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Review

From HBV to HPV: Designing vaccines for extensive and intensive vaccination campaigns worldwide

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ABSTRACT

HBsAg and HPV L1 proteins – the HBV and HPV antigens utilized in current vaccines – share amino acid sequences with human proteins such as cardiomyopathy-associated protein 5, titin, protein-arginine deiminase, E3 ubiquitin-protein ligase RNF19A, bassoon, G-protein coupled receptor for fatty acids, insulin isoform 2, and mitogen-activated protein kinase kinase kinase 10, *inter alia*. Many shared peptides are also part of immunopositive epitopes. The data 1) support the possibility of crossreactions between the two viral antigens and human proteins that, when altered, may associate with neuropsychiatric, cardiovascular and metabolic diseases such as multiple sclerosis, amyotrophic lateral sclerosis, diabetes, and sudden death; 2) confirm the concept that only vaccines based on sequences unique to pathogens might nullify potential crossreactivity risks in vaccination protocols.

Contents

1. Introduction

Since 2000 intensive research has been conducted on human and microbial proteins searching for immunogenic determinants [1–4] and crossreactive common sequences [5–9]. Such studies may have a special relevance to understand the host–pathogen interactions in relation to human diseases. As a matter of fact, host immune responses that follow a pathogen infection may cause crossreactions – and possibly autoimmune diseases – when host and pathogen share identical amino acid (aa) sequences [10–20]. Obviously, the higher the extent of sequence sharing, the greater will be the risk of incurring autoimmune damages and pathologic sequelae. These considerations hold in vaccination procedures too [21–29], especially when considering that vaccines use adjuvants to break the protective self-tolerance mechanisms that prevent harmful autoreactivity. Hence, crossreactions have to be expected when

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antigens with a high percent of sequence identity to host molecules are used in vaccine formulations [30].

Here, the concepts outlined above are investigated by analyzing viral antigens currently used in anti-HBV/HPV vaccines, i.e., the hepatitis B virus (HBV) surface antigen (sAg) and human papilloma virus (HPV) L1 proteins, for short peptides shared with human proteins. Indeed, aa groupings formed by only 5–6 residues are basic functional units in determining the specificity of the antigen–antibody recognition process [31,32]. As validated by the scientific literature, an antibody bound to an epitope covers about 15 aa on the surface of an antigen, with only ~5 of the antigen's aa contributing to the binding energy, and a change in any of the 5 key residues can greatly reduce the strength of antibody binding. Likewise, the paratope, i.e., the part of the antibody molecule that binds to an epitope, has about 15 aa, of which about 5 contribute most of the binding energy for epitope [33]. Currently, the concept that the immunological information of a protein antigen is packed into penta/hexapeptides is a basic datum in immunology [34–50]. Hence, our analyses used short sequences (hexa/heptapeptides) as immune modules to investigate and quantify the crossreactive potential between the viral antigens under analysis (HBsAg and HPV L1 proteins) and the human host. Results highlight a high extent of viral vs. human peptide overlap potentially able to induce crossreactions with human proteins exerting crucial functions in the human host.

2. Methods

Analyses were conducted on (i) HBV large envelope protein (HBsAg; UniProtKB/Swiss-Prot: P17101) from hepatitis B virus, genotype A2, subtype adw2 (isolate Germany/991/1990) (HBV-A), and (ii) HPV L1 from strains 6, 11, 16, 18 with UniProtKB accessions and length in parentheses as follows: 6 (P69899, VL1_HPV6B, 500 aa), 11 (P04012, VL1_HPV11, 501 aa), 16 (P03101, VL1_HPV16, 531 aa), and 18 (P06794, VL1_HPV18, 568 aa).

HBsAg and HPV L1 proteins were searched for peptide matching with the human proteome according to described methodologies [1–9]. In brief, viral aa primary sequences were dissected into hexapeptides (or heptapeptides) sequentially overlapped by five (or six) residues. Viral hexa- or heptapeptides were used to search the human proteome for exact matches by PIR perfect match program [51].

Epitopes that had been validated as immunopositive in humans were retrieved from the Immune Epitope Database and Analysis Resources (IEDB) (http://www.immuneepitope.org/) [52].

