A Peptide Link Between Human Cytomegalovirus Infection, Neuronal Migration, and Psychosis

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Alongside biological, psychological, and social risk factors, psychotic syndromes may be related to disturbances of neuronal migration. This highly complex process characterizes the developing brain of the fetus, the early postnatal brain, and the adult brain, as reflected by changes within the subventricular zone and the dentate gyrus of the hippocampus, where neurogenesis persists throughout life. Psychosis also appears to be linked to human cytomegalovirus (HCMV) infection. However, little is known about the connection between psychosis, HCMV infection, and disruption of neuronal migration. The present study addresses the hypothesis that HCMV infection may lead to mental disorders through mechanisms of autoimmune cross-reactivity. Searching for common peptides that underlie immune cross-reactions, the analyses focus on HCMV and human proteins involved in neuronal migration. Results demonstrate a large overlap of viral peptides with human proteins associated with neuronal migration, such as ventral anterior homeobox 1 and cell adhesion molecule 1 implicated in GABAergic and glutamatergic neurotransmission. The present findings support the possibility of immune cross-reactivity between HCMV and human proteins that—when altered, mutated, or improperly functioning—may disrupt normal neuronal migration. In addition, these findings are consistent with a molecular and mechanistic framework for pathological sequences of events, beginning with HCMV infection, followed by immune activation, cross-reactivity, and neuronal protein variations that may ultimately contribute to the emergence of mental disorders, including psychosis.

Keywords: peptide sharing, HCMV, immune response, schizophrenia, cross-reactivity

INTRODUCTION

Newly generated neurons migrate from their site of origin to specific brain areas and subregions, a process that involves adaptation with different degrees of complexity (1, 2). The cytoskeleton is regulated at the molecular and cellular level to execute neuronal migration (3); polarity in migrating neurons is reached by re-purposing of cytokinetic processes (4, 5); and blood vessels are used as a

physical substrate (6). Cell adhesion, cell cycle, and angiogenesis are implicated in neuronal migration.

Clinically, disruption of this process has been related not only to severe malformations of cortical development (lissencephaly, schizencephaly, neuronal eterotopia, polymicrogyria) (7) but also to psychosis (8–10). However, the relationship between macro- and microscopic structural brain anomalies and psychosis appears to be unclear, and disruption of cellular function has been hypothesized (11, 12). According to current opinion, more subtle alterations starting early during neurodevelopment can alter neural circuits and induce psychotic syndromes during adolescence or young adulthood (13). Indeed, altered migration and development of GABAergic cortical interneurons have been linked not only to schizophrenia but also to depression and anxiety disorders and seem to be strongly dependent on other neurotransmitter networks, such as dopaminergic and glutamatergic systems (14–16).

The present study focuses on HCMV infection as a potential link between neuronal migration and psychosis. On the one hand, it has been shown that herpesvirus infection of the developing brain can disturb migration of neuronal cells in animal models (17–19). On the other hand, HCMV has been discussed in the context of psychosis. Indeed, previous research has demonstrated that maternal HCMV infection and antibodies are associated with psychosis in the offspring (20), that infection during childhood is a risk factor for later psychosis (21), and that concurrent antibody titers are associated with psychosis-related symptoms (22–25). Epidemiological evidence is then not only suggestive of an association between HCMV and psychosis but also points to an influence of the infection on the early development of the central nervous system, possibly on neuronal migration.

Therefore, we here tried to elucidate the associations between HCMV infection, aberrant neuronal migration, and psychosis, building on previous research that had assessed peptide commonality and potential immune cross-reactivity between microbial and human proteins (26–31). More specifically, we investigated the peptide platform shared by HCMV and human proteins involved in neuronal migration.

METHODS

A set formed by primary amino acid (aa) sequences of human proteins involved in neuronal migration was retrieved from the UniProtKB Database (www.uniprot.org) (32). The protein library was obtained by separately searching for "neuron" AND "migration" as well as "neuronal" AND "migration" within the *Homo sapiens* proteins in the reviewed and annotated section of the UniProt database. Duplicates were removed. The procedure yielded 373 protein sequences that are described in **Supplemental Table S1**. Human proteins are expressed as UniProt entry names, if not discussed in detail.

