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The comparative biochemistry of viruses and humans: an evolutionary path towards autoimmunity

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Abstract: Analyses of the peptide sharing between five common human viruses (Borna disease virus, influenza A virus, measles virus, mumps virus and rubella virus) and the human proteome highlight a massive viral vs. human peptide overlap that is mathematically unexpected. Evolutionarily, the data underscore a strict relationship between viruses and the origin of eukaryotic cells. Indeed, according to the viral eukaryogenesis hypothesis and in light of the endosymbiotic theory, the first eukaryotic cell (our lineage) originated as a consortium consisting of an archaeal ancestor of the eukaryotic cytoplasm, a bacterial ancestor of the mitochondria and a viral ancestor of the nucleus. From a pathologic point of view, the peptide sequence similarity between viruses and humans may provide a molecular platform for autoimmune crossreactions during immune responses following viral infections/immunizations.

Keywords: autoimmunity; crossreactivity; human proteome; peptide sharing; sequence similarity; viral proteomes.

Introduction

During last decade, we (Kanduc et al., 2008c; Kanduc, 2010a, 2011; Ricco and Kanduc, 2010; Lucchese et al., 2011, 2014; Lucchese and Kanduc, 2016) described a massive and indiscriminate usage of identical peptide sequences in viral and human proteomes. Such a peptide commonality is exemplified by the human RNA-binding protein endogenous Borna disease virus-like nucleoprotein 1 (EBLN1) and the highly similar Borna disease virus NucleoCAPsid N protein (NCAP) (Horie et al., 2013; Horie, 2017). Indeed, the CLUSTAL sequence alignment (Sievers et al., 2011) of the two proteins highlights exact matches at the 5-, 6-, and 9-mer level:

Human EBLN1: FPNLA---AIDWIN---VTPSLVFLC
Viral NCAP: FPNLA---AIDWIN---VTPSLVFLC

This peptide matching is mathematically unexpected, being 1 out of 20^5 (e.g. 0.0000003125), 1 out of 20^6 (e.g. 0.000000015625) and 1 out of 20^9 (i.e. infinitesimally low) the probability for two proteins to share a penta-, hexa- and a nonapeptide, respectively.

In general, the peptide overlap between viral and human proteomes is in fact much higher than expected mathematically and poses the risk for possible autoimmune pathologies through crossreactivity (Kanduc, 2012a). In this research context, the present study analyses the peptide overlap at the 8-mer level between five ubiquitous viruses – namely, Borna disease virus, influenza A virus, measles virus, mumps virus and rubella virus – and the human proteome, explores the consequent potential crossreactivity and the autoimmune pathologic risk for the human host, and investigates the evolutionary roots of the viral vs. human peptide commonality.

Results

Viral vs. human peptide matching

Basically, an epitope is five or six amino acid (aa) residues in length (Niman et al., 1983; Reddehase et al., 1989; Zagury et al., 1993; Gulden et al., 1996; Oldstone, 1998; Frank, 2002; Tiwari et al., 2004; Kishimoto et al., 2005; Plewnia et al., 2007; Tanabe, 2007; Zeng et al., 2007; Stufano and Kanduc, 2009; Kanduc, 2012b, 2013; Raychaudhuri et al., 2012; Thullier et al., 2013; Tong et al., 2015; Cui et al., 2016; Li et al., 2017). However, although the theoretical probability of a sequence of five or six aa occurring at random in two proteins is extremely low as specified already, nonetheless the viral vs. human peptide overlap is of disproportionate entity and untenable to be analyzed and discussed in detail (Polito et al.,

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2017; Kanduc, 2018; Kanduc and Shoenfeld, 2018). Here, in order to contain the dimension of the peptide overlap and, at the same time, also to obtain highly stringent and significant data, we used the octapeptide as a probe to search for viral vs. human matches.

Analysis of the peptide sharing between the five viruses under analysis (Borna disease virus, influenza A virus, measles virus, mumps virus and rubella virus) and the human proteome at the 8-mer level leads to the data shown in Table 1.