3. Potential adverse events related to HBsAg vaccine

3.1. Peptide sharing between HBsAg and the human proteome

Fig. 1 graphically illustrates the HBsAg vs. human hexapeptide sharing by showing the number of occurrences in human proteins for each HBsAg hexapeptide. It can be seen that viral peptide stretches absent in the human proteome alternate with viral peptide sequences repeatedly present in human proteins. In general, HBsAg hexapeptides are unequally distributed as emphasized, for example, by the HBsAg PAGGSSSGT sequence (aa 142–150) formed by 4 consecutively overlapping hexapeptides shared with numerous human proteins for a total of 45 matches (see oval in Fig. 1).

3.2. Potential crossreactivity of the peptide sharing between HBsAg and the human proteome

The hexapeptide sharing between HBsAg and the human proteome (Fig. 1) represents a potential epitopic crossreactome. Indeed, exploration of IEDB shows that many of the shared hexapeptides are part of experimentally validated HBsAg epitopes, i.e., have an immunologic potential. This supports the possibility that the immune response against HBsAg may crossreact with human proteins with consequent pathologic autoimmune sequelae. Actually, the hexapeptide

- GWSPQA (aa 76–81) is shared with the epididymal-specific lipocalin-12 protein (LCN12) and hosted in five HBsAg epitopes (IEDB IDs: 19913, 20999, 23289, 23290, and 37376). LCN12 is involved in male fertility [53];
- PPLRDS (aa 110–115) is shared with 9 proteins associated with spermatogenesis (S31A1, S31A2, S31A3, S31A4, S31A5, S31A6, S31A7, S31C1, and S31C2) and is present in three HBsAg epitopes (IEDB IDs: 4802, 46957, 48830);
- TPISPP (aa 106–111) is shared with the histone-lysine N-methyltransferase 2D (KMT2D) and is part of two HBsAg epitopes (IEDB IDs: 4802 and 46957). KMT2D alterations may underlie mental retardation [54];
- HQALQD (aa 128–133) is present in protein-arginine deiminase type-4 (PADI4) as well as in three HBsAg epitopes (IEDB IDs: 42428, 42436, and 42437). PADI4 may be involved in rheumatoid arthritis [55] and in multiple sclerosis [56].

3.3. HBsAg sequences as epitopic spaces for multiple autoimmune attacks

In addition, clusters of hexapeptides shared between HBsAg and crucial human proteins may occur in HBsAg-derived epitopes. E.g., the octapeptide $HBsAg_{216–223}$LGGSPVCL is present in two HBsAg epitopes (IEDB IDs: 10274 and 66309) and consists of three sequentially overlapped hexapeptides of which: i) LGGSPV is present in advillin (AVIL), a Ca^{2+}-regulated actin-binding protein with unique function in the morphogenesis of neuronal cells which form ganglia [57], and in doublesex- and mab-3-related transcription factor 1 (DMRT1) that plays a key role in male sex determination and differentiation by controlling testis development and male germ cell proliferation [58];

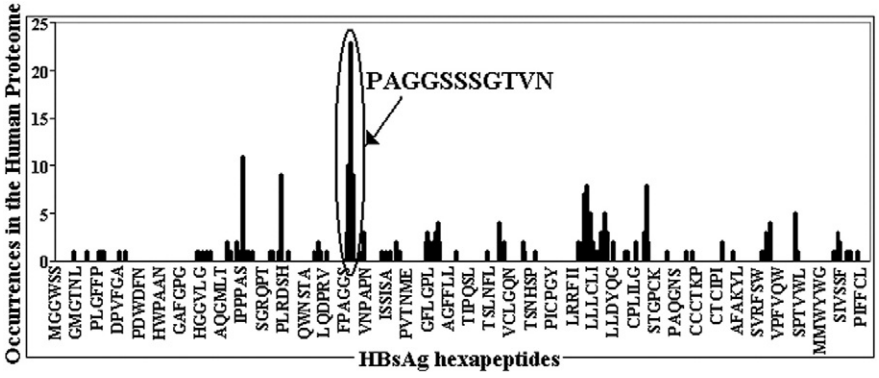

Fig. 1. Intensive and uneven distribution of HBsAg hexapeptides throughout the human proteome. The oval refers to the hexapeptide match cluster along the $HBsAg_{142–152}$PAGGSSSGTVN sequence. Analyses conducted on HBsAg, UniProtKB/Swiss-Prot: P17101.

