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RESEARCH ARTICLE

Inter-Pathogen Peptide Sharing and the Original Antigenic Sin: Solving a Paradox

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Abstract:

Aims:

To analyse the peptide commonality among viral, bacterial, and protozoan pathogens, and the immunopathologic consequences in the human host.

Methods:

HPV16, HCMV, *C. diphtheriae*, *B. pertussis*, *C. tetani*, *T. gondii*, and *T. cruzi* were analysed for common amino acid sequences that are additionally shared with the human host. The pentapeptide, a minimal immune determinant in humoral and cellular immune recognition, was used as a measurement unit of the peptide similarity level. Molecular modeling was applied to compare the amino acid contexts containing common minimal determinants.

Results:

Twenty-nine pentapeptides were found to occur, even hundreds of times, throughout the analyzed pathogen proteomes as well as in the human proteome. Such vast peptide commonalities together with molecular modeling data support the possibility that a pre-existing immune response to a first pathogen can be boosted by a successive exposure to a second different pathogen, *i.e.*, the primary response to a pathogen can be transformed into a secondary response to a previously encountered different pathogen. Two possible consequences emerge. Firstly, no responses might be elicited against the pathogen lastly encountered either by infection or active immunization, but reactions could occur only with the early sensitizing pathogen, which is no more present in the organism. Secondly, the immune response boosted by the pathogen lastly encountered will find a way out by cross-reacting with human proteins.

Conclusion:

This study might explain the “original antigenic sin” phenomenon described seven decades ago [Francis T. Jr. Ann Intern Med 1953;39:203], thus providing explanations for vaccine failures and offering possible clues for designing successful vaccines.

Keywords: Peptide commonality, Infectious pathogens, Crossreactivity, Primary immune response, Secondary immune response, Molecular modeling, Original antigenic sin, Vaccine failures, Autoimmunity.

1. INTRODUCTION

Infections are risk factors for a large spectrum of autoimmune disorders [1 - 15]. Likewise, active immunization may also cause collateral autoimmune events [16] and, in addition, result in the production of a waning/weak immunity [17 - 24]. The issue is of crucial importance, especially when considering the necessity of reinforcing the immune defence of the human population from the intensifying assault of old and new microbial threats [25 - 27].

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In this context, since 2000 [28], this lab repeatedly documented a high level of peptide sharing between pathogen and human proteins [29 - 37], in this way highlighting the risk for cross-reactivity in the human host following infections or active immunization [38 - 41].

The present study further analyzes the amino acid (aa) sequences common to potential pathogens evolutionarily different such as viruses, bacteria and protozoans. The specific question faced here is: given the massive peptide overlap that characterizes the protein world [35], there are peptide commonalities among viruses, bacteria and protozoans that might confound, intensify or weaken the human immune responses that follow infection/active immunization? Searching for answers, we used HPV16 infection/immunization as a research model and the pentapeptide as an operational unit, and define the potential immunologic impact that previous pathogen infections/immunizations might have on the human anti-HPV16 immune responses.

2. METHODS

The following pathogens were analyzed, with Taxonomy ID in parentheses: HPV16, 9 proteins, 2600 aa (333760); HCMV, 168 proteins, 63 460 aa (295027); *C. diphtheriae*, 2265 proteins, 724 668 aa (257309); *C. tetani*, 2415 proteins, 809 352 aa (212717); *B. pertussis*, 3783 proteins, 812 989 aa (520); *T. gondii*, 8404 proteins, 6 625 207 aa (432359); *T. cruzi*, 19242 proteins, 9 424 566 aa (353153). *H. sapiens* proteome consisted of 70941 proteins at the time of this study. Proteomes are described at <http://www.uniprot.org/> [42]. Peptide matching was carried out using PIR Peptide Match program (<http://research.bioinformatics.udel.edu/peptidematch/>) [43].

The immunologic potential of the peptide sharing among infectious pathogens and the human host was investigated using the Immune Epitope Database (IEDB; www.iedb.org) resource [44]. Only epitopes experimentally validated as immunopositive in the human host were considered.