Immunologic potential of the viral vs. human peptide matching

Table 1 highlights a massive, unexpected peptide commonality that involves numerous human proteins with crucial functions in the cell. The data acquire an immunologic value in light of the fact that many of the shared peptides are present in epitopes experimentally validated and cataloged as immunopositive in the human host in the Immune Epitope Database (IEDB; www.iedb.org) resource (Vita et al., 2015) (Table 2).

Pathologic potential of the viral vs. human peptide matching

The potential pathologic burden appears high as crossreactions can occur with human crucial proteins, in this way altering fundamental cellular processes and inducing neuropsychiatric disorders, cardiovascular diseases and cancer. For example, immune reactions to influenza A virus may cause cardiovascular disease and sudden death by crossreacting with cardiac human proteins such as:

- cystathionine β-synthase (CBS) that relates to hyperhomocysteinemia, thrombosis, stroke, infective endocarditis, cerebrovascular disease (Ranawaka et al., 2001; Parnetti et al., 2002; Kelly et al., 2003; Jakubowski et al., 2008; Iossa et al., 2016; Mahale et al., 2017; Mazaheri et al., 2017);
- coiled-coil domain-containing protein 92 (CCD92) that causes coronary heart disease (Zhao et al., 2017);
- gap junction alpha-4 protein (CXA4) that is involved in myocardial infarction (Sheikhvatan et al., 2017), coronary heart disease (Zhao et al., 2014), essential hypertension (Guo et al., 2014); and
- titin protein that may cause cardiac failure, sudden cardiac death and arrhythmia (Satoh et al., 1999; Matsumoto et al., 2005).

In addition, as regards cardiovascular diseases, alterations of

- potassium voltage-gated channel subfamily B member 2 (KCNB2) are associated with Brugada syndrome (Juang et al., 2014);
- Kirsten-ras-revertant interaction trapped protein 1 (KRIT1, also named cerebral cavernous malformations 1 protein) are associated with hemorrhagic stroke, seizures, headaches, and, in addition, focal neurologic deficits (Kehrer-Sawatzki et al., 2002);
- deleted in autism protein 1 may relate to autism (Morrow et al., 2008; Aziz et al., 2011) as well as to heart ischemia-induced damage (Beigi et al., 2013; Bareja et al., 2017).

Moreover, neuropsychiatric disorders may derive from crossreactions with:

- metabotropic glutamate receptor 7 (GRM7), which has been detected in the presynaptic active zones of both excitatory and inhibitory synapses (Somogyi et al., 2003), and alterations of which are linked to susceptibility to attention deficit-hyperactivity disorder, autism, depression and schizophrenia (Yang and Pan, 2013);
- Ras-related C3 botulinum toxin substrate 1 (RAC1) that modulates the forgetting of object recognition memory. The inability to activate Rac1-dependent forgetting contributes to behavioral inflexibility (Dong et al., 2016). Instead, crossreactivity with histone-lysine N-methyltransferase 2B (KMT2B) may alter memory formation (Kerimoglu et al., 2013);
- histone methyltransferase SETD1B that may be associated with autism (Morrow et al., 2008; Aziz et al., 2011; Labonne et al., 2016).

With reference to cancer, alterations of

- Rho GTPase-activating protein 7 (RHG07) may cause human liver cancer (Yuan et al., 1998);
- polyhomeotic-like protein 3 (PHC3) relate to osteosarcoma tumors (Deshpande et al., 2007);
- transforming growth factor β regulator 1 (TBRG1) relate to chronic lymphocytic leukemia and large B-cell lymphoma (Tompkins et al., 2007);
- transmembrane protein 116 (TM116) can lead to clear cell renal cell carcinoma (Wrzesiński et al., 2015);
- pre-B-cell leukemia transcription factor 4 (PBX4) are involved in acute lymphoblastic leukemia (Rosales-Aviña et al., 2011);
- insulin receptor substrate 4 (IRS4) are found in pediatric T-cell acute lymphoblastic leukemia (Karrman et al., 2011);

Table 1: Octapeptide sharing between proteins from Borna disease virus, influenza A virus, measles virus, mumps virus, rubella virus and *Homo sapiens* proteome.