Table 1
Human proteins sharing hexapeptides with $HBsAg_{142–152}$PAGGSSSGTVN undecapeptide.

Hexapeptide[a]	Human proteins[b,c,d]
PAGGSS	DLEC1; FOXE1; NRG2
AGGSSS	CBPC5; CCNL1; CXXC5; INSR2; K1C24; NRG2; PRGR; RN19A; SPSB2; TM131
GGSSSG	ANKS6; BHE22; CCNL1; CNTN3; COLC2; CRML; DMKN; DNJB8; ERF3A; **K1C10**; K1C25; K22E; K2C7; LMO7; M3K10; MYO15; OVOL2; PPR29; RIMB1; RN19A; RNF12; TWST1; ZBTB4
GSSSGT	AFF4; ANKS6; ARHGF; ARI3B; CCNL1; KCNN2; M3K11; MYO15; TGM1
SSSGTV	ANK2; ATP7A; MTF1; CMYA5
SSGTVN	BAG4; ATP7A

[a] Aa sequences in one-letter code.
[b] Human proteins listed as UniProtKB/Swiss-Prot accession names; further details at www.uniprot.org [65].
[c] Proteins sharing more than one hexapeptide with $HBsAg_{142–150}$PAGGSSSGT are given underlined.
[d] K1C10, which contains four GGSSSG sequence (aa pos: 515–520, 523–528, 549–554, 559–564), is given boldface.

ii) GGSPVCL is present in bassoon (BSN), a presynaptic cytomatrix protein that regulates neurotransmitter release from a subset of brain glutamatergic synapses [59]; iii) GSPVCL is present in the G-protein coupled receptor for fatty acids (FFAR1). FFAR1 plays an important role in glucose homeostasis since fatty acid binding increases glucose-stimulated insulin secretion, and may also enhance the secretion of glucagon-like peptide 1 [60].

Even more strikingly, the $HBsAg_{142–152}$PAGGSSSGTVN sequence (see oval in Fig. 1) is present in six HBsAg epitopes (IEDB IDs: 17255, 21221, 46013, 56394, 70732, and 74853) [61–64] and consists of six consecutively overlapping hexapeptides shared with numerous human proteins for a total of 54 matches. The human proteins involved in the peptide sharing are listed in Table 1.

Immunologically, anti-HBsAg immune responses that hit the epitope PAGGSSSGTVN may also trigger a crossreactivity network potentially able to cause multiple and apparently unrelated diseases, depending on the human autoantigen(s) involved in the crossreaction(s). Examples of diseases that might derive from alterations of hittable human autoantigens are the following ones, with autoantigens given as UniProtKB/Swiss-Prot accession entries in parentheses:

- neurological diseases, including stroke, amyotrophic lateral sclerosis and increased susceptibility to schizophrenia (CCNL1, cyclin-L1; NRG2, pro-neuregulin-2; KCNN2, small conductance calcium-activated potassium channel protein 2; RIMB1, peripheral-type benzodiazepine receptor-associated protein 1; CMYA5, cardiomyopathy-associated protein 5) [66–72];
- amyotrophic lateral sclerosis might result from an immune attack against E3 ubiquitin-protein ligase RNF19A, a ligase that specifically ubiquitinates and degrades pathogenic superoxide dismutase (SOD1) variants, thus leading to neuronal protection [73];
- nonsyndromic deafness (Myo15, unconventional myosin-XV) [74];
- muscular dystrophies and cardiomyopathy (CMYA5, cardiomyopathy-associated protein 5) [75,76];
- coronary artery aneurysms (KCNN2, small conductance calcium-activated potassium channel protein 2) [77];
- type 1 diabetes and insulin resistance (INSR2, insulin isoform 2; M3K10, mitogen-activated protein kinase kinase kinase 10) [78–80];
- deregulated retinal angiogenesis (ARHGF, Rho guanine nucleotide exchange factor 15) [81];
- erythroderma, hyperkeratosis, blistering, and abnormal skin scaling (K1C10, K1C24, K1C25, K22E, and K2C7: cytoskeletal keratins; TGM1, protein-glutamine gamma-glutamyltransferase K) [82–84];
- increased expression of the human papillomavirus type 16 E7 mRNA (K2C7, keratin type II cytoskeletal 7) [85];
- breakdown of tumor suppression mechanisms (DLEC1, deleted in lung and esophageal cancer protein 1) [86]. And so forth.

