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Confronting JC virus and *Homo sapiens* biological signatures

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1. ABSTRACT

The present report describes the peptide commonality between JC virus (JCV) and the human proteome at the heptamer level. In total, 53 viral heptapeptides occur in functionally important human proteins with potential consequences for host functions and JCV pathogenesis. A paradigmatic example of a crucial peptide match is the SGKTTLA sequence, shared by JCV LT antigen and human nicotinamide/nicotinic acid riboside kinase, an enzyme involved in myelination processes. In general, the JCV-versus-host heptapeptide overlap may result in a competition between viral sequences and identical motifs in host enzymic active sites, adhesive domains, regulatory signaling motifs, etc., thus interfering with essential reactions and posing disadvantages to the cell. Overall, this study provides a starting point for investigating the role of peptide commonality in host-pathogen interactions.

2. INTRODUCTION

Recent reports showed that an unexpected level of sequence percentage identity at the penta-, hexa-, and heptapeptide levels unifies viruses and *Homo sapiens* (1-5). JCV is no exception to the rule of a widespread and ample distribution of viral peptide motifs through the human proteome, with more than 20 thousands occurrences in the human proteins at the pentapeptide level (including multiple occurrences), and a limited set of unique viral pentapeptides (1).

In general, this large viral-versus-human peptide intersection indicates the possibility that a viral infection may cause a subversion of host cellular processes and immune responses. Indeed, once a viral infection has been established in the host, viral particles can multiply and, following proteolysis by cellular proteases, originate sets of viral peptides potentially able to enhance, inhibit or subvert host functions.

The ability of short viral fragments to alter a cellular process is exemplified by Epstein-Barr virus EBNA-1 Gly-Ala repeats (6, 7). A chimeric protein in which an 8-mer fragment of the EBNA-1 Gly-Ala domain was inserted into the transcriptional repressor IkB, was ubiquitinated, but not degraded (8). Eg, the Gly-Ala repeat prevented proteasomal proteolysis. This datum appears of special importance in light of the role exerted by IkB degradation in activating NF-kB, a pleiotropic transcriptional activator involved in cell growth, differentiation, tumorigenesis, apoptosis, inflammation, and immunity (9).

Additional examples are the following: 1) HIV-1 peptides, such as naturally occurring variants HIV-1 $p24_{259–267}$GDIYKRWII and $p24_{263-272}$KRWIILGLNK, may prevent activation of specific T cells (10). 2) The N-terminal LGASWHRPDKCCLGYQKRPLP peptide, aa 1-21, of the viral macrophage inflammatory protein-II encoded by Kaposi's sarcoma-associated human herpesvirus-8 DNA specifically binds CXCR4 chemokine receptor, with an important role in the binding exerted by the initial pentapeptide LGASW (11). Knowing that CXCR4 may be used by HIV-1 to enter target cells (12), the binding is important since might also lead to new therapeutic approaches for HIV infection. 3) CKS-17 is a 17 amino acids long (LQNRRGLDLLFLKEGG) immunosuppressive sequence which is present in many retroviral envelope proteins. Short synthetic peptides (LQNRRGLD and LDLLFL) derived from this sequence inhibit immune function *in vitro* and *in vivo* (13-15). 4) Viral peptides have been found to trigger proliferative responses in diabetogenic BDC2.5 T-cells. Interestingly, MTAPSWARME, a peptide from the tegument protein of human herpes simplex virus type I, was the most active viral sequence at 1 microg/ml (16).

In short, this representative sampling of data indicates that viral infections may produce viral fragments able to overlap/conflict/interfere with the physiological host cell functions, and supports the utilization of peptide matching as an observable phenetic attribute to define virus-host relationship. Aiming at identifying viral domains that might be linked to the JCV-associated pathogenic sequela in humans, the present study further explores the identity platform between JCV and *Homo sapiens* proteomes at the heptapeptide level and highlights a quantitative/qualitative picture of functional identities (eg, peptide motifs) that might be useful in evaluating the physio-pathological links between viruses and humans. As a note of special importance in regard to JCV-associated encephalopathies, the SGKTTLA peptide matching between the human nicotinamide/nicotinic acid riboside kinase 1 (NRK1) and JCV LT antigen is discussed.