PEP-FOLD3 program (<http://bioserv.rpbs.univ-paris-diderot.fr/services/PEP-FOLD3/>) [45 - 47] was used to obtain 3D peptide structures from linear aa sequences.

3. RESULTS AND DISCUSSION

HPV16 was chosen as a research model since papillomavirus infection or active immunization mostly occur in sexually active subjects [48] or in girls and boys aged 11-12 years [49], *i.e.*, in individuals that have an immunologic past of encounters with numerous infectious agents. The pathogens HCMV, *C. diphtheriae*, *C. tetani*, *B. pertussis*, *T. gondii*, and *T. cruzi* were chosen to analyze the molecular basis of the impact of previous infections/immunizations since scientific-clinical literature and immunization protocols pose the first encounter with such pathogens early in the human life [50 - 53]. Analyses were conducted as already described in detail [54, 55] utilizing the pentapeptide as a measurement unit because a grouping of five residues is endowed with immunogenicity and antigenicity, and can act as a minimal immune determinant in humoral and cellular immune recognition [54 - 65].

3.1. Occurrences of HPV16 Pentapeptides in HCMV, *C. diphtheriae*, *C. tetani*, *B. pertussis*, *T. gondii*, *T. cruzi*, and *H. sapiens* Proteomes

Primary aa sequences corresponding to the 9 HPV16 proteins were dissected into pentapeptides overlapping by four residues each other (eg, MQVTF, QVTFL, VTFLY, TFLYI, and so forth). Each HPV16 pentapeptide was probed for occurrences within HCMV, *C. diphtheriae*, *C. tetani*, *B. pertussis*, *T. gondii*, *T. cruzi*, and *H. sapiens* proteomes. Results are shown in Table 1.

Remarkably, Table 1 shows that HPV16 shares pentapeptides with all of the 7 analyzed proteomes. Even more relevant, HPV16 is more similar to the human host than to HCMV, by being 94% the pentapeptide identity between HPV16 and the human host in front of the 5% pentapeptide identity with HCMV. In other words, only 152 pentapeptides differentiate HPV16 from the human host, whereas 2278 pentapeptides phenetically divide HPV16 from HCMV.

Moreover, Table 1, column 2, indicates that the shared HPV pentapeptides repeatedly occur in the analyzed proteomes. The distribution and multiple occurrences of HPV16 pentapeptides in the analysed pathogens and in the human host are detailed in Table S1.

Table 1. Occurrences of HPV16 pentapeptides in HCMV, *C. diphtheriae*, *C. tetani*, *B. pertussis*, *T. gondii*, *T. cruzi*, and *H. sapiens* proteomes. Column 1: HPV pentapeptide occurrences; Column 2: HPV pentapeptide occurrences (including multiple ones); Column 3: percent of similarity of HPV16 at the pentapeptide level.

Proteome From:	1	2	3*
HCMV	123	271	5
<i>C. diphtheriae</i>	747	1222	31
<i>C. tetani</i>	716	1193	30
<i>B. pertussis</i>	1041	5656	43
<i>T. gondii</i>	1832	18181	76
<i>T. cruzi</i>	1847	17681	77
<i>H. sapiens</i>	2249	102095	94

*% of identical pentapeptides was obtained by dividing the n° of HPV16 pentapeptide occurrences in the proteome (column 1) by the n° of total HPV16 pentapeptides (that is, 2401). Example: the % pentapeptide identity between HCMV and HPV16 proteomes is given by 123/2401, ie, 5% [60].

3.2. Twenty-nine Pentapeptides are Common to HPV16, HCMV, *C. diphtheriae*, *C. tetani*, *B. pertussis*, *T. gondii*, *T. cruzi*, and *H. sapiens*

The 123 pentapeptides common to HPV16 and HCMV (Tables 1 and S1) were tested for occurrences in *C. tetani*, *C. diphtheriae*, *B. pertussis*, *T. gondii*, *T. cruzi*, and the human host. The comparative analysis revealed a common core consisting of 29 pentapeptides, all of which occur at different extent in the 7 analyzed proteomes (Table 2).