4. Potential adverse events related to HPV L1 vaccines

4.1. Hexapeptide sharing between HPV16 L1 and the human proteome

The hexapeptide sharing between HPV16 L1 and human proteins is outlined in Fig. 2 that shows results similar to those obtained in HBsAg analyses. Indeed, Fig. 2 illustrates an uneven distribution of HPV16 L1 hexapeptides throughout the human proteome, with peptide stretches unique to L1 protein and viral peptides repeatedly shared with human proteins.

4.2. Heptapeptide sharing between L1 proteins from HPV strains 6, 11, 16, 18, and the human proteome

Expanding sequence analyses to the four HPV L1 antigens utilized in current anti-HPV vaccines (namely L1 proteins from HPV strains 6, 11, 16, and 18) highlights a vast viral vs. human hexapeptide overlap, the dimension of which precludes detailed match-by-match analyses and leads to use more stringent sequence probes such as heptapeptides. Results are reported in Table 2. It can be seen that 60 heptapeptides are shared between HPV L1s and human proteins involved in a wide array of crucial cellular functions such as transcription (BACH2, SPT6H, TF3C1, PBX4, and TFE3); spermatogenesis (S31C1 and S31C2; and meiosis 1 arrest protein or spermatogenesis-associated protein or M1AP); tumor suppression (NFKB2), and cardiac muscle contraction (titin protein), *inter alia*.

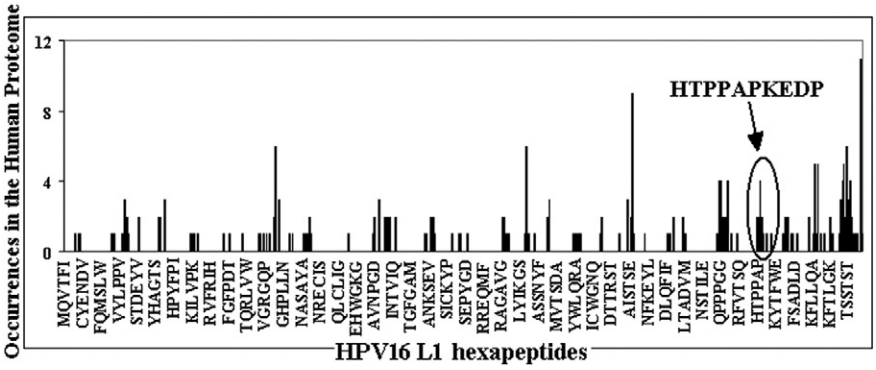

Fig. 2. Intensive and uneven distribution of HPV16 L1 hexapeptides throughout the human proteome. The oval refers to the hexapeptide match cluster along the $HPV16\ L1_{457–466}$HTPPAPKEDP sequence. Analyses conducted on HPV16 L1, UniProtKB/Swiss-Prot: P03101.

Table 2
Heptapeptide sharing between L1 proteins, HPV strains 6, 11, 16, 18, and the human proteome.

