

Immunobiology:

On the Inexistence of a Negative Selection Process

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Abstract

The beliefs that dominate immunology are discussed in light of the pervasive peptide sharing that characterizes the protein world. The data show that a negative selection of self-reactive lymphocytes does not exist, demonstrate the essentially pathogenic nature of the immune response, reveal the inconsistency of an immune system conceived as capable of discerning and reacting against any and all foreign sequences/structures, and highlight an immunologic scenario where the immune response of each individual is restricted and conditioned by the immunological imprinting received from the first pathogens encountered in the early years of life.

Keywords: self-nonself; negative selection; deletion of self-reactive lymphocytes; pathogenic antibodies; the universe of antigenic determinants; the universe of antibodies

Abbreviations: HCV, Hepatitis C virus; EBV, Epstein Barr virus; HPV, human papillomavirus; aa, amino acid

1 Introduction: the four intertwined immunological assumptions

Since the '50s, four assumptions dominate the immunobiology, immunopathology, and immunotherapy studies [1]:

- the concept of human and of microbial immunological specificity, namely the self-nonself issue;
- the selectionist hypothesis according to which self-reactive lymphocytes are deleted from the immunological repertoire, so that autoimmunity is an improbable event;

- the uniquely defensive role of antibodies;
- the belief that an individual can react against an universe of antigenic determinants and evoke a corresponding infinite universe of antibodies.

Here, these beliefs reveal their fragility when analyzed through the lens of proteomics and scrutinized on the basis of experimentally validated data.

2 The self-nonself issue and the microbial vs human peptide sharing

The self-nonself issue can be summarized in a repeatedly posed question [2]: i.e., how can the heptapeptide LSRPSLP that occurs in the human myelin-oligodendrocyte glycoprotein be distinguished from the same identical heptapeptide LSRPSLP that occurs in 336 bacterial sequences?

In 2008 [3], virome-wide analyses showed a massive peptide sharing between viral and human proteins. The vast distribution of viral aa sequences throughout the human proteins suggested that viral and human proteins mostly consist of common peptides and indicated a common evolutionary link between distant entities such as viruses and humans [4, 5]. Likewise, no human protein was found to be exempt from bacterial motifs [6], again highlighting the tight evolutionary connection between microbial organisms and humans. And actually it is well known that mitochondria, evolved from symbiotic bacteria [7]. Then, reports [8-40] based on proteomics and comprehensive resources of protein sequences [41-43] repeatedly documented that a vast peptide platform ties the microbial protein world to the human proteome.

Biologically, such comparative biochemical analyses dismantled the assumption of microbial or of human immunological specificity [44] and, since 1999 [8], suggested that the immunological specificity of an antigen resides in the sequences/structures belonging exclusively to the antigen.

3 The negative selection hypothesis and the self-reactive epitopes

The peptide sharing between microbial entities and the human proteome also affects the Burnet's negative selection hypothesis that represents the major argument against autoimmunity. In fact, the negative selection hypothesis states that autoimmune diseases cannot occur since lymphocytes specific for human sequences, ie, self-reactive lymphocytes, are deleted from the human immunological repertoire on purpose to avoid self-reactivity. It is conceded that, as rare phenomena, only a few self-reactive lymphocytes might accidentally occur, thus representing "immunological holes" that possibly might cause rare cases of autoimmune cross-reaction in the human host [45]. In practice, autoimmune reactions are considered to be fantasies rather than facts [46-48].

In contrast with such opinions, exploration of Immune Epitope DataBase [43] shows that an impressive, unexpected, mathematically improbable peptide sharing exists between human proteins and microbial immunoreactive epitopes. In fact, analyses of only HCV, HPV and EBV [49-51] show that thousands of immunoreactive viral epitopes mostly consist of peptide sequences shared with human proteins, whilst peptide fragments belonging exclusively to the viruses are restricted to a small number.

As an example, Table 2 describes a few of the thousands of experimentally validated immunoreactive viral epitopes that share peptides with human proteins.

Table 1. Re-Framing Immune Responses in Experimentally Validated Data.

Peptide sharing between human proteins and immunoreactive EBV epitopes ^a					
ID ^b	EPITOPE ^{c, d}	ID ^b	EPITOPE ^{c, d}	ID ^b	EPITOPE ^{c, d}
5316	AVFDRKSDAK	23324	Gydvgh GPL	231839	DSIMLTATF
5317	AVFDRKSVAK	23449	GYRTATLRTL	231840	DTRaidqfF
5326	AVFNKSDAK	23994	Hhiwqnll	231880	FLQRTDLSY
5439	AVLL heesm	24170	HLAAQGMAY	231966	HVIQNAFRK
8120	DEPASTEPVHDQLL	24533	HPV geady	232020	KPWLRAHPV
8905	DKiv qapify PPVLQ	24666	HRCQAIRK	232074	LPTPMQLAL
9644	DPh gvpq LSYYD	24667	HRCQAIRKK	232076	LQALSNLIL
10448	DTPLIPLTIF	26480	IIFIFRRDLLCPLGAL	232078	LQSSSYPGY
10858	DYDASTESEL	26538	IIILIFI	232080	LSaerytLF
11804	EENLLDFVRF	42941	MVFLQTHIFAEVLKD	232086	LTQAAGQAF
12183	EGGVGWRHW	44181	NIAEGLRAL	232095	LVSSGNTLY
13628	EPDVPPGAIEQGPAD	45378	Npkfen IAEGLRALL	232096	LVSSSAPSW
16876	FLRGRAYGI	144799	TLNLT	232103	MEQRMATL
17110	FMVFLQTHI	167590	GPQRR	232177	QEPGPVGPL
17600	FRKAQIQGL	186702	PQPRAPIRPIPT	232178	QEQLSDTPL
18328	FVYGGSKTSL	191290	FIVFLQTHI	232199	RESIVCYFM
18438	FY nippm PL	227777	HPVAEADYFEY	232214	RLHRLLLMR
20023	GGSKTSLYNLRRGTA	230798	FYPVLQPI	232276	SEPCEALDL
21719	GPPAA	231136	LAY Arggam	232308	SQISNTEMY
21723	GPPAAGPPAAGPPAA	231402	RRVRRRLV	232332	TEdnvppwl
21870	GQGGSPAM	231547	TVFY nippm	675184	Rppifir
22159	GRPAVFDRKSDAKST	231696	YRTATLRTL	676208	RRIYDLI
22976	GVFVYGGSKTSLYNL	231699	YSQGAFTPL	695961	QAPYPGYEE