3. METHODS

The analysed JCV amino acid (aa) primary sequence (Taxonomy ID: 10632; accession number: J02226; 5 proteins; length: 1,629 aa) is described at the URL http://www.uniprot.org/uniprot/?query=J02226&sort=score Abbreviations, UniProtKB/Swiss-Prot accession numbers, entry names, and length of the five viral proteins are as follows: large T antigen (LT ; P03072; LT_POVJC; 688aa); small T antigen (ST; P03083-1; ST_POVJC; 172aa); agnoprotein (Agno; P03086-1; AGNO_POVJC; 71aa); major capsid protein (VP1; P03089-1; VP1_POVJC; 354aa); minor capsid protein (VP2; P03095; VP2_POVJC; 344aa). The JCV polyprotein primary sequence was dissected into 1623 sequential heptamers that were analyzed for exact peptide matching to the human proteins using the Protein Information Resource (PIR) peptide match program (www.pir.georgetown.edu/pirwww/search/peptide.shtml) (17). The viral 7-mer peptide sequences were offset by one residue each other, ie, sequentially overlapped by six residues. For each viral heptapeptide, the human proteome was searched for instances of the same 7-mer. The human proteins containing viral heptapeptide matches were analyzed utilizing UniProt database (http://www.uniprot.org) (18, 19).

4. RESULTS

Table 1 lists the human proteins hosting JCV heptameric matches. Quantitatively, 53 viral heptapeptides are distributed among 64 human proteins. Qualitatively, an inspection of Table 1 indicates that JCV peptide motifs are located in human proteins that are component of the survival of motor neuron protein complex, catalyze cell adhesion, activate GTPase, (de)polymerize actin, and are involved in oligodendrocyte differentiation. Such proteins may potentially be associated, when altered, to spinal muscular atrophy, leukocyte adhesion-deficiency syndrome, T cell anergy, focal segmental glomerulosclerosis, oncogenesis, neuronal damages, axonal degeneration, and encephalopathies. The examples that follow give a brief survey of the cell subversion potential and possible pathologic correlates of the JCV-versus-human peptide overlap.

4.1. Peptide sharing between JCV and human proteins involved in cell-cell adhesion/repulsion

Table 1 shows the following peptide sharing between the viral polyprotein and the human proteins involved in cell-to cell contacts:

The JCV LT/ST_{46-52}GGDEDKM peptide sequence is shared with the human Rap1 GTPase-activating protein 1 (RGP2), a protein that is abundant in the cerebral cortex. RGP2 down-regulates the activity of Ras proximity 1 (Rap1). Dysregulations of the Rap1 signal in specific tissues result in certain disorders, including myeloproliferative disorders and leukemia, platelet dysfunction with defective hemostasis, leukocyte adhesion-deficiency syndrome, lupus-like systemic autoimmune disease, and T cell anergy (20). Signaling via Rap1 transmits an inside-out signal to the integrins, thereby increasing adhesiveness to ligands such as immunoglobulin superfamily proteins as well as extracellular matrix proteins and plasma proteins. This process induces leukocyte cell adhesion to the endothelium and antigen-presenting cells (21). Specifically, Rap1 promotes VEGFR2 activation and

Table 1. Human proteins sharing hepta- and octapeptide sequence(s) with JCV polyprotein