Heptapeptide[a]	Strain[b]	Human proteins[c]
AAISTSE	16	ANR11. Ankyrin repeat domain-containing protein 11
AGTSRLL	16	DISP2. Protein dispatched homolog 2
ALPDSSL	6; 11	ABCA7. ATP-binding cassette sub-family A member 7
ARVVNTD	18	SDE2. Protein SDE2 homolog
ASSSRLL	6; 11	CASR. Extracellular calcium-sensing receptor precursor
ASVSKSA	11	USH2A. Usherin precursor
ATDAYVK	11	PERF. Perforin-1 precursor
ATTSSKP	18	TM108. Transmembrane protein 108
AVGENVP	16	BACH2. Transcription regulator protein BACH2
DTVPQSL	18	S31C1. Spermatogenesis-associated protein 31C1 S31C2. Spermatogenesis-associated protein 31C2
EKFSADL	16	SPT6H. Transcription elongation factor SPT6
FGVPPPP	18	CPSF7. Cleavage and polyadenylation specificity factor subunit 7
FKQYSRH	18	M1AP. Meiosis 1 arrest protein; Spermatogenesis-associated protein 37
FLQMALW	18	RN213. E3 ubiquitin-protein ligase RNF213
GDTVPQS	18	Q4W4Y1. Dopamine receptor interacting protein 4 PDC6I. Programmed cell death 6-interacting protein
GSGSTAN	16	RCBT1. RCC1 and BTB domain-containing protein 1
GVPPPPT	18	KHDR1. KH domain-containing, RNA-binding, signal transduction-associated protein 1
HPYYSIK	11	H9M5E1. Cytochrome b
IILFLRN	18	CH3L2. Chitinase-3-like protein 2 precursor
KATPTTS	16	C1QR1. Complement component C1q receptor precursor
KFLLQSG	6; 11	ANR16. Ankyrin repeat domain-containing protein 16
KFSSELD	6; 11	B7Z3L9. Polypeptide N-acetylgalactosaminyltransferase 11
KGSGSTA	16	INO80. DNA helicase INO80
KSEVPLD	16	ELMO3. Engulfment and cell motility protein 3
KTVVPKV	6; 11	TITIN. Titin
LCASVTT	6	MUC12. Mucin-12 precursor
LKEKFSS	6; 11	TF3C1. General transcription factor 3C polypeptide 1
LPPPSVA	18	NED4L (isoform 5). E3 ubiquitin-protein ligase NEDD4-like
LQFIFQL	6;11;16;18	APOB. Apolipoprotein B-100 precursor
LQPPPGG	16	SHRPN. Sharpin PBX4. Pre-B-cell leukemia transcription factor 4
LRNVNVF	18	UEVLD. Ubiquitin-conjugating enzyme E2 variant 3
NRSSVAS	11	HELZ2. Helicase with zinc finger domain 2
NRTSVGS	6	TMPS7. Transmembrane protease serine 7
PAVSKAS	6	TFE3. Transcription factor E3
PGGTLED	16	TCPQM. Putative T-complex protein 1 subunit theta-like 2
PPPPTTS	18	SHAN1. SH3 and multiple ankyrin repeat domains protein 1
PPSVARV	18	COQ6. Ubiquinone biosynthesis monooxygenase COQ6 PDE8B. High affinity cAMP-specific, 3′,5′-cyclic phosphodiesterase 8B
PTIGPRK	18	TSNA1. t-SNARE domain-containing protein 1
PTPEKEK	6;11	E2AK1. Eukaryotic translation initiation factor 2-alpha kinase 1
PTPSGSM	16	ANR53. Ankyrin repeat domain-containing protein 53
PVPVSKV	16	EPS8. Epidermal growth factor receptor kinase substrate 8
PVSKVVA	6; 11	FMN1. Formin-1
QLFVTVV	6; 16; 18	ANR17. Ankyrin repeat domain-containing protein 17
RTSVGSS	6	NBPFL. Neuroblastoma breakpoint family member 21 PCLO. Protein piccolo
RVQLPDP	18	NALP6. NACHT, LRR and PYD domains-containing protein 6
SDSQLFN	18	CUL9. Cullin-9
SGNRTSV	6	STX2. Syntaxin-2
SGSGGNP	6	SNRK. SNF-related serine/threonine-protein kinase
SGSLVSS	6; 11	E2AK3. Eukaryotic translation initiation factor 2-alpha kinase 3
SLVDTYR	18	NFKB2. Nuclear factor NF-kappa-B p100 subunit
SPSPSGS	18	D6REQ2. Protein FAM193B
SSSRLLA	6; 11	MYCB2. Probable E3 ubiquitin-protein ligase MYCBP2
SVAITCQ	18	RNAS8. Ribonuclease 8 precursor
TLQANKS	16	LAMA1. Laminin subunit alpha-1 precursor
VARVVNT	18	Q13876. Bone-derived growth factor
VNKTVVP	11	ZN711 (isoforms 2 and 3). Zinc finger protein 711
VPKVSGL	16	FBSL. Fibrosin-1-like protein
VSGHPFL	6	EZH1. Histone-lysine N-methyltransferase EZH1
VTSDSQL	18	OR4D2. Olfactory receptor 4D2
VYSPSPS	18	RPGP2. Rap1 GTPase-activating protein 2

