Journal of NeuroVirology, 14: 341–343, 2008

ISSN 1355-0284 print / 1538-2443 online
DOI: 10.1080/13550280802348222

informa
healthcare

EDITORIAL

The bone marrow, B cells, and JC virus

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The article by Marzocchetti and colleagues in this issue of the *Journal of NeuroVirology* (Marzocchetti *et al,* 2008) adds important information to our evolving understanding of the pathogenesis of progressive multifocal leukoencephalopathy (PML). Based on studies of the humoral immune response to JC virus(Weber *et al*, 2001), the rare appearance of PML in children (Berger *et al*, 1992), and the observations of the pathogenic virus in tissues months or years prior to development of the disease (Katz *et al*, 1994; Major *et al*, 1992), PML is almost invariably the consequence of reactivation of latent JC virus. Proposed sites of JC viral latency include brain, kidney, and lympocytes (Degener *et al*, 1997). Of these, B lymphocytes appear to offer the most attractive site of JC virus latency.

Evidence for the role of JC virus–infected lymphocytes in the pathogenesis of PML has been steadily increasing. We first reported JC virus infection in B cells from the spleen and bone marrow of two PML patients (Houff *et al*, 1988). Subsequently, JCV DNA was detected in circulating B lymphocytes in patients with PML, human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) patients without PML, and a small number of normal patients without immunosuppression (Tornatore *et al*, 1992). JC virus is capable of productive infection of the B-cell line, BJA-B, and primary B cells (Major *et al*, 1990; Monaco *et al*, 1998b). JC virus has been found in tonsillar tissues, including lymphocytes and stromal cells (Monaco *et al*, 1998a). Most JC virus isolates from these tissues have rearranged regulatory regions but archetype JC virus has also been found in tonsillar tissue (Kato *et al*, 2004). In an elegant series of experiments, Monaco *et al* have shown that $CD34^+$ progenitor cells are susceptible to JC virus infection (Monaco *et al*, 2001). When these cells are driven to a macrophage phenotype with phorbol ester, the cells lose the ability to support JC virus replication. JC virus replication correlates with the expression of nuclear factor (NF)-1X, which is expressed by CD34+ progenitor cells but is down-regulated in macrophage-like cells, following phorbol ester treatment. Past experience suggests there is a unique predisposition of patients with B-cell lymphoproliferative diseases to develop PML: in fact, before the AIDS pandemic, these illnesses were those most often associated with the disorder (Brooks and Walker, 1984). Finally, the monoclonal antibodies natalizumab and rituximab have been associated with the development of PML. Natalizumab mobilizes B cells and $CD\ 34^+$ progenitor cells from the bone marrow and spleen (Ransohoff, 2007). Rituximab-associated PML occurs at a time when the B-cell repertoire is being reconstituted in the peripheral blood. All these results taken together strongly support the role of JC virus–infected B cells in the pathogenesis of PML.

How do B lymphocytes support JC virus latency and reactivation? Expression of JC virus is controlled in large part by nucleotide sequences in the viral regulatory region and host cell nuclear transcription factors that recognize those sequences. The greatest variability in JC virus isolates is found in the regulatory region. This variability in the viral regulatory region is associated with host cell tropism. Jensen and Major have classified the viral regulatory region into four types (Jensen and Major, 2001). The archetype sequences with or without inserts have been isolated from urine, tonsil tissue, bone marrow, liver, and gastrointestinal tract. Rearranged viral regulatory regions are classified into two groups. Type I regulatory sequences have 98–base pair tandem repeats, with a 19–base pair deletion in Mad-4. JC virus with type I regulatory region has been isolated from tonsillar tissue, bone marrow, gastrointestinal tract, and brains of PML patients. The type II JC virus regulatory region has been found in isolates from tonsil, spleen, bone marrow, lymph

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Received 10 July 2008; accepted 14 July 2008

node, lung, urine, and brains of PML patients. Rearranged viral regulatory sequences can be accounted for by repeats and/or deletions from the archetype sequence that are generated in the host (Ault and Stoner, 1993; Yogo *et al*, 1991). The complex processes of genomic rearrangement, including somatic recombination and hypermutations, used by B lymphocytes to produce immunoglobulin genes may also facilitate the modification of the JC virus genome with viral regulatory regions containing tandem repeats, insertions, and/or deletions.

Host cell nuclear transcription factors (NTFs) are, at least in part, responsible for JC virus expression. The control of B-cell development and maturation is dependent on inducible NTFs that are expressed at different stages of B-cell development (Matthias and Rolink, 2005). It may be that JC expression occurs only when the necessary NTFs are present, which depends on the stage of B-cell development. Natalizumab has been shown to up-regulate NTFs involved in lymphocyte differentiation (Lindberg *et al*, 2008). We propose that JC virus remains latent or quiescent when cells do not produce NTFs that recognize sequences in the viral regulatory region. However, when cells in the B-cell lineage are stimulated to continue development into plasma cells, latent JC virus may be up-regulated by either undergoing rearrangements of the virus regulatory region and/or recognition of JC virus nucleotide sequences by inducible NTFs normally involved in B-cell development Activated B cells then are able to carry virus into the brain where normal lymphocyte apoptosis could release JC virus, which subsequently infects neuroglial cells, leading to PML.

