a link between XMRV and CFS (5), distinct MLV-related sequences are found in serial samples collected from the mid-1990s to 2010 from patients with CFS reported in the study by Lo et al. (6) in PNAS. However, the reasons for the current geographical restriction and the source of the infection are baffling.

Originally, a viral etiology of familial prostate cancer was pursued in patients with RNase L deficiency, an antiviral endoribonuclease that relays the antiviral IFN response (7). Because modulated RNase L activity has been linked with CFS, similar case-control studies were conducted, and XMRV was found in 67% of CFS patients (2). Since then, XMRV has been found in prostate-cancer patients with no link to RNase L deficiency (4) and in 3.7% of healthy donors in the original CFS study (2). Lo et al. detect MLV-related sequences in 88% of their CFS samples and 6.8% of control blood donors (6). If verified, this perplexing frequency of detecting MLV-like sequences in blood donors suggests a more widespread source of infection.

The gag gene sequences identified by Lo et al. (6) share 96.6% homology with XMRV, but they seem divergent in a region that has long puzzled virologists. Over 30 y ago, extracellular glycosylated forms of the MLV Gag proteins were identified (8) and found to be translated from an alternative CTG initiation codon in-frame with the conventional gag ATG to append a type II leader sequence to the Gag precursor (9) (Fig. L8). Glycosylated forms of Gag, or glycoprecursor, can be incorporated in virions (10) and are required for efficient viral release (11), spread, and pathogenesis (12, 13) (Fig. L4). Intriguingly, the hepatitis B virus harbors a similar precore region that encodes the e antigen (HBcAg) in-frame with the core protein, and natural mutants with stop codons preventing expression of HBcAg have been reported to arise during the natural course of infection (14). Similarly, the 24-bp in-frame deletion common to all XMRV isolates located in the glycoprecursor leader sequence maintains the ORF, whereas the ORF is eventually occluded by an upstream point deletion (Fig. L8). The sequences reported by Lo et al. (6) with a 9-bp deletion are distinct from that of XMRV.

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