Published in final edited form as:
J Neuroimmune Pharmacol. 2010 September ; 5(3): 404–417. doi:10.1007/s11481-010-9203-1.

Molecular Regulation of JC Virus Tropism: Insights into Potential Therapeutic Targets for Progressive Multifocal Leukoencephalopathy

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Abstract

Progressive multifocal leukoencephalopathy (PML) is a growing concern for patients undergoing immune modulatory therapies for treatment of autoimmune diseases such as multiple sclerosis. Currently, there are no drugs approved for the treatment of PML that have been demonstrated in the patient to effectively and reproducibly alter the course of disease progression. The human polyoma virus JC is the causative agent of PML. JC virus (JCV) dissemination is tightly controlled by regulation of viral gene expression from the promoter by cellular transcription factors expressed in cells permissive for infection. JCV infection likely occurs during childhood, and latent virus containing PML-associated promoter sequences is maintained in lymphoid cells within the bone marrow. Because development of PML is tightly linked to suppression and or modulation of the immune system as in development of hematological malignancies, AIDS, and monoclonal antibody treatments, further scrutiny of the course of JCV infection in immune cells will be essential to our understanding of development of PML and identification of new therapeutic targets.

Keywords

JC virus; progressive multifocal leukoencephalopathy; virus latency; virus tropism; molecular regulation; host cell–virus interactions

Introduction

JC virus (JCV) is a member of the primate genus of the polyoma family of viruses that includes simian virus 40 (SV40), which was a major contaminant of the poliovirus vaccine, BK virus, which causes polyomavirus BK-associated nephropathy in kidney transplant recipients, and the newly identified Karolinska Institute (Allander et al. 2007), Washington University (Gaynor et al. 2007), and Merkel cell (Feng et al. 2008) polyoma sequences that have been associated with disease in the respiratory tract and Merkel cell carcinoma, respectively (Dalianis et al. 2009). JCV is the causative agent of the often fatal but rare demyelinating disease progressive multifocal leukoencephalopathy (PML), which occurs in immune-suppressed individuals. Development of PML in individuals with autoimmune diseases treated with immune modulatory therapies is a growing concern due to rising

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numbers of patients with confirmed cases of PML (Major 2009). PML results from lytic replication of JCV in oligodendrocytes within the brains of infected individuals. JCV destroys white matter by slowly replicating in initially infected oligodendrocytes, followed by necrotic lysis and subsequent infection of neighboring cells (Seth et al. 2004). Destruction of oligodendrocytes as the infection progresses causes development of lesions that are visible by magnetic resonance imaging and high levels of progeny virus present in the cerebrospinal fluid (CSF), both of which are prognostic indicators of PML progression. Currently, there is no effective treatment for PML, and in most cases, patients succumb to the disease within 1 year. Because development and use of immune modulatory therapies continues to be effective for treatment of chronic autoimmune diseases, it is probable that the incidence of PML in these patients will also continue to rise. Further investigation on the relationship between modulation of the immune system and JCV infection could offer significant insight into PML progression and development of molecularly targeted therapeutics.

JCV dissemination

PML is an extremely rare disease of the central nervous system; however, approximately 60–80% of immune competent individuals contain JCV antibodies in their sera and may periodically shed virus in the urine (Egli et al. 2009). JCV has been detected in the genitourinary tract (Hogan et al. 1980) and has been specifically found in the kidneys (Chesters et al. 1983; Dorries and ter Meulen 1983). Importantly, JCV shed in the urine contains a different sequence than that found in the brain (Loeber and Dorries 1988; Yogo et al. 1990; Flaegstad et al. 1991) and is not infectious in tissue culture models (Daniel et al. 1996). A subsequent study identified nonintegrated viral DNA in the spleen, lymph nodes, lungs, liver, and kidneys of PML patients suggesting that the virus disseminated throughout the body (Grinnell et al. 1983).

JCV is capable of infecting a variety of cell types through the respiratory tract including tonsillar stroma (Monaco et al. 1996, 1998) and tonsillar B cells (Monaco et al. 1996); therefore, initial infection likely occurs in the respiratory tract. In addition, JCV DNA and viral protein synthesis has been detected in B cells present in bone marrow and perivascular spaces in the brain (Houff et al. 1988; Marzocchetti et al. 2008; Tan et al. 2009) and in circulation (Tornatore et al. 1992; Schneider and Dorries 1993; Dorries et al. 1994). It is likely that JCV enters the host through infection of lymphoid cells such as stromal cells in the tonsil and that these cells transfer the virus to B lymphocytes. B lymphocytes are capable of circulating throughout the body and would be able to deliver infectious virus to sites of latency or lytic replication in the brain. Replication of infectious JCV progeny has been demonstrated in vitro in B cell lines including BJAB and Namalwa (Atwood et al. 1992). Replication of JCV in B cells correlates directly to expression of the nuclear proteins that bind the viral promoter similar to those found in the brain (Major et al. 1990).