JCV peptide: Ag[2]	Aa pos	Sequence	**Human protein description**[1]
LT/ST	14	MDLLGLD[3]	**SMAP2**: Stromal membrane-associated protein 2. GTPase activating protein.
	38	CKELHPD[3]	**UBP32**: Ubiquitin carboxyl-terminal hydrolase 32 precursor. Deubiquitinating enzyme 32. Renal carcinoma antigen NY-REN-60. Overexpressed in breast cancers.
	42	HPDKGGD[3]	**SEC63**: Translocation protein SEC63 homolog.
	43	PDKGGDE[3]	**SEC63**: See previous entry.
	46	GGDEDKM[3]	**RGP2**: Rap1 GTPase-activating protein 1. Abundant in the cerebral cortex.
LT	124	STPPKKK	**ZEB1:** Zinc finger E-box binding homeobox 1. Inhibits interleukin-2 gene expression.
	125	TPPKKKK	**TLX1**: T-cell leukemia homeobox protein 1. Controls the genesis of the spleen.
	126	PPKKKKK	**Q5T3I0**: G patch domain-containing protein 4 **SMF**: HMG box-containing protein 3 **ZCH10**: Zinc finger CCHC domain-containing protein 10. ZCCHC10
	128	KKKKKVE	**REST**: RE1-silencing transcription factor. Transcriptional repressor which binds neuron-restrictive silencer element and represses neuronal gene transcription in non-neuronal cells.
	129	KKKKVED	**Q9ULE4**: Protein FAM184B
	259	NPEEPEE	**Q4W5N1**: Putative ATP-binding cassette sub-family A member 11
	429	IDSGKTT	**EFG1**: Elongation factor G. Mitochondrial GTPase that plays a central role in protein elongation. Defects in GFM lead to early fatal progressive hepatoencephalopathy.
	430	DSGKTTL	**EFG1**: see previous entry.
	431	SGKTTLA	**NRK1**: Nicotinamide/nicotinic acid riboside kinase 1. Phosphorylates nicotinamide riboside and nicotinic acid riboside to form nicotinamide mononucleotide and nicotinic acid mononucleotide. **Q5TBJ9**: Novel protein. **N42L1**: NEDD4-binding protein 2-like 1 **Q5W125**: Chromosome 9 open reading frame 95
	483	SRDLPSG	**RPTOR**: Regulatory-associated protein of mTOR. p150 target of rapamycin (TOR)-scaffold protein.
	542	FVRQIDF	**Q6ZV29**: PLPL7. Patatin-like phospholipase domain-containing protein 7. Serine hydrolase, whose chemical modification by certain organophosphorus compounds leads to distal axonopathy
	556	KSLSCSE	**Q3MIR3**: MCM10. Protein MCM10 homolog. Acts in DNA replication.
	557	SLSCSEY	**CUTC**: Copper homeostasis protein cutC homolog.
	561	SEYLLEK	**MYO3A**: Myosin IIIA**.** Actin-based motor with a protein kinase activity. Plays a role in vision and hearing. Strongest expression in retina, retinal pigment epithelial cells, cochlea and pancreas. **MYO3B**: Myosin-IIIB**.** Actin-based motor with a protein kinase activity. Expressed in retina, kidney and testis.
	612	TFSTMKA	**Q27J81**: Inverted formin-2. INF2. Severs actin filaments and accelerates their polymerization and depolymerization. Defects in INF2 are the cause of focal segmental glomerulosclerosis type 5.
	632	EEDSEAE	**EST1A**: Telomerase-binding protein EST1A. Ever shorter telomeres 1A. Component of the telomerase ribonucleoprotein complex that is essential for the replication of chromosome termini.
	658	EASGADT	**PGS1**: Biglycan. Bone/cartilage proteoglycan I. Found especially in articular cartilages.
ST	125	FLRSSPL	**LTK**: Leukocyte tyrosine kinase receptor. Expressed in T- and B-cell lines.
	149	DLTQEAL	**GEMI4**: Gemin-4. p97. Component of the survival of motor neurons protein complex.
	157	CWEKVLG	**Q9UL60**: Heat-shock suppressed protein 1.
Agno	31	FLLEFLL	**P49019**: G-protein coupled receptor 109B. Nicotinic acid receptor 2. **Q9H380**: Pro2946
	35	FLLDFCT	**Q6ZSF4**: Zinc finger ZZ-type and EF-hand domain-containing protein 1. ZZEF1. Cell-cycle regulation.
VP1	23	GGVEVLE	**Q86W50**: Methyltransferase 10 domain-containing protein
	26	EVLEVKT	**ATF6B**: Cyclic AMP-dependent transcription factor ATF-6 beta. Acts in the unfolded protein response (UPR) pathway by activating UPR target genes induced during ER stress.
	32	TGVDSIT	**Q5JRC1**: Serine/threonine-protein kinase WNK3. Protein kinase with no lysine 3. Expressed in brain, lung, kidney, liver and pancreas, and in fetal tissues including fetal brain, lung and kidney.
	150	EALELQG	**SEM4C**: Semaphorin-4C precursor. Location in postsynaptic cell membrane.
	220	GENVPPV	**Q96GR2**: Long-chain-fatty-acid--CoA ligase ACSBG1**.** Acyl-CoA synthetase bubblegum family 1.
	249	GDNLYLS	**PSG2**: Pregnancy-specific beta-1-glycoprotein 2 precursor.
	295	SFLLTDL	**LRFN3**: Leucine-rich repeat fibronectin type-III domain-containing protein 3. Mediates Ca2+-independent homophilic cell-cell adhesion. Promotes neurite outgrowth in hippocampal neurons.