Peptides[a] from[b]:	Human protein involved in the peptide sharing[c]	Functions/disease involvement[d]	References
Borna disease virus			
LRRERPGS	AMPB. Aminopeptidase B	Alzheimer' disease	Puertas Mdel et al., 2013
VTPSLVFLC	EBLN1. Endogenous Bornavirus-like nucleoprotein 1	Apoptosis in human oligodendroglia cells	He et al., 2016
PLLGTEVS	KCNB2. Potassium voltage-gated channel subfamily B2	Brugada syndrome	Juang et al., 2014
TTTGTTGVT	MUC19. Mucin-19 precursor	Crohn's disease	Kumar et al., 2013
IDLFQKSS	OPRM. Mu-type opioid receptor. Isoform 2	Altered homeostasis of pain signalling pathways	Chan et al., 2017
LLKKLLQL	TBRG1. Transforming growth factor β regulator 1	Tumor suppressor	Tompkins et al., 2007
GSFVLSLLT	TM116. Transmembrane protein 116	Down-regulated in clear cell renal cell carcinoma	Wrzesiński et al., 2015
Influenza A virus			
VEESSIGK	APC10. Anaphase-promoting complex subunit 10	Crucial for destroying cyclin B1, a marker of pancreatic cancer	Izawa and Pines, 2011; Zhou et al., 2014
LKPGDTII	CBS. Cystathionine β-synthase	Hyperhomocysteinemia, thrombosis, stroke, endocarditis	Ranawaka et al., 2001; Parnetti et al., 2002; Kelly et al., 2003; Jakubowski et al., 2008; Iossa et al., 2016; Mahale et al., 2017; Mazaheri et al., 2017
AESRKLLL	CCD92. Coiled-coil domain-containing protein 92	Susceptibility to type 2 diabetes and coronary heart disease	Zhao et al., 2017
LVLLVSLG	CD8B. T-cell surface glycoprotein CD8 β chain	Inversely associated with mortality in septic patients	Stojanov et al., 2011; Almansa et al., 2015
LVVGLISL	CXA4. Gap junction alpha-4 protein	Infertility. Myocardial infarction, hypertension	Guo et al., 2014; Zhao et al., 2014; Sheikhvatan et al., 2017; Bachelot et al., 2018
ALSRGFGS	EDC4. Enhancer of mRNA-decapping protein 4	Regulates IL-6 that relates to rheumatoid arthritis systemic juvenile	Seto et al., 2015
VLLCALAAA	GRM7. Metabotropic glutamate receptor 7	Susceptibility to attention deficit, autism, schizophrenia	Somogyi et al., 2003; Yang and Pan, 2013
NNGDDATA	PZRN3. E3 ubiquitin-protein ligase PDZRN3	Contributes to terminal myogenic differentiation	Ko et al., 2006; Lu et al., 2007; Sewduth et al., 2014
AELLVLLE	TITIN. Titin	Risk of cardiac failure, sudden cardiac death, and arrhythmia	Satoh et al., 1999; Matsumoto et al., 2005
Measles virus			
LLNEELEE	CC160. Coiled-coil domain-containing protein 160	–	
ADVEINPD	CFA47. Cilia- and flagella-associated protein 47	–	
AKELLESS	CP250. Centrosome-associated protein CEP250	Retinitis pigmentosa-deafness, Usher syndrome	Khateb et al., 2014
RLLDRLVR	DIA1. Deleted in autism protein 1 precursor. HASF	Associated with susceptibility to autism. Cardioprotector	Morrow et al., 2008; Aziz et al., 2011; Beigi et al., 2013; Bareja et al., 2017
GLLAIAGI	FXYD4. FXYD domain-containing ion transport regulator 4	Tissue-specific regulators of the ubiquitous Na,K-ATPase	Crambert and Geering, 2003
GSRRLVDV	KDM2B. Lysine-specific demethylase 2B. JHDM1B	Contributes to acute myeloid leukemia cell proliferation	Nakamura et al., 2013; Han et al., 2016
DKDTIEKL	RAC1. Ras-related C3 botulinum toxin substrate 1	Regulates dendritic spines, excitatory synapses	Dong et al., 2016
DKDTIEKL	RAC2. Ras-related C3 botulinum toxin substrate 2	Involved in atherosclerotic calcification	Ceneri et al., 2017
AVKRLRES	RBM43. RNA-binding protein 43	–	