Intact JCV DNA sequences have been detected in bone marrow biopsies of patients procured years prior to the development of PML (Houff et al. 1988; Tan et al. 2009). Importantly, JCV sequences obtained from bone marrow tissue contain similar sequence to that of the virus present in the brains of PML patients (Marzocchetti et al. 2008; Tan et al. 2009). JCV detection in the bone marrow has been limited to DNA in the presence of capsid protein (Houff et al. 1988) and DNA in the presence of the early viral large T antigen protein (Tan et al. 2009). Importantly, viral proteins were detected by immunofluorescence alone, and intact infectious progeny virus has not been detected in the bone marrow. The presence of viral DNA in the absence of progeny virus in the bone marrow suggests that JCV may be latent in these cells. In addition, a study using $CD34^+$ hematopoietic precursor surrogate cell culture demonstrated that susceptibility of these cells correlated directly with

expression of a transcription factor required JCV replication in the brain, nuclear factor (NF)-1X (Monaco et al. 2001). These studies provide compelling evidence that cells in the bone marrow, specifically CD34 $^{+}$ hematopoietic precursors, are susceptible to JCV infection by a latent mechanism where genome is maintained in the absence of viral progeny.

The sum of these studies supports a model of JCV dissemination, illustrated in Fig. 1, in which virus is acquired via an inhalational route and initial infection occurs in the stroma and B cells of the tonsil or other lymphoid organs. Infected B cells, capable of synthesizing progeny virus, enter circulation and deliver the virus to the bone marrow where CD34 $^{+}$ hematopoietic precursors become infected and latently maintain viral genome. In states of immune suppression or modulation, the latently infected CD34^{+} hematopoietic precursors in the bone marrow can enter circulation and differentiate into mature B cells capable of viral multiplication and transporting virus to the brain. Infected B cells in the brain can produce progeny virus that infects oligodendrocytes. Lytically infected oligodendrocytes replicate virus at high levels and allow spread through the white matter leading to demyelination and development of PML. Interestingly, in each compartment where JCV sequence associated with PML is detected (B cells, bone marrow, and brain), virus replication is restricted by expression of early and late genes from the viral genome through binding of host cell transcription factors.

Viral promoter and gene expression

Similar to all other polyoma sequences, the JCV genome is a closed, super-coiled, circular chromosome that contains the noncoding viral regulatory region (RR) and the early and late viral genes as shown in Fig. 2 (Frisque 1983a; Frisque et al. 1984; Ault and Stoner 1993; Iida et al. 1993). The early and late genes are physically separated by the RR, and early viral gene expression is temporally separated from late viral gene expression by viral DNA replication. Polyomavirus early and late viral genes are highly conserved sequences; however, the RRs are the most variable portions of the viral genome within a single virus as well as across genera (Fiers et al. 1978; Reddy et al. 1978; Law et al. 1979; Seif et al. 1979; Yang and Wu 1979; Frisque 1983b; Frisque et al. 1984). The minimal JCV RR always contains the origin of replication that directs DNA replication, T antigen binding sites, and enhancer elements that contain one or more TATA boxes and multiple transcription factor binding sites (Martin et al. 1985). Alignment of JCV RR sequences from multiple patients and tissues defines six blocks of sequence, A to F, that compose all JCV RR enhancers as shown in Fig. 2 (Ault and Stoner 1993).

The RR from the original isolate of JCV, MAD1, contains an enhancer element that exists as a 98-bp tandem repeat (A-C-E-A-C-E-F) resulting in duplication of the TATA box and transcription factor binding sites (Frisque 1983a). The TATA boxes contained in the 98-bp repeat structure are essential for transcription of early and late viral genes (Kenney et al. 1986; Khalili et al. 1986; Vacante et al. 1989; Daniel and Frisque 1993; Krebs et al. 1995). MAD1 has been termed the “prototype” JCV RR sequence. Numerous RR variants containing tandem repeat-like structures have been isolated from tissues of patients with PML (Martin et al. 1985). A naturally occurring variant of the RR, termed the “archetype” sequence, is composed of a single A-C-E unit that contains the 23-bp B block and the 66-bp D block resulting in an A-B-C-D-E-F enhancer (Yogo et al. 1990). Insertion of the B and D block sequences in archetype RR results in the absence of transcription factor binding sites essential for viral gene expression including YB-1/Purα, Oct-6, and NF-1. JCV archetype RR sequence, found in the kidney and urine, is not associated with PML (Loeber and Dorries 1988; Yogo et al. 1990; Flaegstad et al. 1991) and is not infectious in tissue culture models (Daniel et al. 1996). The nomenclature prototype and archetype was proposed based

on the hypothesis that the prototype enhancer results from a rearrangement of the archetype sequence (Ault and Stoner 1993). Prototype RRs are often referred to as rearranged RRs based on this hypothesis; however, there is no direct evidence to demonstrate that the prototype sequence is derived from the archetype sequence in vivo. Therefore, we will refer to prototype RR sequence as tandem repeats for the duration of this review.