As regards the human proteome, the 29 pentapeptides common to the analyzed pathogens are dislocated in 1310 human proteins that are described in Table S2. *Ictu oculi*, space does not permit a detailed analysis of the human proteins involved in the microbial peptide sharing. An extreme example is the 5-mer GGS GG, which occurs 215 times throughout the human proteome (see Tables 2 and S2).

Immunologically, such an impressive peptide overlap clearly indicates the possibility that the seven analyzed infectious agents might trigger a cross-reactivity network capable of causing multiple and apparently unrelated autoimmune pathologies in the human host, depending on the human proteins involved in the cross-reactions. Biochemically, a noteworthy annotation is that the unexpected, massive, and apparently unexplainable microbial vs human peptide matching may have its evolutionary roots in the critical role played by bacteria and viruses in the origin of the eukaryotic mitochondrion and nucleus, respectively, as detailed in the Endosymbiotic Theory [66] and the Viral Eukaryogenesis Hypothesis [67, 68].

Table 2. List and occurrences of the 29 HPV16 pentapeptides common to HCMV, *C. tetani*, *C. diphtheriae*, *B. pertussis*, *T. gondii*, *T. cruzi*, and *H. sapiens*.

HPV16 Pentapeptide ¹	HCMV	<i>C. diphtheriae</i>	<i>C. tetani</i>	<i>B. pertussis</i>	<i>T. gondii</i>	<i>T. cruzi</i>	<i>H. sapiens</i>
DLLIR	1	1	1	2	11	1	3
LIPIV	2	2	1	5	2	5	7
SLCAA	2	1	1	11	28	10	7
TGSGT	2	2	1	10	31	18	13
STIST	3	1	1	7	7	21	16
TASTT	2	2	1	13	18	50	16
ANLAS	2	2	1	8	11	11	17
RAAKR	2	1	1	7	15	24	17
VALGT	2	4	1	25	19	4	19
TAASA	2	3	3	35	79	51	21
QPPTP	2	1	1	6	8	8	28
TTVTT	2	2	1	5	9	22	30
LLNKL	2	1	6	15	13	15	30
STSET	1	1	2	4	19	11	33
FLTAL	1	3	2	4	23	15	36
STAAA	4	2	2	20	94	100	37
AGAVG	3	11	1	21	43	14	38
ILVLL	2	2	4	5	17	27	38
TAAAL	2	14	1	55	109	62	46

(Table 2) contd.....

HPV16 Pentapeptide ¹	HCMV	<i>C. diphtheriae</i>	<i>C. tetani</i>	<i>B. pertussis</i>	<i>T. gondii</i>	<i>T. cruzi</i>	<i>H. sapiens</i>
LEDLL	2	2	4	6	38	25	47
LLSVS	1	2	1	11	62	45	49
AVALG	1	8	5	26	45	28	50
VVLLL	2	4	1	25	41	70	59
LSSST	3	1	3	11	157	58	64
LLKLL	2	5	4	13	44	37	64
PLLLS	2	2	1	8	120	68	64
VLLLV	2	4	5	13	53	140	82
LVLLL	7	3	4	18	96	111	164
GGSGG	15	6	4	33	105	150	215

¹Pentapeptides are listed according to their frequency in the human proteome (last column in bold).

3.3. Immunologic Potential of the Pentapeptide Commonality

In like manner, analysis of the publicly available epitope database IEDB [44] shows an unexpected immunologic potential of the peptide sharing, with 26 out of the 29 pentapeptides being widely, repeatedly, and massively represented in experimentally validated epitopes cataloged as immunopositive in humans (Table S3). Again we observe that a detailed discussion of the possible cross-reactivity scenario is prevented by the high number of epitopes. *De facto*, even using as an example the least redundant pentapeptide DLLIR (see Table 2), it can be seen that numerous epitope sequences contain DLLIR (Table 3).

Table 3. Epitopic sequences containing the pentapeptide DLLIR common to HCMV, *C. tetani*, *C. diphtheriae*, *B. pertussis*, *T. gondii*, *T. cruzi*, and *H. sapiens*. Data from IEDB (www.iedb.org) [44].