The report by Marzocchetti and colleagues demonstrates that both archetype and rearranged JCV regulatory sequences are found in the bone marrow lymphocytes and undefined cells, which may be $CD34^+$ hematopoietic progenitor cells, in a patient with rheumatoid arthritis and PML. This study, along with those reporting archetype viruses in tonsillar tissue (Monaco *et al*, 1998a), suggests B lymphocytes at these sites may be involved in the rearrangement of the virus regulatory region and supports JC virus expression following activation of B cells. We may have the initial answers needed to control JC virus expression and either treat or prevent PML. Future studies of JC virus infection in B cells may provide these answers.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

Ault GS, Stoner GL (1993). Human polyomavirus JC promoter/enhancer rearrangement patterns from progressive multifocal leukoencephalopathy brain are unique derivatives of a single archetypal structure. *J Gen Virol* **74 Pt 8:** 1499–507.

Berger JR, Scott G, Albrecht J, Belman AL, Tornatore C, Major EO (1992). Progressive multifocal leukoencephalopathy in HIV-1-infected children. *AIDS* **6:** 837–841.

Brooks BR, Walker DL (1984). Progressive multifocal leukoencephalopathy. *Neurol Clin* **2:** 299–313.

Degener AM, Pietropaolo V, Di Taranto C, Rizzuti V, Ameglio F, Cordiali Fei P, Caprilli F, Capitanio B, Sinibaldi L, Orsi N (1997). Detection of JC and BK viral genome in specimens of HIV-1 infected subjects. *New Microbiol* **20:** 115–122.

Houff SA, Major EO, Katz DA, Kufta CV, Sever JL, Pittaluga S, Roberts JR, Gitt J, Saini N, Lux W (1988). Involvement of JC virus-infected mononuclear cells from the bone marrow and spleen in the pathogenesis of progressive multifocal leukoencephalopathy. *N Engl J Med* **318:** 301–305.

Jensen PN, Major EO (2001). A classification scheme for human polyomavirus JCV variants based on the nucleotide sequence of the noncoding regulatory region. *J NeuroVirol* **7:** 280–287.

Kato A, Kitamura T, Takasaka T, Tominaga T, Ishikawa A, Zheng HY, Yogo Y (2004). Detection of the archetypal regulatory region of JC virus from the tonsil tissue of patients with tonsillitis and tonsilar hypertrophy. *J NeuroVirol* **10:** 244–249.

Katz DA, Berger JR, Hamilton B, Major EO, Post MJ (1994). Progressive multifocal leukoencephalopathy complicating Wiskott-Aldrich syndrome. Report of a case and review of the literature of progressive multifocal leukoencephalopathy with other inherited immunodeficiency states. *Arch Neurol* **51:** 422–426.

Lindberg RL, Achtnichts L, Hoffmann F, Kuhle J, Kappos L (2008). Natalizumab alters transcriptional expression profiles of blood cell subpopulations of multiple sclerosis patients. *J Neuroimmunol* **194:** 153–164.

Major EO, Amemiya K, Elder G, Houff SA (1990). Glial cells of the human developing brain and B cells of the immune system share a common DNA binding factor for recognition of the regulatory sequences of the human polyomavirus, JCV. *J Neurosci Res* **27:** 461–471.

Major EO, Amemiya K, Tornatore CS, Houff SA, Berger JR (1992). Pathogenesis and molecular biology of progressive multifocal leukoencephalopathy, the JC virus-induced demyelinating disease of the human brain. *Clin Microbiol Rev* **5:** 49–73.

Marzocchetti A, Wuthrich C, Tan CS, Tompkins T, Bernal-Cano F, Bhargava P, Ropper AH, Koralnik IJ (2008). Rearrangement of the JC virus regulatory region sequence in the bone marrow of a patient with rheumatoid arthritis and progressive multifocal leukoencephalopathy. *J NeuroVirol* **14:** 455–458.

Matthias P, Rolink AG (2005). Transcriptional networks in developing and mature B cells. *Nat Rev Immunol* **5:** 497–508.

Monaco MC, Jensen PN, Hou J, Durham LC, Major EO (1998a). Detection of JC virus DNA in human tonsil tissue: evidence for site of initial viral infection. *J Virol* **72:** 9918–9923.

Monaco MC, Sabath BF, Durham LC, Major EO (2001). JC virus multiplication in human hematopoietic progenitor cells requires the NF-1 class D transcription factor. *J Virol* **75:** 9687–9695.

Monaco MC, Shin J, Major EO (1998b). JC virus infection in cells from lymphoid tissue. *Dev Biol Stand* **94:** 115–122.

Ransohoff RM (2007). ''Thinking without thinking'' about natalizumab and PML. *J Neurol Sci* **259:** 50–52.

Tornatore C, Berger JR, Houff SA, Curfman B, Meyers K, Winfield D, Major EO (1992). Detection of JC virus DNA in peripheral lymphocytes from patients with and without progressive multifocal leukoencephalopathy. *Ann Neurol* **31:** 454–462.

Weber T, Weber F, Petry H, Luke W (2001). Immune response in progressive multifocal leukoencephalopathy: an overview. *J NeuroVirol* **7:** 311–317.

Yogo Y, Kitamura T, Sugimoto C, Hara K, Iida T, Taguchi F, Tajima A, Kawabe K, Aso Y (1991). Sequence rearrangement in JC virus DNAs molecularly cloned from immunosuppressed renal transplant patients. *J Virol* **65:** 2422–2428.

This paper was first published online on iFirst on 16 October 2008.