The consistent isolation of tandem repeat RR sequences from tissues obtained from PML patients strongly suggests the importance of this structure in viral pathogenesis (Frisque et al. 1984; Martin et al. 1985; Jensen and Major 1999; Vaz et al. 2000; Marzocchetti et al. 2008). Additional support for the role of the tandem repeat structure in pathogenesis has been the isolation of tandem repeat RRs from cells harboring latent virus including lymphocytes in peripheral blood (Tornatore et al. 1992; Schneider and Dorries 1993; Dorries et al. 1994; Monaco et al. 1996) and in the bone marrow (Houff et al. 1988; Marzocchetti et al. 2008; Tan et al. 2009). Interestingly, maturation of $CD34^+$ hematopoietic progenitors to mature B cells capable of producing infectious JCV progeny requires the expression of genes that support and carry out recombination (Soulas-Sprauel et al. 2007). It is possible that the JCV genome present in latently infected lymphoid cells is subject to genetic alterations made possible by the molecular environment in the developing B cell resulting in the diverse JCV RRs present in the tissues of PML patients.

Importantly, activation of viral gene expression from the RR is strictly regulated by both the presence of essential host transcription factors, listed in Table 1, in susceptible cells and the physical binding of these factors to the RR. Tandem repeat RRs contain multiple binding sites for host transcription factors including Oct-6/tst-1/SCIP (Krebs et al. 1995; Leger et al. 1995; Renner et al. 1996a, b; Sock et al. 1999), AP-1 (Kim et al. 2003; Sadowska et al. 2003; Ravichandran et al. 2006), NFκB (Ranganathan and Khalili 1993; Mayreddy et al. 1996; Safak et al. 1999), DDX1 (Sunden et al. 2007a, b), NFAT4 (Manley et al. 2006), C/EBPβ (Romagnoli et al. 2009), HIF-1α (Pina-Oviedo et al. 2009), EGF-1 (Romagnoli et al. 2008), Purα (Chen et al. 1995; Chen and Khalili 1995; Chang et al. 1996; White et al. 2009), YB-1 (Kerr et al. 1994; Chen et al. 1995; Chen and Khalili 1995; Safak and Khalili 2001; Safak et al. 2002), LCP-1 (Tada and Khalili 1992), GF-1 (Chen et al. 1997), NF-1 (Tamura et al. 1988; Amemiya et al. 1989, 1992; Shivakumar and Das 1994), Sp1 (Henson et al. 1992; Henson 1994; Mischitelli et al. 2005; Kim et al. 2006), and Spi-B (Marshall et al. 2009; Major 2010). In most cases, binding of host transcription factors activates viral gene expression; however, repression of viral gene expression has been reported for AP-1 (Kim et al. 2003; Ravichandran et al. 2006), C/EBPb (Romagnoli et al. 2009), and NF-1A (Ravichandran and Major 2008). Studies on the activity of Oct-6/tst-1/SCIP, AP-1, DD1X, NFAT4, C/EBPβ, HIF-1α, Purα, YB-1, LCP-1, and GF-1 in relation to JCV suggest a role for these proteins in glial cells. NF-1X and Spi-B are the only cellular transcription factors reported to have elevated protein expression in all cell types susceptible to JCV infection (Sumner et al. 1996; Shinohara et al. 1997; Marshall et al. 2009; Major 2010). Targeting of host factors involved in latent JCV infection in the immune compartment as well as lytic JCV infection in the brain could be a potent method to prevent dissemination of the virus and development of PML.

NF-1: a case study on the molecular nature of viral dissemination

The literature strongly demonstrates a role for the NF-1 family of proteins in regulating expression from the JCV RR (Tamura et al. 1988; Amemiya et al. 1989, 1992, 1994; Shivakumar and Das 1994; Kumar et al. 1996; Sumner et al. 1996; Shinohara et al. 1997; Monaco et al. 2001; Kim et al. 2004; Ravichandran et al. 2006; Ravichandran and Major 2008). NF-1 is a family of transcription factors that contains four members—A, B, C, and X—that each can activate or repress transcription through a variety of mechanisms

(Gronostajski 2000). NF-1 proteins bind as dimers to the dyad symmetric consensus sequence TTGGC (N5)GCCAA on duplex DNA (Gronostajski et al. 1985; Hennighausen et al. 1985; Leegwater et al. 1985; Nowock et al. 1985). NF-1 sites are important for glial cell specificity (Kumar et al. 1993) by transactivation of the viral late promoter (Kumar et al. 1996). Therefore, the NF-1 sites in the tandem repeat enhancer are possible determinants of glial cell specificity during infection. However, NF-1 binding to the JCV genome occurs in a variety of cell types, suggesting that NF-1 activity is not restricted to the brain and could be involved in basal activity of the JCV promoter (Amemiya et al. 1992).