IEDB ID	Epitopic Sequence
110462	ygttleqqynkplc DLLIR cincqkplcpeek
110919	kplc DLLIR cincqkplcpeekqrhldkkq
111018	seyrhycyslygttleqqynkplc DLLIR c
112757	clkfyskiseyrhycyslygttleqqynkplc DLLIR
112758	clkfyskiseyrhycyslygttleqqynkplc DLLIR cincqkplcpee
112797	kplc DLLIR cincqkplcpeek
112865	ygttleqqynkplc DLLIR cin
113015	gttleqqynkplc DLLIR cinc
113111	plc DLLIR cincqkplcpeekq
118769	DLLIR cincqkplcpeekqrhl
119057	ygttleqqynkplc DLLIR c
436905	DLLIR thm
439790	r DLLIR thm

3.4. Inter-Pathogen Peptide Sharing and the Human Immune Response Following HPV16 Infection/Immunization: The Questions

In synthesis, Tables 2, S1, S2, and S3 show that most of the 29 pentapeptides occurring among the analyzed pathogens also massively recur in human epitopes and, hence, might be involved in a complex and dense autoimmune cross-reactivity network.

In the context of the HPV16 research model analyzed here, the data reported above suggest that an already primed epitopic peptide network can exist in an individual who undergoes HPV16 infection (or active immunization) during adolescence or in the adult age. Hence, the data raise two main intertwined questions:

- firstly: might immune reactivity against the HPV16 minimal determinants be modified/warped/confounded by previous immune responses against the same determinants present in other pathogen proteins?
- in the second place: following immune reactivity against an HPV determinant, which one(s) among the human proteins containing that same determinant(s) might be hit by immune cross-reactivity? One, a few or all of them? And why that or those ones?

3.5. The Biochemical Constraint of the Context-Dependent Conformation and the Immunological/Clinical Consequences

Actually, identical pentapeptides in different proteins can have completely different conformations. The same five residues may be part of an α -helix in one protein and part of a β -strand in another protein [69]. The same pentapeptide may be embedded in the protein foldings or exposed on the protein surface, and, in general, the pentapeptide conformation in the intact protein is influenced by the 3D aa context that surrounds the pentamer [69, 70]. Immunologically, antibodies made against one pentapeptide do not recognize all the possible pentapeptide conformations but react with only one or a few of the pentapeptide conformers depending on the flanking amino acids [71 - 73].

Keeping on in analysing for simplicity only the HPV pentapeptide DLLIR, we compared the aa context of the pentapeptide DLLIR in pathogen and human proteins. Specifically, we searched for the flanking sequences of the DLLIR pentapeptide, ie, the five NH2- and COOH framing residues, in the pathogen and human proteins (Table 4).

Table 4. N and C termini context of the minimal determinant DLLIR in pathogen and human proteins.

Protein	Aa Sequence Context
HPV16 Protein E6	nkplcDLLIRcincq
HCMV Unique short US6 glycoprotein precursor	mDLLIRlgfll
<i>C. diphtheriae</i> Mycothiol acetyltransferase	rrlgDLLIRmgllh
<i>C. tetani</i> Methyltransferase	ismdkDLLIRedeti
<i>B. pertussis</i> Aldehyde dehydrogenase	gdrhtDLLIRfaeac
<i>B. pertussis</i> Peptidase M61	valgIDLLIRdsgg
<i>T. gondii</i> Patatin-like phospholipase domain-containing protein	aerlyDLLIReifvr
<i>T. gondii</i> Pyridoxal phosphate enzyme, YggS family protein	dasslDLLIRenlkr
<i>T. gondii</i> Glucose-6-phosphate isomerase	dearnDLLIRstdqg
<i>T. gondii</i> Tubulin-tyrosine ligase family protein	eltrkDLLIRnlrrh
<i>T. gondii</i> Histone H3	fqkstDLLIRklpfq
<i>T. gondii</i> Actin-like family protein	ggrdlDLLIRddlla
<i>T. gondii</i> Uncharacterized protein	idnlkDLLIRgvml
<i>T. gondii</i> WD domain, G-beta repeat-containing protein	iklltDLLIRhials
<i>T. gondii</i> Dishevelled/Egl-10/leckstrin domain protein	krllsDLLIRvqgdl
<i>T. gondii</i> VRR-NUC domain-containing protein	veqaeDLLIRhlsrg
<i>T. gondii</i> Histone H3	yqkstDLLIRklpfq
<i>T. cruzi</i> Uncharacterized protein	isafyDLLIRqltvs
<i>H. sapiens</i> Septin-12	fpllrDLLIRshlqd
<i>H. sapiens</i> Septin-9	faylrDLLIRthmqn
<i>H. sapiens</i> Putative serpin A13	qegfwDLLIRlrgqg