	305	RTPRVDG	**MICA2**: MHC class I polypeptide-related sequence A precursor. Anti-MICA antibodies and ligand shedding are involved in the progression of monoclonal gammopathy to multiple myeloma. **Q5KTR3**: Flavoprotein oxidoreductase MICAL2PV2 **Q5KTR4**: Flavoprotein oxidoreductase MICAL2PV1
	306	TPRVDGQ	**MICA2**: See previous entry. **Q5KTR3**: See previous entry. **Q5KTR4**: See previous entry.
	323	EVRVFEG	**Q6PIU2**: Neutral cholesterol ester hydrolase 1. Arylacetamide deacetylase-like 1. May contribute to cancer pathogenesis by promoting tumor cell migration. Expressed in monocyte-derived macrophages.
VP2	2	GAALALL	**CD99**: CD99 antigen. T-cell surface glycoprotein E2. Involved in T-cell adhesion processes.
	3	AALALLG	**ANGL6**: Angiopoietin-related protein 6. Angiopoietin-related growth factor. AGF. May promote epidermal proliferation, remodeling and regeneration, and neovascularization.
	17	EAAAATG	**SPB11**: Serpin B11. **SPB13**: Serpin B13. Plays a role in the proliferation or differentiation of keratinocytes.
	43	ASLATVE	**SPTN5**: Spectrin beta chain, brain 4. Detected in the outer segments of photoreceptor rods and cones and in the basolateral membrane and cytosol of gastric epithelial cells.
	72	TGAPGAV	**LIMD1**: LIM domain-containing protein 1 Inhibits E2F-mediated transcription. Tumor suppressor.
	74	APGAVAG	**NUDC3**: NudC domain-containing protein 3
	80	GFAALVQ	**HRSL5**: HRAS-like suppressor 5
	85	VQTVTGG	**EHD4**: EH domain-containing protein 4. Hepatocellular carcinoma-associated protein 10/11 PAST homolog 4
	158	FSTISQA	**ABCAC**: ATP-binding cassette transporter 12. Probable transporter involved in lipid homeostasis. Defects in ABCAC are the cause of harlequin fetus. Affected babies rarely survive the perinatal period.
	260	VTQRLDL	**Q5IBP3**: Cytospin-B. Nuclear structure protein 5. Highly expressed in some cancer cell lines.
	295	MLPLLLG	**C1QT4**: Complement C1q tumor necrosis factor-related protein 4 precursor
	296	LPLLLGL	**C1QT4**: see previous entry **2DMB**: HLA class II histocompatibility antigen, DM beta chain. Really interesting new gene 7 protein. Involved in freeing the peptide binding site for acquisition of antigenic peptides. **BMP1**: Bone morphogenetic protein 1. Induces cartilage and bone formation. Participates in dorso-ventral patterning during early development by cleaving chordin. **MERTK**: Tyrosine-protein kinase Mer. Defects in MERTK are a cause of retinitis pigmentosa. **STRA6**: Stimulated by retinoic acid gene 6 protein homolog. **RISC**: Retinoid-inducible serine carboxypeptidase. Serine carboxypeptidase 1. SCPEP1
	299	LLGLYGT	**PERL**: Lactoperoxidase.
	304	GTVTPAL	**PDIP3**: Polymerase delta interacting protein 3. SKAR. Is involved in regulation of translation.
	338	RSRSSRS	**NKTR**: NK-tumor recognition protein. NK-TR protein. Involved in the function of NK cells. **CHERP**: Calcium homeostasis endoplasmic reticulum protein. ERPROT 213-21.

[1] UniProt/Swissprot accession numbers are given in bold. Human proteins were analyzed for functions and potential disease associations using Universal Protein Resource (see uniprot.org/uniprot and pertinent references therein) [2]Ag, viral antigens; abbreviations described under Methods. [3]Peptide sequences common to JCV LT and ST antigens

angiogenesis by a mechanism involving integrin {alpha}v{beta}3 (22).