Table 1 (continued)

Peptides[a] from[b]:	Human protein involved in the peptide sharing[c]	Functions/disease involvement[d]	References
SGFGPLIT	S12A1. Solute carrier family 12 member 1	Hypokalemic metabolic alkalosis; hypercalciuria	Simon et al., 1996
LSRPSPSA	YI025. Putative uncharacterized protein FLJ37218	–	
TCHRRRHT	ZN761. Zinc finger protein 761	–	
Mumps virus			
PTTSSFTT	ASAP1. Arf-GAP with SH3, ANK and PH domains	Regulates focal adhesions, cell spreading and migration	Chen et al., 2016
TGISSTIS	IGS10. Ig superfamily member 10 precursor	Controls migration of neurons expressing gonadotropin-releasing hormone	Howard et al., 2016
GSYRSVEL	KRIT1. Krev interaction trapped protein 1	Associates with stroke, seizures, and focal neurologic deficits	Kehrer-Sawatzki et al., 2002
TLSTSISA	LRIT3. Leu repeat, Ig-like domain, TM domain- protein3	Impaired night vision, nystagmus and myopia	Zeitz et al., 2013
GAAAQGQT	P4K2A. Phosphatidylinositol 4-kinase type 2-alpha	Regulator of vesicular trafficking and neurotransmission	Robinson et al., 2014
PTLTASQA	PHC3. Polyhomeotic-like protein 3	Lost in osteosarcoma tumors	Deshpande et al., 2007
DARGEHGNT	PLPL9. Calcium-independent phospholipase A2	Neurodegenerative disorder. Extrapyramidal dysfunction	Morgan et al., 2006
LRRSFSDH	RHG07. Rho GTPase-activating protein 7	Frequently deleted in human liver cancer	Yuan et al., 1998
QSLTPLPT	RN165. E3 ubiquitin-protein ligase RNF165	Regulator of motor axon elongation	van Wijk et al., 2009
VLKPGGLL	RRP8. Ribosomal RNA-processing protein 8	Part of the eNoSC complex that senses the cell energy status	Murayama et al., 2008
Rubella virus			
RKLATALA	ABCA7. ATP-binding cassette family A member 7	Alzheimer neurodegenerative disorder	Steinberg et al., 2015
PPLDEDGR	CDK2. Cyclin-dependent kinase 2	Essential for meiosis; involved in tumorigenesis	Berthet et al., 2003; Gopinathan et al., 2014
PSPPAPPR	GA2L2. Growth arrest-specific protein2-like2	Regulates apoptosis and cytoskeleton organization	Liebisch et al., 2017
SGDDSGRD	HIRP3. HIRA-interacting protein 3	Involved in chromatin function and histone metabolism	Assrir et al., 2007
PPPAPSPP	IRS4. Insulin receptor substrate 4	Altered in pediatric T-cell acute lymphoblastic leukaemia	Karrman et al., 2011
PAPSPPAP	K121L. Uncharacterized protein KIAA1211-like	–	–
PPQQPQPP	KAT6A. Histone acetyltransferase KAT6A	Acute myeloid leukemias and developmental delay	Deguchi et al., 2003; Arboleda et al., 2015
PPQQPQPP	KLF4. Krueppel-like factor 4	Inhibits neurogenesis	Moon et al., 2018
TPATAPAPC	KLH29. Kelch-like protein 29	Involved in cancer	Sun et al., 2017
PPPPAPSPP	KMT2B. Histone-lysine N-methyltransferase 2B	Required for memory formation. Involved in dystonia	Kerimoglu et al., 2013; Siow and Kumar, 2017; Gorman et al., 2018
AVGTARAG	OBSL1. Obscurin-like protein 1	3M syndrome	Hanson et al., 2009
PAPSPPAP	PBX4. Pre-B-cell leukemia transcription factor 4	Involved in acute lymphoblastic leukemia	Rosales-Aviña et al., 2011
APPPLPPA	SET1B. Histone-lysine N-methyltransferase SETD1B	Involved in intellectual disability, autism, epilepsy	Labonne et al., 2016
VAPRRPRD	SMAD6. Mothers against decapentaplegic homolog6	Protects from valvular and vascular cell calcification	Li et al., 2015
PSPPAPPR	SNTB2. B-2-syntrophin	Regulation of secretory granules	Schubert et al., 2010
RPAQRSAS	TATD2. Putative deoxyribonuclease TATDN2	–	