Afterwards, 3D molecular modeling [45 - 47] was applied to the resulting 15-mer peptides containing the DLLIR minimal immune determinant (Table 4) in order to single out similar decapeptide structures Fig. (1).

Preliminarily, it has to be underscored that the structural modeling data reported in Fig. (1) aim at illustrating in a simplified manner the role of peptide conformation in immunological recognition and do not reflect the numerical and structural complexity of the peptide conformers [45 - 47, 69 - 73]. Given this necessary caveat, we observe that Fig. (1) shows that the structural conformation of the common DLLIR peptide varies in decapeptides listed in Table 4, with a few conformers being more similar than others to the HPV16 decapeptide nkplcDLLIRcincq (see in Fig. 1, decapeptide structures in blue: b) HCMV mDLLIRlgfll; j) *T. cruzi* isafyDLLIRqltvs; and l) *H. sapiens* faylrDLLIRthmqn, with the epitopic DLLIR site encircled in the oval).

Immunologically, Fig. (1) implies that, following HPV16 infection or active immunization, an anti-HPV16 DLLIR response could represent a booster for memory cells already primed to react rapidly and powerfully against DLLIR present in previously encountered structures, i.e., against DLLIR in b) and j) decapeptides described in Fig. (1). Otherwise said, the primary response against HPV16 DLLIR might result into a secondary response against conformers of infectious agents encountered early in the life. Hence, a first consequence is that the anti-HPV16 infection/vaccination will miss the goal of defending the body from HPV16.

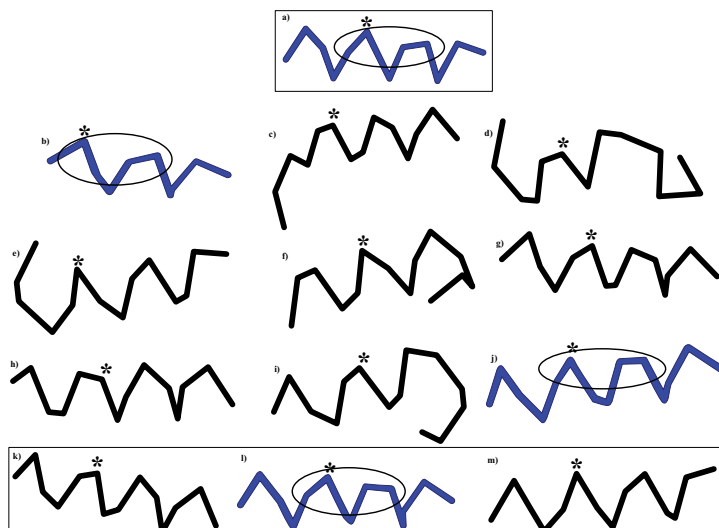


Fig. (1). Context-dependent conformations of decapentapeptides containing DLLIR. Decapentapeptide sequences with the common 5-mer DLLIR in capital letters: **A)** HPV16: nkpleDLLIRcincq; **B)** HCMV: mDLLIRlgfll; **C)** *C. diphtheriae*: rrglgDLLIRmgllhh; **D)** *C. tetani*: ismdkDLLIRedatl; **E)** *B. pertussis*: gdrhtDLLIRfaeac; **F)** *B. pertussis*: valglDLLIRdsgg; **G)** *T. gondii*: aerlyDLLIReifvr; **H)** *T. gondii*: dasslDLLIRenlkr; **I)** *T. gondii*: dearmDLLIRstdqg; **J)** *T. cruzi*: isafyDLLIRqltvs; **K)** *H. sapiens*: fpllrDLLIRshlqd; **L)** *H. sapiens*: faylrDLLIRthmqn; **M)** *H. sapiens*: qegfwDLLIRlrgqg.