[a] Shared heptapeptides given in 1-letter code and listed in alphabetical order.
[b] Analyses conducted on L1 from HPV strains 6, 11, 16, and 18. See details under Section 2.
[c] Human proteins given as UniProtKB/Swiss-Prot entry names (http://www.uniprot.org/).

4.3. Potential crossreactivity of the peptide sharing between HPV L1s and the human proteome at the heptapeptide level

The viral vs. human peptide sharing described in Fig. 2 and Table 2 suggests that immune responses against HPV L1 proteins might crossreact with numerous and different human proteins, thus opening the door to many and different pathologies. *Ad adiuvandum*, Table 3 shows that 18 out of the 60 L1 heptapeptides listed in Table 2 are also present in 25 epitopes experimentally validated as immunopositive in humans [87–96].

4.4. Potential pathologic sequelae associated with HPV L1 vs. human crossreactivity at the heptapeptide level

Data from Tables 2 and 3 suggest that immune response(s) against HPV L1 proteins might crossreact with 20 human proteins and lead to disorders and pathologies that depend on the function(s) exerted by the human proteins. More specifically:

- cardiovascular disorders and sudden death might arise from alterations of APOB, C1QR1, CASR, NALP6, and TITIN since
  - alterations of APOB (or Apolipoprotein B-100) may be linked to disorders of lipoprotein metabolism leading to hypertension, hypercholesterolemia and increased proneness to coronary artery disease [97,98];
  - alterations in C1QR1 (or complement component C1q receptor or cluster differentiation antigen CD93) have been associated with risk of coronary artery disease [99], moreover, being C1QR1 allocated on platelets [100], an immune attack against C1QR1 might lead to thrombocytopenia;
  - alterations of CASR (parathyroid cell calcium-sensing receptor) have been associated with coronary heart disease, myocardial infarction, and cardiovascular mortality [101];
  - defects of NALP6 (or angiotensin II/vasopressin receptor) are related to hypertension [102];
  - interference with TITIN functionality might cause fatal cardiomyopathy, hypotonia, muscle weakness, ventricular dilation and impaired systolic function, resulting in congestive heart failure, arrhythmia, dyspnea, syncope, collapse, palpitations, and chest pain. This pathologic sequela is readily provoked by exercise [103–105];
- hypercalcemia, epilepsy, pancreatitis, and diabetes: CASR, when altered, may be also involved in additional disparate and unrelated pathologies. CASR senses changes in the extracellular concentration of calcium ions. Alterations affecting CASR may cause diseases such as hypercalcemia, chondrocalcinosis, hypercalciuria with nephrocalcinosis; hypocalcemia; paresthesias; basal ganglia calcifications; epilepsy with seizure types that may include myoclonic seizures, absence seizures, febrile seizures, complex partial seizures, and generalized tonic–clonic seizures [106–108]; altered CASR may also be related to pancreatitis and diabetes [109,110];
- myelination and diabetes: E2AK3 (or pancreatic eukaryotic translation initiation factor 2-alpha kinase 3, also called PERK) is involved in the regulation of myelination [111]. Moreover, defects of E2AK3 associate with Wolcott–Rallison syndrome, a disorder with infancy-

Table 3
HPV L1 heptapeptides shared with human proteins and also present in immunopositive epitopes.

