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Orderly Steps in Progression of JC Virus to Virulence in the Brain

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Abstract

Progressive multifocal leukoencephalopathy is a neurodegenerative disease caused by demyelination in the brain. The demyelination is due to infection of oligodendroglial cells by polyomavirus JC, a circular DNA virus. The virus resides as an archetype form in uroepithelial cells and bone marrow of more than 70% of adults, in whom it seldom causes overt symptoms. The JC viral form infecting the brain differs from the archetype. This viral form contains two deletions and a duplication in the non-coding control region that are thought to be derived from the archetype. These rearrangements are necessary for neurovirulence. This review considers how these rearrangements occur in the context of transit to the brain and adaptation to infect glial cells.

Keywords: Leukoencephalopathy; Neurodegenerative disease; Polyomavirus; Bone marrow

Description

Progressive multifocal leukoencephalopathy (PML) is a frequently fatal demyelinating disease of the brain caused by infection of oligodendroglial cells with polyomavirus JC (JCV). It is rare in the general population, but it is often seen in AIDS, where it affects 4-5% of patients. It is also seen, at a low incidence, in patients being treated with certain immunosuppressive agents, for example, in patients with multiple sclerosis being treated with natalizumab [1,2] or other agents, e.g., TNF- α-blockers, etc.

We have recently reported that there is an orderly sequence of NCCR rearrangement events that can generate a Mad-1 like sequence from an originating archetype [3]. This is based on the frequency of reporting of individual sequence changes, in the absence of other changes, in large sequence databases. For example, the larger deletion, 66 bp, alone is reported more than 10- fold more frequently than the smaller deletion, 23 bp alone. Thus it is inferred that the 66 bp deletion occurs more frequently, and prior to, the 23 bp deletion. Both deletions necessarily occur prior to the duplication. The Mad-like forms of JCV are more responsive to agents stimulating JCV replication, such as the HIV-1 protein, Tat [3]. The question is, do these changes occur as a progression within a given individual, or do two forms of JCV, archetype and Mad-like, created at some earlier time, simultaneously infect the given person? The answer is at present not resolved, but it seems to favor the concept of a progression within an individual. One reason is that whereas multiple genotypes of the JCV NCCR are associated with PML, only a single version of the archetype is usually found in the urine of an infected individual [4,5]. This genetic drift could only occur so quickly if a form of the mutated archetype is highly adaptable, versus the archetype, to a particular cell type en route from distal sites to the brain. At present one must exercise caution in considering whether there is a progression of changes in the NCCR sequence during development of PML within a given individual. In any case, one conclusion is clear: the Mad-like forms of JCV, with their sequence rearrangements, are most adaptable to pathologically infect oligodendrocytes in the brain, most likely due to their response to replicative signals.

There are two major sites distal to the brain that have been identified as harboring JCV in adults. They are uroepithelial tissue and bone marrow [5,6]. The intestines have also been reported as a site of JCV outside the brain [7], but there are fewer reports for that site. There is no firm consensus as to which cell type can carry JCV from these distal sites to the brain or as to whether there is cross-talk between the uroepithelium and bone marrow, but in either case the cells would be cells circulating in the blood. B cells are currently the most appealing potential carrier of JCV [6], but one cannot rule out other cells such as neural crest cells (NCC) in the bone marrow [8]. Reports indicate that B cells can support JCV DNA synthesis in a T-antigen-dependent manner [3,9], but it is not clear to what extent this replication can generate viable virus particles. Even without full viral proliferation, B cells can carry JCV to the brain [10], and they can support initiation of JCV recombination [3] (Figure 1).

B cells and NCCs each have specific features that would facilitate carrying JCV to the brain and allowing infection of oligodendrocytes. B cells have an abundance of lymphocyte-specific recombination mechanisms and enzymes. B cells also harbor Epstein- Barr virus (EBV). A complex inter-regulatory link between JCV and EBV in B cells has been noted [11]. Preliminary evidence from our laboratory indicates that EBV can recombine with JCV. NCC are stem cells capable of differentiating into oligodendrocytes upon transit to the brain. B cells and NCC both remain to be further characterized with respect to JCV: it is not known that JCV can productively infect them. NCC are capable of differentiating into oligodendroglia, which can be infected. It should be determined at which point in differentiation NCC are susceptible to infection by JCV. More is known about JCV presence in B cells, some of which also harbor EBV. EBV can infect epithelial cells, and these may conceivably harbor JCV. EBV can induce cell fusion [12] and can induce transfer of genetic material among B cells and epithelial cells via a cell-cell contact mechanism [13]. B cells may carry JCV to the brain as a rearranged sequence form amenable to growth in glial cells.