Proteins from HCMV (human herpesvirus 5, Tax Id: 295027; 168 proteins) were dissected into heptapeptides overlapped by six residues (that is, MPATDTN, PATDTNS, ATDTNST, TDTNSTH, and so forth). Then, each viral heptapeptide

served as a probe to screen the library for exact matches within the proteins related to neuronal migration.

The viral heptapeptides shared with the neuronal migration-associated proteins were successively analyzed for occurrences in the entire human proteome using the Peptide Match program (https://research.bioinformatics.udel.edu/peptidematch/index.jsp) (33). The 373 human proteins listed in **Supplemental Table 1** were filtered out.

The Immune Epitope Database (IEDB; www.iedb.org) resource (34) was used to investigate the immunological potential of the peptide sharing among HCMV and human proteins related to neuronal migration. Only epitopes that had been experimentally validated as immunopositive in the human host were considered.

RESULTS AND DISCUSSION

Heptapeptide Sharing Between HCMV and Human Proteins Related to Neuronal Migration

Following the procedure described under *Methods*, we found that 41 HCMV heptapeptides are repeatedly distributed among 26 proteins associated with neuronal migration (see **Table 1**). An example of potential neuropathological relevance is the protein expression level in the hippocampus, a brain region where neurogenesis occurs in the adult stage.

The viral versus human peptide sharing displayed in **Table 1** is specific, unexpected, intensive, and endowed with an immunologic potential, as outlined in the following paragraphs.

Specificity: The shared heptapeptides found in this analysis are, in general, scarcely represented in the entire human proteome assumed as a control (see **Table 1**, 1st column). In other words, most of the matches illustrated in **Table 1** do not reflect an unspecific viral heptapeptide over-representation throughout the human proteome. Extreme examples for the specificity of the heptapeptide overlap are the sequences AVENGDS, DRGGGGG, INKRVKR, KPGASAA, LKPGASA, QTVTSTP, SSSSTSH, and YQRFLRE that are uniquely present in proteins related to neuronal migration and absent in the remaining human proteins (see **Table 1**). Actually, the heptapeptides AVENGDS, DRGGGGG, INKRVKR, KPGASAA, LKPGASA, QTVTSTP, SSSSTSH, and YQRFLRE are HCMV molecular signatures of the human proteins associated with neuronal migration SAV1, SHH, MAGI2, SMAD2, SMAD3, ULK1, and ACK1, respectively. Exceptions to such a specific sharing are represented by simple aa repeats such as EEEEEED. GGGGGGG, SSSSSSS, AAAAAAA, and EEEEEEE, known for being common in eukaryotic proteomes (36, 37).

Unexpectedness: The heptapeptide sharing between HCMV and human proteins associated with neuronal migration is largely unexpected in light of the fact that the probability of finding the same heptapeptide fragment in two proteins is 1 out of 20^7.

Intense peptide sharing: The overlap is not just extensive by affecting many of proteins examined, but also intensive, meaning that, in spite of the low probability, many of the proteins

TABLE 1 | Heptapeptide sharing between HCMV and human proteins related to neuronal migration.