The JCV $VP1_{295\text{-}301}$SFLLTDL peptide belongs to leucine-rich repeat fibronectin type-III domain-containing protein 3 (LRFN3) also called synaptic adhesion-like molecule 4. It is strongly expressed in the adult brain and is also present in the adult gastrointestinal tract and kidneys. It is distributed throughout the neuron, including the growth cone. This molecule mediates homophilic cell-cell adhesion in a Ca2+-independent manner and promotes neurite outgrowth in hippocampal neurons (23).

The JCV $VP2_{2\text{-}8}$GAALALL sequence is present in human T-cell surface glycoprotein E2 (or CD99 antigen or protein MIC2). This molecule is involved in T-cell adhesion processes, and in spontaneous rosette formation with erythrocytes (24).

JCV also shares a heptapeptide (EALELQG) with human semaphorin-4C (Sema4C), a repulsive molecule that negatively alters the movement of cells and their processes (25). In particular, Sema-4C mutants display distinctive defects of the cerebellar granule cell layer, including gaps in rostral lobules, fusions of caudal lobules, and ectopic granule cells in the molecular layer (26). Finally, Sema4C-Plexin B2 signalling modulates ureteric branching in developing kidney (27). This last datum may represent a potential link between JCV infection and renal disease (28).

An octapeptide (RTPRVDGQ) from JCV VP1 is also present in human MICAL2PV2 and MICAL2PV2, two flavoprotein oxidoreductases that function in plexin-mediated axonal repulsion (29).

As repeatedly highlighted by scientific literature (30), adhesive and repellent molecules guide cell migration, modulate neurite growth, contribute to synaptic transmission and neuronal plasticity. Hence, the above described heptapeptide sharing involving the RGP2, LRFN3, CD99, Sema4C and MICALs proteins might interfere in essential steps of nervous system development.

4.2. Examples of peptide sharing between JCV and the neural network

The JCV LT/ST$_{14-20}$MDLLGLD peptide sequence is present in the human stromal membrane-associated protein 2 (SMAP2), a GTPase activating protein that acts on ADP-ribosylation factor (ARF) 1, which, in turn, is involved in synaptic vesicle formation and has been implicated in mesial temporal lobe epilepsy, a sub-type of Epilepsy that disrupts inflammation processes, cell death, and synaptic reorganization in the hippocampus (31).

The JCV LT$_{124-130}$STPPKKK peptide sequence is found in the human zinc finger E-box binding homeobox 1 (ZEB1), a protein that inhibits interleukin-2 gene expression. In turn, interleukin-2 is thought to be important in lesion formation in acute disseminated encephalomyelitis (32)

The JCV LT$_{128-134}$KKKKKVE sequence is present in the human RE1-silencing transcription factor (REST), a transcriptional repressor which binds neuron-restrictive silencer element and represses neuronal gene transcription in non-neuronal cells. REST function is required for the differentiation of oligodendrocyte precursor cells into mature MBP-positive oligodendrocytes (33).

The JCV LT$_{561-567}$SEYLLEK sequence is present in Myosin IIIA and Myosin-IIIB, two actin-based motor with a protein kinase activity, plays a role in vision and hearing. And expressed in retina and retinal pigment epithelial cells (34).

4.3. JCV LT$_{429-437}$IDSGKTTLA sequence and human EFG, FANCJ, and NRK1 proteins

The JCV LT aa 429-437 sequence is of special relevance in the present analysis since it hosts:

An octapeptide (IDSGKTTL) shared with the human elongation factor G, a mitochondrial GTPase that, when altered, leads to early fatal progressive hepatoencephalopathy (35, 36). It is noteworthy to mention that the viral IDSGKTTL peptide constitutes the nucleotide binding site of the mitochondrial GTPase (http://www.uniprot.org/).