Table 1 (continued)

Peptides[a] from[b]:	Human protein involved in the peptide sharing[c]	Functions/disease involvement[d]	References
PPPPAPSP	UNC4. Homeobox protein unc-4 homolog	Connections of hypothalamic neurons to pituitary elements	Schneider et al., 2012
APPPLPPA	WASP. Wiskott-Aldrich syndrome protein	Immunodeficiency, thrombocytopenia, recurrent infections	Schindelhauer et al., 1996
PPPRRARR	WNK4. Serine/threonine-protein kinase WNK4	Hypertension, hyperkalemia, hyperchloremia	Heise et al., 2010; Wilson et al., 2001

[a]Nonapeptides formed by overlapping octapeptides given bold.
[b]Viral proteomes are described at http://www.uniprot.org (The UniProt Consortium, 2017).
[c]Proteins given as UniProtKB entry and name. Further details at http://www.uniprot.org.
[d]–, not defined.

Table 2: Immunopositive epitopic sequences containing octapeptides common to viral pathogens and human proteins (see Table 1).

IEDB ID[a]	Epitope[b]
1166	AESRKLLLi
1848	aiakledAKELLESS
11286	edAKELLESSdqilr
36538	liGLLAIAGIrlhraaiytaeihk
36890	lkikiaSGFGPLITh
52588	tpapkpsraPPQQPQPPrmqtgrg
54638	RLLDRLVRl
55937	rsqtpapkpsraPPQQPQPPrmqt
79241	gtPPLDEDGRwdpalmynpcgpeppahv
79399	sraPPQQPQPPrmqtgrggsaprpelgp
79981	pwyafALSRGFGS
80101	yafALSRGFGSgi
87732	qtpapkpsraPPQQPQPPrmqtgr
95697	pwyafALSRGFGSgiits
96007	wtynAELLVLLEnertld
128526	eirriwrqaNNGDDATA
129015	iwtynAELLVLLEnert
143419	keeirriwrqaNNGDDATAg
151075	ynAELLVLLEnertl
152823	nAELLVLLEnqktldehdan
152915	qiqdvwaynAELLVLLEnqk
182409	stvassLVLLVSLGa
188707	ldiwtynAELLVLLEnertl
238618	idiwtynAELLVLLEnertdfhds
489419	yLLKKLLQL
538658	fALSRGFGSg
538701	kvddgfldiwtynAELLVLLEnert
538781	vyqilaiystvassLVLLVSLGais
544981	rVLKPGGLLk
552793	ilvgtkldlrdDKDTIEKLkekklapi
552794	ilvgtkldlrdDKDTIEKLkekkltpi
638490	VLKPGGLLkv
723710	rVLKPGGLLkv

[a]Epitopes listed according to the IEDB ID number. Epitope details and references at www.immuneepitope.org/ (Vita et al., 2015).
[b]Peptide fragments common to viruses and human proteins are given in capital letters.

– histone acetyltransferase KAT6A may be a cause of acute myeloid leukemias (Deguchi et al., 2003) and developmental delay (Arboleda et al., 2015).

The evolutionary origin of the viral vs. human peptide matching: the viral eukaryogenesis hypothesis

On the whole, the data exposed lead to the question: what are the roots of the unexpected peptide commonality between viruses and the eukaryotic human cell, two entities which we consider to be the at the extremes of an evolutionary timeline measured in millions of years?