NF-1 proteins are expressed in variety of tissues, but NF-1X expression directly correlates with a productive JCV infection. NF-1X is overexpressed in the brain where it binds the JCV RR and affects both early and late viral transcription (Sumner et al. 1996; Shinohara et al. 1997). Interestingly, expression of NF-1X protein in nonsusceptible neurons restores JCV susceptibility (Messam et al. 2003). NF-1X activity on the JCV RR has been linked to viral activity in the lymphoid system as well. The NF-1X protein is expressed in some B cells, stromal cells, and $CD34^+$ surrogate cell cultures (KG-1 cells), all of which vary in their susceptibility to JCV infection (Monaco et al. 2001). Introduction of NF-1X into nonsusceptible B cell progenitor permits a productive JCV infection as was the case in nonpermissive neuronal cultures (Monaco et al. 2001). These results indicate that NF-1X is an important regulator of JCV activity that contributes to the tissue restriction of virus replication. Interestingly, the NF-1A isoform has recently been reported as a negative regulator of JCV activity (Ravichandran and Major 2008), and this may be the negative regulatory activity identified earlier in HeLa cells (Sharma and Kumar 1991). NF-1A is expressed comparable if not higher levels than NF-IX in hematopoietic progenitor cells (Monaco et al. 2001) and neurons (unpublished data). Expression from the JCV promoter in these cells is minimal suggesting that NF-1A may contribute to repression of viral activity in non-susceptible cells or cells where the virus remains latent.

These results demonstrate that the NF-1 family of proteins has antagonistic effects on JC viral gene expression in both the immune system and in the brain. Expression of NF-1X in nonsusceptible cells was sufficient to activate viral gene expression (Monaco et al. 2001; Messam et al. 2003), while suppression of NF-1A expression in nonsusceptible cells was sufficient to activate viral gene expression (Ravichandran and Major 2008). The effect of immune suppression on modulation of NF-1 protein expression has not been defined, however would be important to furthering our understanding of the importance of NF-1 proteins during JCV infection throughout the host. In addition, direct targeting of NF-1X during JCV infection may be an effective way to restrict replication and prevent disease progression in PML patients.

Current state of treatment for PML

Currently, there are no treatments that have been demonstrated as uniformly successful for the treatment of PML. Drugs tested for activity against JCV infection in PML patients, described in Table 2, include cytarabine (also known as cytosine arabinoside (Ara-C)), vidarabine (also known as adenosine arabinoside (Ara-A)); (Rand et al. 1977), azidothymidine (AZT) (Singer et al. 1994), acyclovir, cidofovir, chlorpromazine (Pohlmann et al. 2007), mirtazapine (Vulliemoz et al. 2006), interleukin 2 (Przepiorka et al. 1997), interferon (Tashiro et al. 1987; Steiger et al. 1993; Garrels et al. 1996), and mefloquine (Brickelmaier et al. 2009). These courses of treatment mainly target two steps in the viral life cycle: inhibition of viral replication in the host cell and inhibition of virus entry into the host cell.

Nucleoside analogs

AZT, acyclovir, cidofovir, Ara-A, and Ara-C are all nucleoside analogs that exert their effect by interfering with DNA or RNA synthesis and are used as antiviral treatments for human immunodeficiency virus, herpes simplex virus, varicella zoster virus, cytomegalovirus, and JC virus (De Clercq 2009). Ara-C has been shown to significantly decrease active JCV replication and multiplication in an in vitro tissue culture model (Hou and Major 1998). However, these drugs can be toxic in patients because they not only disrupt viral DNA synthesis but cellular DNA synthesis as well. In fact, Ara-C is used a chemotherapeutic for the treatment of hematological malignancies such as acute myelogenous leukemia, acute lymphocytic leukemia, and non-Hodgkin lymphoma (Hamadani and Awan 2009). Nucleoside analogs have been used for treatment of PML with varying reports of efficacy. Ara-C alone (Marriott et al. 1975; Buckman and Wiltshaw 1976; O'Riordanet al. 1990; Portegies et al. 1991; Nicoli et al. 1992; Garrels et al. 1996; De Luca et al. 1999; Aksamit 2001; Levy et al. 2001) or in combination with cidofovir (Happe et al. 1999; Vulliemoz et al. 2006; Terrier et al. 2007), methotrexate (Gay et al. 1989), or interferon (Steiger et al. 1993; Heide et al. 1995; Garrels et al. 1996) has been associated with a positive prognosis in many patients. In additional cases, Ara-C treatment of PML has also been associated with further deterioration and death (Conomy et al. 1974; Rand et al. 1977; Horn et al. 1978; Smith et al. 1982; Hwang et al. 1986; Antinori et al. 1994; Moreno et al. 1996; Hall et al. 1998; Tubridy et al. 2000). The result of the clinical trial ACTG 243 demonstrated no benefit with a statistical difference in survival rates for PML patients undergoing Ara-C treatment (Hall et al. 1998).