Three pentapeptide matches (namely DSGKT, KTTLA, and TTLAA) are in ATP-dependent RNA helicase BRIP1 protein or hFANCJ, a human protein associated to Fanconi anemia. The three pentapeptide matches assume relevance in the light of a report relating cerebroretinal vasculopathy and leukoencephalopathy and Fanconi's anemia-like phenotypes (37)

A heptapeptide (SGKTTLA) occurring in the human nicotinamide/nicotinic acid riboside kinase 1 (NRK1), that may have a remarkable significance as a potential link between JCV infection and multiple sclerosis. Indeed, NRK1 is a key enzyme in the synthesis of nicotinamide adenine dinucleotide (NAD) (38). Under conditions of NAD deficiency, neurons are susceptible to the degeneration characteristic of multiple sclerosis (39), and Kaneko *et al.* (40) have demonstrated that increased nicotinamide adenine dinucleotide levels protects axonal degeneration in experimental autoimmune encephalomyelitis models. Moreover, NAD is essential for the mammalian silent information regulator 2 (SIRT2), an NAD-dependent histone deacetylase with important roles in brain oligodendroglia, where it modulates the oligodendrocyte cytoskeleton during its differentiation and maturation (41).

The substantial importance of the SGKTTLA heptapeptide matching is suggested by the fact that the viral SGKTTLA sequence is present in the NRK1 enzymatic region (42), so that this viral-versus-human overlap may be critically involved in (and possibly alter) nicotinamide binding and/or catalysis (see Figure 1).

In essence, active JCV infection might cause a subversion of the functional NRK1 enzyme dynamics by binding and sequestering the NRK1 substrate(s) at level of LT SGKTTLA sequences. Such a *de facto* enzyme inactivation might lead to NAD shortage and depletion with the consequent neuronal damages as described above.

4.4. JCV VP2$_{295-302}$MLPLLLGL sequence and human protein signal peptides

Of note, JCV motifs are also present in the N-terminal signal peptides of human proteins. Signal peptides govern protein transport and localization in the cell (44). A viral-vrs-human overlap at level of signal sequences may cause a competition for signal peptide peptidases with consequent protein unprocessing and failure to reach the correct cellular localization. As a specific example, Table 1 shows that the JCV VP2$_{295-302}$MLPLLLGL octapeptide is present in the signal peptide of human complement C1q tumor necrosis factor-related protein 4 precursor (C1QT4). This matching might cause a competition between viral and C1QT4 MLPLLLGL sequences for signal peptide peptidase and, eventually, determine unprocessing of human C1QT4 and failure to be secreted.

A part of the octamer MLPLLLGL, the heptapeptide LPLLLGL, is present in the signal peptide sequence of other crucial proteins such as a HLA class II histocompatibility antigen involved in freeing the peptide binding site for acquisition of antigenic peptides; and bone morphogenetic protein 1, that participates in dorsoventral patterning during early development by cleaving chordin.

Finally, a pentapeptide of the octamer MLPLLLGL (LPLLL) is present in the signal peptide of HtrA serine peptidase/protease 1 (HTRA1). Of note, defects in HTRA1 are associated to cerebral arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL) (45- 47), characterized by homogeneously confluent white-matter changes and multiple lacunar infarctions in the basal ganglia and thalamus (48).

In passing, it is of interest to note that viral-vrs-human overlaps at level of signal sequences may be a harbinger of autoimmune reactions as signal peptides are broadly immunogenic (49).