HCMV heptapeptide[1]	Occurrences in the human proteome[2]	Occurrences in the set of proteins related to neuronal migration[3]	Human proteins related to neuronal migration[4,5]		
			UniProt Name	Cellular location[6]	Protein expression in the hippocampus[7,8]
AVENGDS	0	1	SAV1	I	l
DRGGGGG	0	1	SHH	I	–
KPGASAA	0	1	MAGI2	I	M
LKPGASA	0	1	MAGI2	I	M
LLLPPPS	0	1	ACK1	I	M
QTVTSTP	0	2	SMAD2	I	h
			SMAD3	I	m
STTAAAA	0	1	BARH2	I	–
YQRFLRE	0	1	ACK1	I	M
AAGPPEA	1	1	CAC1B	M	l
RRERERR	1	1	CAC1B	M	l
SGLGDLS	1	1	AP2A	I	l
TDSSLEA	1	1	MK10	I	M
PPAPRGP	2	1	RTN4	I	h
SGSSASS	2	1	LMNA	I	h
SSGSSAS	3	1	LMNA	I	h
SAVAAAA	4	1	SOX1	I	–
SEEEDDD	5	1	TOP2B	I	h
SGGAGGG	5	1	SMAD2	I	h
DNLTLWT	6	1	1433E	I	h
LAVADLL	11	2	5HT2B	M	nd
			DRD2	I	m
EDDDDDD	21	1	FGFR1	I	M
AAAAASS	24	1	SOX1	I	–
SSGGGGG	26	1	ALK	I	h
EEEDDDD	27	1	APBB1	I	M
AAAAAAP	30	2	CADM1	I	nd
			VAX1	I	–
DDDDDDD	30	1	FGFR1	I	M
QQPPPPP	33	1	BARH2	I	–
GAGGGGG	40	1	SOX1	I	–
AVAAAAA	43	1	SOX1	I	–
EEEEEDD	47	1	APBB1	I	M
VAAAAAA	51	1	SOX1	I	–
AGGGGGG	56	2	ALK	I	h
			SOX1	I	–
GGGGGGA	62	2	ALK	I	h
			SOX1	I	–
AAAAAAS	70	1	SOX1	I	–
QPPPPPP	70	1	BARH2	I	–
SAAAAAA	72	1	VAX1	I	nd
EEEEEED	140	3	ndF4	I	nd
			PAK3	I	–
			RTN4	I	h
GGGGGGG	170	2	ALK	I	h
			SOX1	I	–
SSSSSSS	173	1	ULK1	I	–
AAAAAAA	258	4	BARH2	I	–
			CADM1	I	nd
			SOX1	I	–
			VAX1	I	nd
EEEEEEE	301	4	CELR2	M	M
			NDF4	I	nd
			PAK3	I	–
			RTN4	I	h

[1]HCMV heptapeptide sequences in 1-letter aa code.

[2]HCMV heptapeptide occurrences in the human proteome, with proteins related to neuronal migration (**Table S1**) filtered out.

[3]HCMV heptapeptide occurrences in human proteins related to neuronal migration.

[4]Human proteins related to neuronal migration and sharing HCMV heptapeptide(s). Proteins indicated according to UniProtKB entry name.

[5]Data from the Human Protein Atlas (35).

[6]I, intracellular; M, membrane.

[7]Expression level: nd, not detected; l, low; m, medium; h, high.

[8]Data pending.

associated with neuronal migration share more than one HCMV heptapeptide. An example is the human transcription factor SOX1 that shares 10 heptapeptides with HCMV (see **Table 1**). Of note, the 10 viral heptapeptide matches that are disseminated along the SOX1 primary amino acid consecutively overlap to form long peptide stretches which may be targeted by anti-HCMV immune responses (see **Figure 1**).

Immunological potential: Finally, many of the heptapeptides shared between HCMV and the 26 human proteins related to neuronal migration are endowed with an immunologic potential by being part of epitopes that have been experimentally validated as immunopositive in humans (see **Table 2**).

Immunological Relevance of the Heptapeptide Sharing Between HCMV and Human Proteins Associated With Neuronal Migration

Tables 1 and **2** support the possibility that immune responses against HCMV may cross-react with brain proteins involved in neuronal connectivity, synaptogenesis, and transmitter networks. Although the protein cell location is mainly intracellular (see **Table 1**), proteins involved in the viral overlap nonetheless remain fully accessible to immune cross-reactions, given the availability of intracellular antigens to the immune system, which is a well-known phenomenon (38, 39). Immune cross-reactions with these proteins can (1) impair brain development, structure, and function; (2) alter cognitive processes and behavior; and (3) be involved in complex mental disorders: in particular, disorders from the psychotic spectrum.

Indeed, examples are, *inter alia*:

1. BarH-like 2 homeobox protein (BARH2) and sonic hedgehog protein (SHH) contribute to establish the positional identities of progenitor cells in the diencephalon (40), while alterations of BARH2 and SHH can affect cerebellum development (41, 42). Notably, reduced cerebellar volume has been reported in first-time psychotic episodes (43).
2. Ventral anterior homeobox 1 (VAX1) is a transcription factor, and its deficit causes severe depletion of GABAergic neurons in the neocortex (44), thus possibly