Serotonin receptor antagonists

JC viral entry into host cells utilizes the alpha 2–6-linked sialic acid receptor (Liu et al. 1998). Because sialic acid is ubiquitously expressed throughout the body, including cell types that have been described as nonpermissive for JCV, binding to the primary receptor is not considered a major determinant of viral tropism. A more recent study identified the serotonin receptor 2A ($5HT_{2A}R$) as a secondary receptor used by JCV for entry into the host cell (Elphick et al. 2004). Elphick and colleagues went on to demonstrate that serotonin receptor agonists could block JCV entry and therefore inhibit JCV infection of glial cells (Elphick et al. 2004; Altschuler and Kast 2005) and human embryonic stem cell-derived oligodendrocytes (Schaumburg et al. 2008). Chlorpromazine was previously shown to inhibit JCV (Baum et al. 2003) and a subsequent study using chlorpromazine in combination with neutralizing antibodies inhibited the spread of JCV in a tissue culture model (Atwood 2001). Based on these results, the $5HT_{2A}R$ agonist chlorpromazine was used in combination with cidofovir for the treatment of PML (Pohlmann et al. 2007). In this study, combinational chlorpromazine/cidofovir treatment was ineffective in significantly lowering JCV loads in the plasma or CSF, and the patient succumbed to the disease 3 months after the onset of neurological symptoms. A similar study using the $5HT_{2A}R$ agonist mirtazapine and Ara-C in combination demonstrated a favorable outcome for the patient (Vulliemoz et al. 2006). Recent studies on the role of $5HT_{2A}R$ in JCV infection have demonstrated that JCV can infect cells, such as human brain microvascular endothelial cells (Chapagain et al. 2008) and human brain progenitor-derived astrocytes and oligodendrocytes (Monaco and Major 2009) independent of the presence of $5HT_{2A}R$. These results suggest that $5HT_{2A}R$ may play a role in the binding of JCV to certain subsets of host cells but that it is not sufficient or essential for infection in certain cell types in the brain capable of replicating virus. Additional studies are necessary to determine the significance of $5HT_{2A}R$ agonists on the outcome of PML in the clinic.

Mefloquine

Recently, mefloquine was identified as a compound able to inhibit JCV replication in a cell culture model (Brickelmaier et al. 2009). In this study, the Spectrum Collection of 2000 approved drugs and biologically active molecules was screened using in vitro assays for the ability to inhibit JCV replication. Several drugs including anti-inflammatories such as diclofenac sodium, mefanamic acid, flunixin meglumine, the antimalarial mefloquine, and the antineoplastic drug isotretinoin were shown to have inhibitory effects on JCV replication. However, mefloquine was the only drug known to cross the blood–brain barrier and concentrate in the brain where JCV replicates (Jones et al. 1994; Pham et al. 1999). Mefloquine is an antimalarial drug for which the molecular nature of its action is not well understood. In addition, neurotoxicity has been associated with mefloquine administration (Toovey 2009) and as a result is no longer the drug of choice for treatment or prevention of malaria (Jacquerioz and Croft 2009). Biogen Idec has announced a clinical trial to test the efficacy of mefloquine against PML in AIDS patients (IDEC 2008). Importantly, in the mefloquine study, the majority of the work described by Brickelmaier and colleagues utilized the M1/SVEΔ strain of JCV in which the JCV RR contained sequences from the SV40 RR (Vacante et al. 1989) in SVG-A cells that are transformed by SV40 T antigen. As described in “Viral promoter and gene expression” section, the RR determines tropism of JCV by restricting viral gene expression based on the presence or absence of transcription factors. Because the cell culture model used a virus containing SV40 RR sequence in cells containing the SV40 T antigen, the majority of this study measured the effect of these drugs on SV40 replication and not of JCV. More appropriate studies using authentic JCV RR sequences in primary cell culture models is necessary to determine any affect that mefloquine could have on JCV infection.