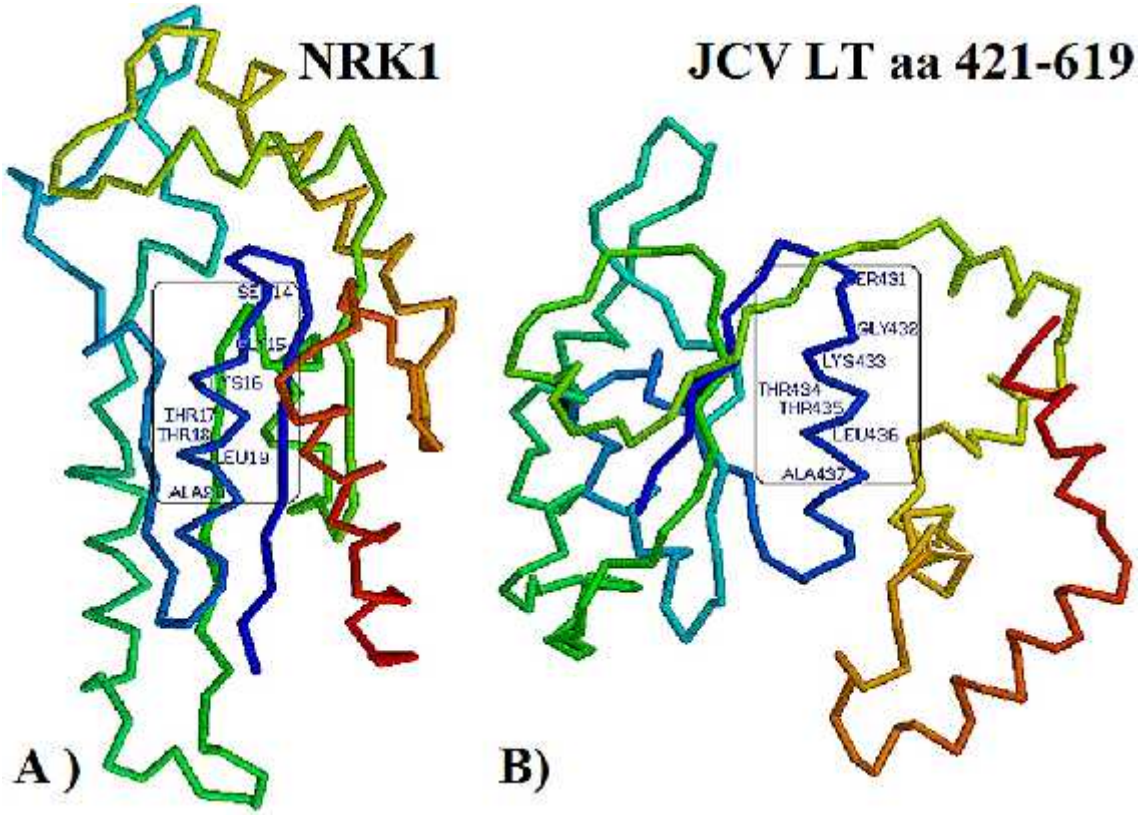

Figure 1. Sharing of a heptapeptide (SGKTTLA) between the human nicotinamide/nicotinic acid riboside kinase 1 (NRK1) and JCV LT antigen: a potential link between JCV (re)activation and multiple sclerosis. $NRK1_{14-20}$SGKTTLA sequence is involved in substrate binding (42). The same peptide motif is present in the JCV LT antigen (aa 431-437) and may compete for the NRK1 substrate binding. Under conditions of enhanced JCV expression, the viral peptide might block th**e** NRK1 reaction and, eventually, synthesis of NAD+, a compound which may have a role in myelin-associated processes (see in text). Schematic representation of the structure of **(A)** human NRK1, and (**B**) JCV LT aa 421-619 sequence, with the shared zig-zag SGKTTLA sequence reported in a rectangle. The figures were produced with ESyPred3D Web Server 1.0, a program developed by Lambert *et al.* (43) (see www.fundp.ac.be/sciences/biologie/urbm/bioinfo/esypred).

5. CONCLUSION

JCV infection may be associated to progressive multifocal leukoencephalopathy (PML). However, although PML was first described in 1958 as a complication of chronic lymphatic leukaemia and Hodgkin's disease (50), and JCV isolated from the brain of a patient with Hodgkin's disease in 1971 (51), to date the pathogenesis of PML and the molecular link(s) to JCV remain unclear (52). The present study shows that human proteins contain numerous JCV consensus sequences, sometimes allocated in critical sites and potentially able to interfere with crucial cellular functions. Among the examples discussed above, the sharing of SGKTTLA motif between the human NRK1 and JCV LT antigen (Figure 1) is of special significance since it might represent a direct link between active JCV infection and demyelinating leukoencephalopathies.

In sum, the present study is of note especially when considering the role exerted by short peptide modules in cell biology and immunology (53). Indeed, protein-protein interactions appear to occur at level of minimal modules; as a general rule, a pentapeptide is the minimal catalytic motif functionally involved in enzymic catalysis and immune recognition (54-58). Also, pentameric motifs can mimic several of the effects of the full-length peptide/protein (59, 60). Hence, the viral-versus-human heptapeptide described here offers a significant platform for investigating the still ill-defined physio-pathological network linking JCV and the human host.

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