Epitope ID[a]	Epitope[b]	Immune context	Ref.[c]	Potentially crossreactive human target(s)[d]
109716	pPVPVSKVvstdeyvartniyyha	HLA-DR4Dw4	[87]	EPS8
110012	tviqdgdmvhtgfgamdftTLQANKS	HLA-DR4Dw4	[87]	LAMA1
110454	vsayqyrvfRVQLPDP	HLA-DR4Dw4	[87]	NALP6
110696	qsqaitcqkPTPEKEKpdpyk	B cell	[88]	E2AK1
110863	glkakpkftlgkrKATPTTS	B cell	[89]	C1QR1
110965	pnnnkilVPKVSGLqyrvfr	B cell	[90]	FBSL
111581	ngicwgnQLFVTVVdttrst	B cell	[91]	ANR17
111585	nKSEVPLDictsickypdyi	B cell	[91]	ELMO3
111915	vhtgfgamdftTLQANKSev	B cell	[91]	LAMA1
112377	vfRVQLPDPnkfglp	HLA-Class II	[92]	NALP6
112526	glevgrgqplgvgVSGHPFL	HLA-Class II	[92]	EZH1
112530	grssirtgvkrPAVSKASaa	HLA-Class II	[92]	TFE3
112532	gvgVSGHPFLnkyddvensg	HLA-Class II	[92]	EZH1
112547	ikranKTVVPKVsgyqyrvf	HLA-Class II	[92]	TITIN
112552	itcqkPTPEKEKpdpyknls	HLA-Class II	[92]	E2AK1
112556	kaqghnngicwgnQLFVTVV	HLA-Class II	[93]	ANR17
112576	lfvtvvdttrstnmtlcASVSKSAtytnsdykeymrhve	HLA-Class II	[93]	USH2A
112606	mwrpsdstvyvppppnPVSKVVATDAYVKrtnif	HLA-Class II	[93]	FMN1; PERF
112618	pdpnkfALPDSSLfdpttqrlvwactglevgrgqpl	HLA-Class II	[93]	ABCA7
112663	siyvhtpSGSLVSSe	HLA-DR	[93]	E2AK3
112676	tnifyhASSSRLLAv	HLA-DRB1*07:01	[93]	CASR; MYCB2
112677	tniyyhAGTSRLLav	HLA-Class II	[93]	DISP2
112683	tpSGSLVSSeaqlfn	HLA-Class II	[94]	E2AK3
147941	LQFIFQLck	HLA-A11	[95]	APOB
176936	aePTPEKEKrf	HLA-B*44:27	[96]	E2AK1

[a] Epitopes experimentally validated as immunopositive and containing heptapeptides shared between HPV L1 and human proteins (see Table 2) were retrieved from IEDB (http://www.iedb.org), and are listed according to IEDB IDs.
[b] Epitope sequences given in 1-letter code with fragments common to viral and human proteins given in capital letters.
[c] Epitope reference(s); further details at http://www.iedb.org/idsearch.php.
[d] Human proteins reported as UniProtKB/Swiss-Prot entry names.

onset diabetes mellitus, osteopenia, mental retardation, and hepatic and renal dysfunction [112];
- seizures and ataxia: PERF (or perforin) promotes cytolysis and apoptosis of virus-infected or neoplastic cells. Alterations in PERF protein may associate with hemophagocytic lymphohistiocytosis, a disorder characterized by immune dysregulation with hypercytokinemia. Clinically, the features may include fever, hepatosplenomegaly, and neurological abnormalities such as irritability, hypotonia, seizures, and ataxia [113,114];
- vision and hearing disorders: USH2A. Immune crossreactivity with the usherin protein (USH2A) might underlie the temporary vision and hearing loss that often accompanies anti-HPV vaccine administration (http://www.cdc.gov/vaccines/hcp/vis/vis-statements/hpv-gardasil.html). In fact, usherin alterations may be associated to pigmentary retinopathies with night vision blindness and loss of midperipheral visual field and hearing impairment [115,116].
- spermatogenesis: Eps8. Suppression of the expression of Eps8 (epidermal growth factor receptor kinase substrate 8) appears to disrupt spermatogenesis [117–119];
- cancer and neurological disorders: MYCB2. The E3 ubiquitin-protein ligase MYCBP2 is exceptionally abundant in brain and thymus. Can function as an E3 Ub ligase toward the tumor suppressor tuberin, thus regulating cell growth and proliferation as well as neuronal function [120].