New concerns: PML as a result of monoclonal antibody therapy

PML is an extremely rare, yet fatal, disease that primarily occurs in immune suppressed individuals such as individuals suffering from leukemia (Behar 1965; Aur et al. 1978; GiaRusso and Koeppen 1978; Hofeler et al. 1987; Yamamoto et al. 1987; Flanagan and Costello 1989; Heikens et al. 1992; Nowak-Michalska et al. 1993; Farge et al. 1994; Ganguly et al. 1995; Seong et al. 1996; Coppo et al. 1999; Attout et al. 2000; Cid et al. 2000; Mata et al. 2000; Alla et al. 2001; Bagnato et al. 2001; Leonard et al. 2002; Saumoy et al. 2002; Kiewe et al. 2003; Swamy and Nardino 2003; Hasan and Taylor 2005; Malkoun et al. 2006; Robb et al. 2006; Matsuo et al. 2007; Kesari et al. 2008). During the AIDS epidemic, PML emerged as an AIDS defining illness that occurs in approximately 3% of HIV-infected patients (Major 2010). Of current concern are PML cases reported in patients undergoing immune modulatory therapies, listed in Table 3, including natalizumab for multiple sclerosis (MS) and Crohn’s disease (Kleinschmidt-DeMasters and Tyler 2005; Langer-Gould et al. 2005; Van Assche et al. 2005; Biogen 2009; Chen et al. 2009; Hartung 2009; Linda et al. 2009; Wenning et al. 2009), rituximab for systemic lupus erythematosus, rheumatoid arthritis, and B cell lymphoma (Goldberg et al. 2002; Freim Wahl et al. 2007; Pelosini et al. 2008; Yokoyama et al. 2008; Carson et al. 2009), efalizumab for chronic plaque psoriasis (Sobell and Weinberg 2009), and CellCept for organ transplantation (Neff et al. 2008). Because of the ability of JCV to infect and remain latent in cells of the immune system, it is essential to understand the impact of these immune modulatory drugs on the molecular events that control JCV infection in the immune system.

Monoclonal antibody therapies as treatment for autoimmune inflammatory diseases are increasing in both development and use in the clinical setting. These drugs are designed to target key molecules on immune cells and block their biological function (Rommer et al. 2008). Natalizumab (Tysabri®, Biogen IDEC) is a humanized monoclonal antibody directed against the α4-chain of α4β1 integrin, also known as very late activating antigen-4 (VLA-4;

Engelhardt and Kappos 2008) approved for use in MS patients. VLA-4 is an adhesion molecule expressed on the surface of leukocytes that permits their binding to the vascular cell adhesion molecules (VCAM-1) and fibronectin. These molecules are involved in infiltration of lymphocytes into sites of damage or infection during the inflammatory process. Therefore, natalizumab blocking VLA-4 interaction with VCAM-1 or fibronectin prevents infiltration of lymphocytes during inflammation (Rice et al. 2005). Rituximab (Rituxan®, IDEC Pharmaceuticals) is a chimeric mouse–human monoclonal antibody directed against CD20, which is expressed on B cells (Grillo-Lopez et al. 2000) and is used for the treatment of non-Hodgkin lymphomas (Fanale and Younes 2007), rheumatoid arthritis (Schuna 2007), autoimmune hematological disorders including autoimmune hemolytic anemia, acquired hemophilia, thrombotic thrombocytopenic and purpura (Garvey 2008), SLE (Ramos-Casals et al. 2009), myasthenia gravis (Stieglbauer et al. 2009), and MS (Cree et al. 2005; Wingerchuk and Weinshenker 2005; Bar-Or et al. 2008; Hauser et al. 2008; Linker et al. 2008). Binding of rituximab to CD20 on B cells results in their lysis and subsequent depletion of the B cell population in peripheral blood and CSF (Maloney et al. 1997; Monson et al. 2005). Efalizumab (Raptiva®, Genentech, Merck-Sorono) is a recombinant, humanized IgG1 monoclonal antibody directed against CD11a, a component of LFA-1 present on all lymphocytes (Schon 2008), and used in the treatment of plaque psoriasis (Frampton and Plosker 2009). CD11a targeting of T cells results in inhibition of T cell activation and trafficking to sites of cutaneous inflammation (Cather and Menter 2003). These drugs have proven efficacious against their disease targets in clinical trials; however, in each case, the unexpected development of PML in patients demonstrates the lack of understanding of the effects that these drugs have on the immune system in its entirety and the consequences that this has for development of secondary conditions such PML.

Immune modulatory drugs associated with the development of PML cause the mobilization and expansion of cells that have the potential to harbor latent JCV infection. Specifically, natalizumab mobilizes $CD34^+$ hematopoietic precursors from the bone marrow to peripheral blood (Zohren et al. 2008), chronically maintains $CD34^+$ hematopoietic precursors in peripheral blood (Bonig et al. 2008), and increases circulating pre-B and B cells in peripheral blood (Krumbholz et al. 2008). Rituximab also induces pre-B lymphocyte expansion in response to depletion (Leandro et al. 2006; Roll et al. 2006, 2008) and is associated with higher level of mobilized $CD34^+$ hematopoietic precursors (de Latour et al. 2007). In addition, microarray analysis of peripheral blood lymphocyte gene expression in patients treated with natalizumab demonstrated a significant increase in expression of genes involved in B cell differentiation (Lindberg et al. 2008). As discussed in “Viral promoter and gene expression” and “NF-1: a case study on the molecular nature of viral dissemination” sections, the intranuclear environment in the host cell, specifically the presence of absence of certain transcription factors, is essential to efficient replication of JCV in host cells. Because JCV latency has been associated with cells undergoing hematopoietic development, it is probable that lymphoid specific transcription factors regulate JCV gene expression.