MYSMMMETDLHSPGGAQAPTNLSGPA**GAGGGGGGGGGGGGGGGGA**KA
NQDRVKRPMNAFMVWSRGQRRKMAQENPKMHNSEISKRLGAEWKVM
SEAEKRPFIDEAKRLRALHMKEHPDYKYRPRRKTKTLLKKDKYSLA
GGLLAAGAGGGGGAAVAMGVGVGVGAAAVGQRLESPGGAAGGGYAHV
NGWANGAYPGS**VAAAAAAA**MMQEAQLAYGQHPGAGGAHPHAHPAH
PHPHHPHAHPHNPQPMHRYDMGALQYSPISNSQGYMSASPSGYGGL
PYG**AAAAAAAA**GGAHQN**SAVAAAAAAAAASS**GALGALGSLVKSEP
SGSPPAPAHSRAPCPGDLREMISMYLPAGEGGDP**AAAAAAA**QSRL
HSLPQHYQGAGAGVNGTVPLTHI

FIGURE 1 | Distribution of overlapping HCMV heptapeptides through SOX1 primary aa sequence. HCMV peptide sequences are highlighted.

TABLE 2 | Immunopositive epitopes containing heptapeptides shared between HCMV and human proteins associated with neuronal migration.

IEDB ID[1]	Epitopes[2,3]	IEDB ID[1]	Epitopes[2,3]
71055	vsnappvaspsiLKPGASAA	512030	asggAAAAAAAPaap
424109	AVENGDSgsryyy	515004	epAAAAASSacaapsq
429240	aSAAAAAAAAlly	516191	gAAAAAAAPaapaapr
432006	qtdprAGGGGGGdy	516566	GGGGGGAaaagray
433931	fvrepedEEEEEEEEEED	517250	gptGGGGGGGGfntvgr
440752	srevftSSSSSSS	518048	hqpsasggAAAAAAAPa
440782	sSSGGGGGGGrfssssgy	519007	ipSAAAAAAAAgria
441180	tSSSSSSSrqtrpilk	519995	kkwenEEEEEEEEQppp
456753	mAAAAAAAPs	521695	lppkpgtmEEEEEDDdy
457859	QPPPPPPpm	525008	rlAAAAAAAqsvy
465590	glAAGPPEA	525963	sggAAAAAAAPaapa
466037	gprpAAAAAAAtpav	530324	ypdppgtmEEEEEDDd
474480	AAAAAAAqsvy	541856	esnGGGGGGGGAgsgggp
483230	qeSAAAAAA	542212	gaavVAAAAAASm
510536	AAAAAAAAPaaaat	542215	GAGGGGGeagagggaaava
510982	AGGGGGGAaaagray	544474	pQPPPPPPp

[1]Epitope IEDB IDs are listed according to numerical order. Further details and references are reported in http://www.iedb.org/.
[2]Epitope peptides are given in one-letter codes.
[3]Epitope fragments shared between HMCV and human proteins associated with neuronal migration are indicated in capital letters.

triggering the emergence of disorders within the psychotic spectrum. Indeed, a deficit in GABAergic system is one of the predominant pathophysiological features in psychotic disorders (45–47).

3. Fibroblast growth factor receptor 1 (FGFR1) may be involved in aberrant dopaminergic firing in psychotic disorders. Altered FGFR1 affects development and function of dopamine neurons, resulting in psychotic disorders in transgenic mice (48).

4. Cell adhesion molecule 1 (CADM1) expression has been detected in glutamatergic neurons, including the granule cells of the dentate gyrus, the pyramidal cells of the CA1 and CA3 regions (namely, in parvalbumin-positive neurons in the CA3 region), and in a subset of GABAergic neurons in the hippocampus (49, 50).

5. The 1433E epsilon protein (1433E or tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein [YWHAE]); 5-hydroxytryptamine receptor 2B (5HT2B or serotonin receptor 2B); and dopamine D2 receptor (DRD2) are three proteins, that—when altered—appear to be involved in the genesis of psychotic disorders. Actually, theories on potential causes of psychotic disorders assign a causal role to altered serotonin and dopamine neurotransmission (51–58). Specifically, the HCMV peptide sharing with 5HT2B and DRD2 consists of the heptapeptide LAVADLL (**Table 1**). The HCMV LAVADLL peptide is present in the transmembrane domain 2 (TMD2) of 5-HT2B and is involved in the interaction with TMD7 that allows the human 5-HT2B to adopt a conformation able to bind the neurotransmitter serotonine (59). Moreover, the LAVADLL sequence is endowed with an immunogenic potential by being part of the epitope KLAVADLEK (IEDB ID: 213202), derived from human centromere protein F (aa pos 557–565) (60). Therefore, cross-reactions targeting LAVADLL may hit multiple proteins involved in neurotransmission as well as centriolar proteins involved in brain malformations (microcephaly and ocular anomalies) (61).