Figure 1 depicts steps in the transit of JCV from distal sites in the body to the brain (Figure 1, central column) as carried by either B

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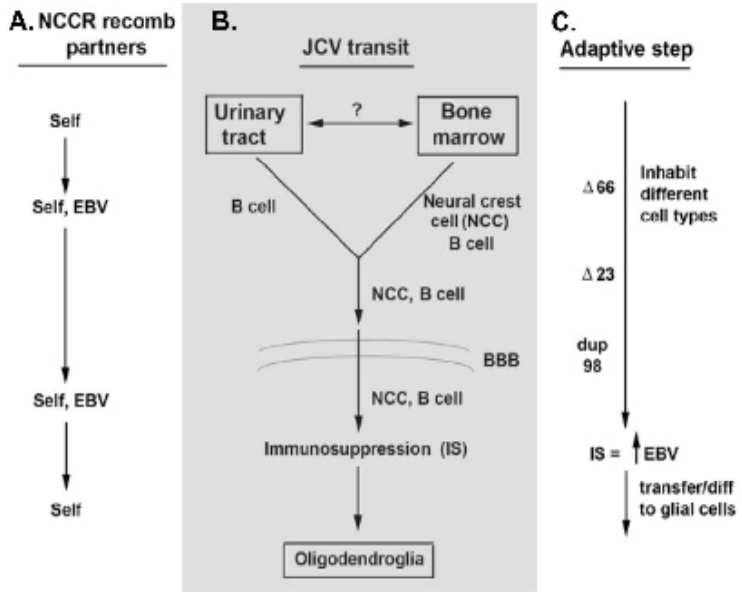

Figure 1: Each column, A, B and C in this figure represents a flow of events over time as JCV progresses from distal sites to infect the brain, as indicated by downward-pointing arrows. Events noted with arrows in each column may occur approximately simultaneously with events noted in each other column. Column A shows reported partners that can recombine with JCV: self=JCV recombination with other JCV genomes; EBV=JCV recombination with Epstein-Barr virus. Recombination of JCV with chromosomal DNA is possible but considered unlikely because no transduction with JCV has been reported. Column B shows the types of cells that may be inhabited by JCV at times in transit from distal body sites to the brain. NCC=neural crest cell; BBB=blood-brain barrier, IS=immunosuppression. Column C shows the recombination events undergone by JCV during transition from a non-neurovirulent archetype form to a neurovirulent Mad-like form. Timing of these events may be compared with timing of events in columns A and B. Δ66=deletion of 66 bp; Δ23=deletion of 23 bp; dup98=duplication of 98 bp. IS= up-arrow EBV means that immunosuppression enhances levels of Epstein-Barr virus present in cerebrospinal fluid.

cells or NCC. The left column shows the simultaneous opportunities for JCV to recombine with different partners during transit. The right column shows the simultaneous steps in adaptation of JCV to different cell environments during this transit. Depiction of transit in this way highlights several important questions. 1) Is there interaction between uroepithelium and bone marrow mediated by circulating blood cells? 2) Can either JCV or EBV infect NCC? 3) To what extent is recombination between JCV and EBV critical for entry of JCV into glial cells? Finally, does this progression of recombination events lead to potential biomarkers for predisposition to PML? Although it is early to speculate about biomarkers, the Figure presented here suggests some events to be investigated. The deletions in the JCV archetype are shown to occur as JCV is in cells circulating in the blood. Assaying for each of these deletions, especially the more frequent 66 bp deletion may be fruitful. Recombination with EBV may itself be a biomarker. Answers in the near future will be crucial to solving the mysteries of JCV in PML.

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