5. "The vaccine": using peptides unique to pathogens

As a main perspective, the data exposed above further support the concept that only using peptides unique to the antigen can lead to vaccine preparations exempt from the crossreactivity risk [9]. The concept is graphically illustrated in Fig. 3. Moreover, as already discussed elsewhere [1,5,9,30–32], applying such a principle might also lead to the

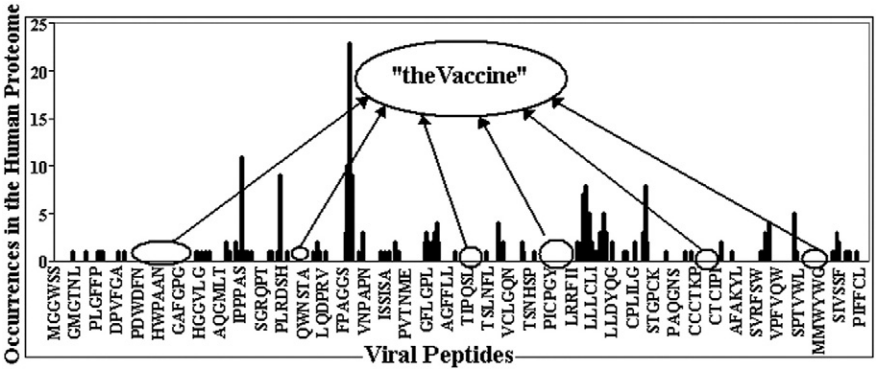

Fig. 3. Vaccines based on peptide sequences uniquely owned by pathogens and absent in host proteins may open the way to highly specific immunotherapies exempt of collateral crossreactions.

elimination of vaccine adjuvantation procedures. Indeed, peptides uniquely owned by pathogens will presumably evoke powerful immunogenic response in the human host to by being unknown to the human host, this way representing the "non-self" that can elude the immunosuppressive tolerogenic mechanisms of the host [9,121–123]. That would allow the possibility of repeated vaccinations too. In synthesis, vaccines based on the principle of peptide uniqueness would be endowed by a highest level of immunogenicity and the maximum safety, thus offering the concrete tool for effective eradication of infectious diseases in the world.

6. Conclusions

Using HBsAg and HPV L1 antigens as models, this study analyzed the viral vs. human peptide overlap to evaluate the potential crossreactivity impact of immune responses evoked by HBV and HPV vaccines in the human host. Three main points emerge as follows.

Firstly, HBsAg and HPV L1 peptides are sparse among human proteins that play crucial roles in cardiovascular functions, myelination, spermatogenesis and so forth. Secondly, many of the shared peptides are part of validated experimental epitopes endowed with immunogenic potential, thus making crossreactions a possible event. Hence, this study depicts a crossreactivity context that might contribute to determine the undesired collateral damages that have been related to the immune response against HBV and HPV [24–29,124–152]. As a third point, it has to be underlined that the data illustrated here are a marked underestimation of the potential crossreactivity that may arise following exposure to HBV and HPV antigens. Indeed, the sequence analyses used in the present study utilized hexa- and heptapeptide units as search probes whereas, as discussed above [31–51], a grouping of 5 aa residues may represent a minimal unit of immune recognition in cellular and humoral responses. In the present context, an illustrative example is the HBsAg KPTDG pentapeptide, a B-cell epitope (IEDB ID: 32889) [153] that is shared with angiotensin-converting enzyme (ACE). ACE is involved, when altered, in ischemic stroke, microvascular complications of diabetes, and intracerebral hemorrhage [154], so that an immune crossreaction centered on the pentapeptide KPTGD may have pathologic consequences. Another case in point is the HPV16 L1-derived ACQKH epitope (IEDB ID: 112442) [155], which is shared with the human transcription factor rhombotin-2 (also known as LMO2), expression of which is correlated with longer survival in diffuse large-B-cell lymphoma [156].

In essence, this study offers a scientific rationale to explain the adverse events related to immunizations procedures and invites to undertake new approaches in vaccinology. Possibly only vaccines based on sequences unique to pathogens might allow immunotherapies exempt of risks for the human host [9,121–123].

Take-home messages

- Harmful autoimmune reactions may accompany preventive and therapeutic vaccinations
- Crossreactions between vaccine antigens and human proteins may be at the root of the harmful autoimmune reactions
- Using peptides unique to pathogens and absent in human proteins may lead to safe and effective vaccines

Conflicts of interest

None.

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