Viruses are ubiquitous molecular particles that have no metabolism, do not self-replicate and can multiply only within the living cells of a host (Koonin et al., 2015). In the common view, clinicians and immunologists consider viruses as harmful non-self entities that have to be fought and destroyed. However, viruses and humans do not seem to be in such hostile relationships. Rather, reporting *verbatim* from Forterre (2006): "*viruses played a critical role in major evolutionary transitions, such as the invention of DNA and DNA replication mechanisms, the formation of the three domains of life, or else, the origin of the eukaryotic nucleus*". Actually, viruses appear to have had a central role in the entire evolution of life (Villarreal and DeFilippis, 2000; Forterre, 2006; Villarreal and Witzany, 2010; Koonin and Dolja, 2013; Durzyńska and Goździcka-Józefiak, 2015).

De facto, Bell's papers (Bell, 2001, 2006, 2009, 2013) delineate the viral eukaryogenesis hypothesis, according to which and in the scenario outlined by the endosymbiotic theory (Margulis, 2010; Lazcano and Peretó, 2017), the eukaryotic cell descends from a consortium of three entities: an archaeon without nucleus and membrane-bound

organelles, which gave origin to the eukaryotic cytoplasm; a proteo-bacterium that invaded the archaeon cytoplasm and gave origin to the eukaryotic mitochondrion; and a virus, possibly a nucleocytoplasmic large DNA virus, that infected the archaeon and became the eukaryotic nucleus.

Conclusions

Mathematics, sequence similarity data and immunologic assays converge on describing 'a human self' that evolved from viral and bacterial proteins using the archaeal cytoplasm as a metabolic platform. Today, beyond the obvious difficulties of reconstructing a process that sinks its roots in millions of years ago and that developed under physico-chemical conditions far from the current ones, such an evolutionary context indicates that viruses and mammalian cells possibly evolved from a common primordial sequence pool, in this way offering the unique logical explanation for the massive peptide sharing that links viral and human proteins (Kanduc et al., 2008c).

Immunologically, such a million-years old interaction is protected by human immunotolerance, so that the immune system acts to defend from infectious agents while protecting the integrity of the human host. In fact, it seems that the mammalian immune system succeeds in avoiding the crossreactivity risk intrinsic to the sharing of peptide sequences with viral and microbial proteomes. Actually, a robust set of experimental data (Kanduc et al., 2004, 2007, 2008a,b; Polimeno et al., 2008; Kanduc, 2009, 2010a,b,c, 2012b; Lucchese et al., 2009a,b, 2010, 2012a,b; Stufano et al., 2010; Novello et al., 2012) show that, following infection, the anti-pathogen immune responses are generally directed against epitopic peptide sequences with low/no similarity to the host's proteome.

Hence, the described evolutionary scenario not only could further our understanding of autoimmune phenomena, but also casts a shadow on the current immunization practices and suggests that only immunizations based on peptide platforms that specifically barcode infectious agents are expected to specifically hit pathogens without the risk of harmful autoimmune crossreactions against the proteins of the human host.

Materials and methods

Sequence similarity analyses were conducted on the following viruses, with Tax ID, n° of proteins, and n° of aa in parentheses: Borna disease virus (928296; 6 proteins; 3014 aa); influenza A virus, subtype H1N1 (211044; 13 proteins; 4788 aa); measles virus (11235; 7 proteins; 4680 aa); mumps virus (11171; 8 proteins; 4977 aa); rubella virus (11045; 2 proteins; 3179 aa). The viral proteomes are described in detail at http://www.uniprot.org (The UniProt Consortium, 2017).

Viral aa sequences were dissected into octamers sequentially overlapping each other by seven residues, i.e. MQPSMSFL, QPSMSFLI, PSMSFLIG, and so forth. Then, each viral octamer was analyzed for occurrences within the human proteome using PIR match program (https://research.bioinformatics.udel.edu/peptidematch/index.jsp) (Chen et al., 2013). Human proteins hosting viral matches were recorded and analysed for functions and associated pathologies using Medline/PubMed.

Peptide sharing was analyzed for immunologic potential using the Immune Epitope Database (IEDB; www.iedb.org) resource (Vita et al., 2015). Epitopes that had been experimentally validated as immunopositive in the human host were considered.

Conflict of interest statement: None to declare.

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