6. The transcription factor Sex-determining Region Y-related HMG-box 1 (SOX1) is uniquely expressed at a high level in the majority of telencephalic neurons that constitute the ventral striatum (62), a brain area closely associated with decision making and belonging to the reward-salience circuitry (i.e., ventral striatum, dorsal caudate, and anterior cingulate cortex) (63–65). SOX1 regulates the neural primordia and promotes neurogenesis not only by acting as a transcription factor but also by forming protein-protein interactions through its COOH-terminus (66). Of note, the HCMV *versus* SOX1 peptide overlap is mainly allocated in the COOH-terminus (**Figure 1**). Consequently, cross-reactions targeting the SOX1 C-terminus may have multiple pathologic consequences, from disruption of the molecular network underlying neurodevelopment to alteration of specific neural circuits that produce complex behavior.

7. The anaplastic lymphoma kinase (ALK) protein is a tyrosine kinase receptor that, when altered, is involved in psychotic disorders (67, 68) and in neuroblastoma, a common neoplasm of early childhood that arises from cells of the primitive neural crest, giving rise to the adrenal medulla and the sympathetic nervous system (69).

8. The serine/threonine-protein kinase (PAK3) (also known as oligophrenin-3) plays a role in dendrite spine morphogenesis as well as synapse formation and plasticity, and its dysregulation may lead to synaptic deficits in psychotic disorders (70–72).

9. The reticulon-4 (RTN4) protein is implicated in the stabilization of wiring and restriction of plasticity in the adult central nervous system (73). RTN4 is differentially expressed in the dorsolateral prefrontal cortex from individuals with psychotic disorders (74).

10. MAGI2 is a membrane-associated guanylate kinase that acts as a scaffold molecule at synaptic junctions by assembling neurotransmitter receptors and cell adhesion proteins. MAGI2 seems to be involved in psychotic disorders (75–77).

11. The brain calcium channel III or voltage-dependent N-type calcium channel subunit alpha-1B (CAC1B) may have a key role in etiology of bipolar disorder and psychosis (78).

The variety of proteins involved in peptide sharing with HCMV presented here is consistent with the complex multifactorial nature of mental disorders in general, and psychosis in particular. These proteins were examined in the present study in light of their involvement with neuronal migration, while it is highly likely that any alteration of their function or structure may affect higher cognitive processes through impairment of different mechanisms above and beyond migration (i.e., axon guidance, neurotransmission, excitatory-inhibitory balance, oscillatory neuronal firing, and others). Notably, these mechanisms can also be directly affected by cross-reactive targeting of proteins allowing membrane excitability (26–30), in a complex endotypical scenario that mirrors the phenotypical complexity of mental disorders without the need for a biunivocal match between them.

CONCLUSIONS

The present study demonstrates that numerous human proteins related to neuronal migration are involved in a specific heptapeptide overlap with HCMV. Such a wide peptide sharing supports the possibility that, following HCMV active infection, anti-HCMV human immune responses may cross-react with proteins involved in peptide sharing with the herpesvirus. In the case of cross-reactions, neuropathological consequences might include the development of mental disorders, such as psychotic syndromes. In fact, the 26 human proteins listed in **Table 1** hold the key to specifying brain processes, such as neuronal connectivity, synaptogenesis, and neurotransmission in a prolonged temporal window that runs

from fetal-early postnatal neurodevelopment to adult neurogenesis. In the context of peptide sharing described here, GABAergic and glutamatergic circuitry might play a central role, with disturbances potentially leading to psychotic syndromes by altering excitatory-inhibitory balance in oscillating brain networks underpinning higher cognitive functions (79–84). Different strategies could allow to test this hypothesis *in vivo*. Observationally, sera from human patients suffering from psychotic disorders might be examined for immunoreactivity against the sequences analyzed here. Causally, animal models of neuropsychiatric disorders might be obtained by immunizing pregnant and young animals with the same sequences.

DATA AVAILABILITY STATEMENT

All datasets analyzed for this study were retrieved from publicly accessible curated databases: UniProtKB (http://www.uniprot.org/), The Immune Epitope Database (IEDB; http://www.iedb.org/), and the Human Protein Atlas (https://www.proteinatlas.org/).

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2020.00349/full#supplementary-material

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