Asterisk indicates the position of the first Leu in the shared pentapeptide DLLIR. The HCMV mDLLIRlgfll lacks a 5-aa sequence at the NH2 terminus (see Table 4). For simplicity, only 3 out of the 11 *T. gondii* decapentapeptides containing **DLLIR** (see Table 4) are reported. Epitope structures similar to that of the HPV decapentapeptide are given in blue, with the oval encircling the DLLIR sequence. PEP-FOLD3 [45 - 47] was used to obtain the 3D peptide structures.

Then, a second consequence is that the anamnestic, high affinity, high avidity immune responses triggered by HPV16 infection/active immunization against immune determinants already primed in the immunological memory of the subject will remain without a target. Indeed, no reaction can occur with the early sensitizing infectious agents that evoked the primary response and are no more present in the organism (that is, HCMV and *T. cruzi* in the examples discussed above).

Therefore, a third consequence is that the boosted anamnestic, immediate, high-avidity, high-affinity immune responses will take the road towards available crossreactive targets. In the case in point, towards the human similar conformer, *i.e.*, the human Septin-9 pentapeptide in the faylrDLLIRthmqn sequence (see Fig. 1) with potential heavy autoimmune consequences on the human host. Actually, altered Septin-9 leads to focal neuropathy characterized by recurrent episodes of brachial plexus neuropathy, with muscle weakness and atrophy preceded by severe pain in the affected arm [74, 75].

CONCLUSION

In the 40's, Francis and Colleagues [76, 77] observed that, when influenza A vaccines were given to children and young and older adults, the antibody response did not correspond to the vaccinating influenza antigen. Rather, it seemed to depend on the age of the recipients, each group responding with antibodies that reacted best with the virus subtype they experienced first in their life. That is, humans vaccinated against an influenza strain produced antibodies of higher titer against a different influenza strain that was their first childhood experience of influenza, even if that strain happened to be absent from the vaccine. The phenomenon was named 'original antigenic sin' [76 - 78] and is also known as the Hoskins effect [79]. As clearly described by Fazekas de St. Groth and Webster [80], '*Immunological memory, then, seems to cover families of antigens rather than only the particular member involved in the primary response. Such a mechanism makes for rapid anamnestic response, at the expense of specificity*'.

The original antigenic sin was interpreted as the cause of the absence of effect of revaccinations [76 - 78]. However, after seventy years, the molecular basis and the mechanism underlying the antigenic sin phenomenon remained unknown [81].

More recently, Lucchese and Kanduc [40, 41] suggested that the massive sharing of minimal epitopic determinants among pathogens – namely Zika virus, Epstein-Barr virus, Cytomegalovirus, Influenza virus, *Campylobacter jejuni*,

and *Mycoplasma pneumoniae*, among others – and the consequent potential cross-reactivity might represent the molecular basis and mechanism by which different infections over time can irrevocably imprint the host immunological memory, thus leading to subsequent anamnestic, misled, immune responses. Said data [40, 41] and the present ones add biochemical evidence in supporting the view that ‘*a cell, which has once produced antibody, is not only preempted to performing the same task again but does this on the slightest provocation by accepting what we may regard as not quite appropriate stimuli*’ [80].

In essence, our studies suggest that inter-pathogen peptide commonality and the consequent peptide cross-reactivity underlie the “original antigenic sin”, in this way explaining not only the failures of vaccination protocols [19 - 26, 82 - 100] but also the burden of vaccine-associated adverse events [1 - 17, 101]. Indeed, last and perhaps most important is the observation that the massive microbial vs human peptide overlap reiterates the concept that only vaccines based on peptide sequences uniquely owned by the infectious agent and absent in the human proteome may lead to safe, effective, and specific immunotherapies [102 - 108].

AUTHORS’ CONTRIBUTION

DK proposed the original idea and developed analyses. YS contributed to the analytical discussion of the data and to the writing of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are base of this research.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICTS OF INTEREST

DK declares no conflicts. YS appears as a medical consultant in vaccine compensation court, USA.

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Declared none.

SUPPLEMENTARY MATERIAL

Supplementary material is available on the publishers Web site along with the published article.

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