Recently, a potential role for the lymphotrophic transcription factor Spi-B, one of genes upregulated in lymphocytes in response to natalizumab treatment (Lindberg et al. 2008), was described for JCV in cells from the immune system and the brain (Marshall et al. 2009; Major 2010). Interestingly, Spi-B has also been shown to activate gene expression from a lymphotrophic variant of SV40 (Pettersson and Schaffner 1987) and lymphotrophic papovavirus (Erselius et al. 1990). Because Spi-B is expressed in both immune cells and in the brain, drugs that target Spi-B may act as inhibitors of viral dissemination and as a potent treatment for the development of PML. Further analysis of the molecular changes that occur during treatment with immune modulatory therapies linked to the development of PML could offer new understanding of the molecular nature of JCV infection in the immune

system, including risk factors for the development of PML, as well as new therapeutic targets for the treatment and/or prevention of PML.

Conclusions

Without an efficacious drug available for treatment of PML, development of this disease is an important consideration for patients undergoing immune modulatory therapies and should be of particular interest for physicians as similar types of therapies continue to enter drug development pipelines and exit into the market for use in the clinic. Therapeutics targeting general processes like DNA replication, such as nucleoside analogs, can be toxic to the patient and have never been reproducibly demonstrated as effective for altering the course of disease progression. Development of PML and dissemination of JCV throughout the body is tightly linked to the immune system. Therefore, understanding of the role of the immune system in JCV dissemination will be essential to development of new potential therapeutics.

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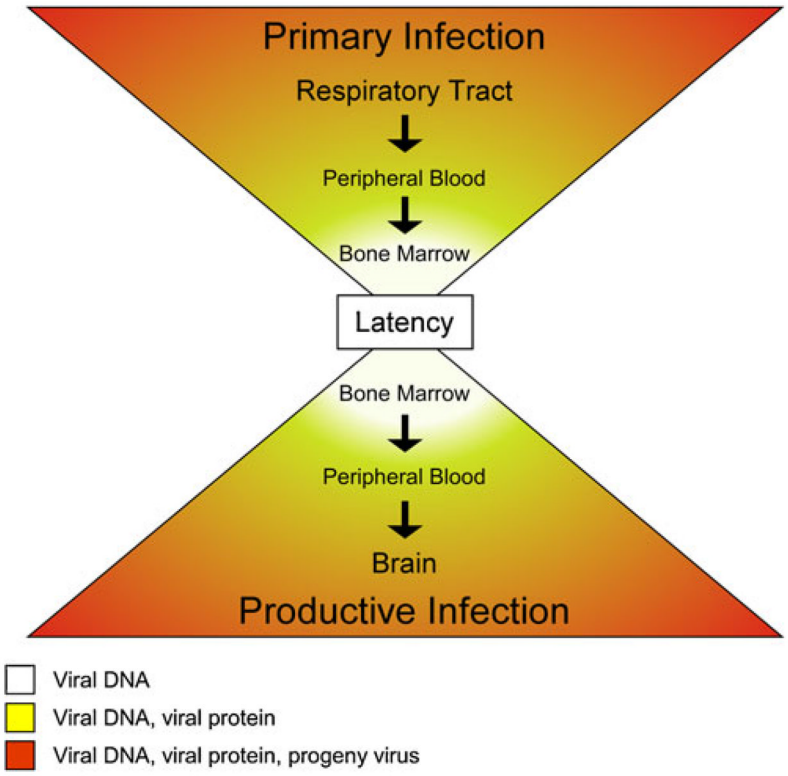

Fig. 1.

Model of JC virus dissemination throughout host tissue. Lytic infection (*orange*—DNA replication, protein expression, progeny virus) occurs at widest points of the hour glass at the probable initial site of infection in the respiratory tract and the terminal site of infection in the brain. Establishment of and reactivation from latency (*yellow*—DNA replication, protein expression) occurs within the peripheral blood in the B cell compartment. Latency (*white*—maintenance of viral DNA) occurs at the center of the hour glass in lymphocyte precursors within the bone marrow

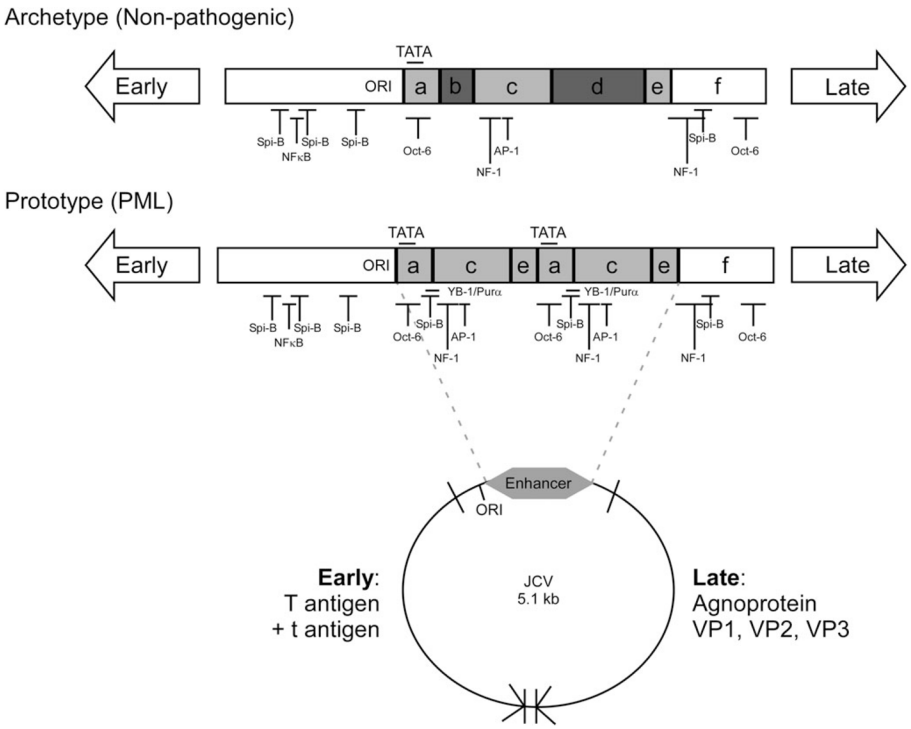

Fig. 2.

Host transcription factor binding sites present in JC virus archetype and prototype regulatory region sequences. The circular map represents the 5.1-kb circular double-stranded DNA genome of JC virus. Early (large T antigen and small t antigen) and late genes (agnoprotein, VP1, VP2, and VP3) are separated by the noncoding viral regulatory region that contains the origin of DNA replication (*ORI*) and enhancer sequences (*gray*). The noncoding regulatory regions from the nonpathogenic archetype and PML-associated prototype variants of JC virus are represented in the late orientation for transcription. The origin of DNA replication (*ORI*), enhancer regions (*gray*), TATA boxes, and transcription factor binding sites are labeled on each regulatory region diagram. The following cellular transcription factor binding sites are represented: AP-1, NF-1, NFκB, Oct-6, Spi-B, YB-1/Purα

Table 1

Host transcription factors that bind the JC virus promoter and affect viral replication

Protein	Activity for JC virus	Activity		
		Glial	Lymphoid	Stromal tonsil
AP-1	Activator/repressor	+	−	+
C/EBPβ	Repressor	+	−	−
DDX1	Activator	+	−	−
Egr-1	Activator	+	−	−
GF-1/Sμpb-2	Activator	+	−	−
HIF-1α	Activator	+	−	−
LCP-1	Activator	+	−	−
NFAT4	Activator	+	−	−
NFκB	Activator	+	−	−
NF-1A	Repressor	+	−	−
NF-1X	Activator	+	+	+
Oct-6/tst-1/SCIP	Activator	+	−	−
Purα	Activator/repressor	+	−	−
Spi-B	N.D.	+	+	−
Sp1	Activator	+	−	−
YB-1	Activator	+	−	−

N.D. not determined for JC virus infection, - activity not determined in this cell type

Table 2

Therapies tested for treatment of progressive multifocal leukoencephalopathy

Drug name	Alternative names	Abbreviations	Classification	Target
Cytosar-U	Cytarabine, cytosine arabinoside	Ara-C	Nucleoside analog	DNA
Vidarabine	Adenosine arabinoside	Ara-C	Nucleoside analog	DNA
Zovirax	Acyclovir, acycloguanosine	ACV	Nucleoside analog	DNA
Vistide	Cidofovir	CDV	Nucleoside analog	DNA
Thorazine	Chlorpromazine	CPZ	Antipsychotic	Serotonin receptor binding
Remeron	Mirtazapine	–	Antipsychotic	Serotonin receptor binding
Proleukin	Interleukin 2	IL-2	Cytokine	Cellular immunity
Interferon	Beta Interferon	IFN	Cytokine	Cellular immunity
Lariam	Mefaquin, mefloquine	–	Antimalarial	DNA

Table 3

Immune modulatory therapies associated with the development of progressive multifocal leukoencephalopathy

Drug name	Alternative names	Classification	Target
Tysabri	Natalizumab	Monoclonal antibody	α4-Chain of α4β1 integrin
Rituxan	Rituximab	Monoclonal antibody	CD20
Raptiva	Efalizumab	Monoclonal antibody	CD11a
Remicade	Infliximab	Monoclonal antibody	Tumor necrosis factor α
CellCept	Mycophenolate mofetil	Small molecule prodrug	Inosine monophosphate dehydrogenase