^aA total of 3197 EBV epitopes were downloaded from IEDB (www.iedb.org) [43] and analyzed for sharing of minimal pentapeptide immune determinants with the human proteome as described [51]. A sample of 69 epitopes are reported in the table. ^bEpitopes listed according to IEDB ID number; references available at www.iedb.org [43]. ^cEpitope sequences given in 1-letter code. ^dSequences shared between EBV and human proteins are in capital letters; sequences present only in EBV are in bold small format.

Table 1 and previous reports [49-51] reify an indisputable evidence: only a minimal part of the viral immunoreactive epitopes belong to viruses, whilst almost all of the viral epitopes are composed of human peptide sequences. Said otherwise, the defense from EBV is entrusted to a small patrol of lymphocytes targeting the limited number of minimal immune EBV determinants. Actually, the most part of the antibody response elicited by EBV infection will target also the human host (Table1) with immunopathological consequences [51].

4 Antibodies: between protection and autoimmunity

The fact that pathogen-derived immunoreactive epitopes mostly consist of peptide fragments common to human proteins is the unquestionable evidence that the

“negative selection” of self-reactive lymphocytes does not exist. The abnormous peptide sharing between microbial immunoreactive epitopes and human proteins inficiates the current model of self-tolerance based on a negative selection process according to which lymphocytes with specificity for sequences that are expressed in the host are deleted from the immunological repertoire to avoid self-reactivity and the consequent autoimmunity [45].

As a corollary of the self-reactivity of the anti-microbial immune response, also the uniquely defensive role attributed to antibodies breaks down. Currently, antibodies are defined as the main defence against infections [52]. In contrast, the massive peptide sharing between human proteins and pathogen-derived immunoreactive epitopes (Table 1) [49-51] indicates that self-reactivity and consequent autoimmunity characterize the immune response to infections. A paradigmatic example is offered by the symmetrical correspondence that ties the EBV epitopes to the EBV diseasome, from lymphomas to cardiac diseases, through peptide sharing [51]. In more or less light forms, cross-reactivity and autoimmunity appear to be a constant consequence following infection or active immunization, thereby conferring a pathogenic character to the immune response against infectious agents [53].

5 The restricted and constrained repertoire of antibodies

Finally, the questions: is the antibody repertoire really infinite? Can every individual specifically respond to every immune determinant? The potentially infinite antibody universe deriving from gene recombination and affinity maturation led to assume that the antibody repertoire of each individual is unique. Likewise, the number of the potential target epitopes on pathogen antigens led to suppose that generation of specific anti-pathogen antibody patterns has to follow to every encounter with a foreign antigen. Actually, the terms ‘infinite’ and ‘universe’ should be cancelled, by being five-six aa residues sufficient to delineate an antigenic immune determinant [54-57]. This yields a finite number (between 20^5 and 20^6) of antigenic immune sequences and related antibodies.

Moreover and most importantly, Setliff *et al.* [58] report that public antibody clonotypes exist in HIV-1 infection and, likewise, public antibody clonotypes that are shared among multiple individuals have been observed for dengue infection (59), after influenza vaccination (60), and in other immune settings (61-64).

The discovery of public antibody clonotypes in pathogen-infected individuals goes in parallel with the clinical observation that a person’s first encounter with a pathogen shapes and conditions how the immune system reacts to subsequent pathogen exposures. This phenomenon called “original antigenic sin” or “immunologic imprinting” was first described in the ‘40s [65] and remained unexplained until recently, when it found a logical explanation in the massive peptide sharing among infectious pathogens and the human host [66].

Indeed, according to Kanduc and Shoenfeld [66], pre-existing immune responses against the immune determinants of a first pathogen can be boosted by a successive exposure to the same identical immune determinants present in a second similar or different pathogen. This means that the primary response to a pathogen is transformed

into a secondary response to a previously encountered different pathogen. An anamnestic, high avidity, high affinity, and quantitatively abnormous secondary response is unleashed against the early sensitizing pathogen that, on the other hand, is no more present in the organism, whilst no immune responses is elicited against the pathogen lastly encountered either by infection or active immunization.

Translated to the immunological maturation process, the immunogenic encounters during the first years of life of an individual form a pattern of immune responses — and, at the cellular level, a set of reactive lymphocytes — that will determine, control and dominate the immune system in the adult's life. Such early imprinting or 'immunological memory' becomes firmly fixed in the individual's early immune system and cannot be forgotten. It will condition the future immune responses in the adult organism since — during any infection or active immunization — the immune system will prioritize the production of lymphocytes reactive against the already encountered immune determinants. And this also explains why efforts to activate the lymphocyte population in order to protect by active immunizations are destined to remain vain efforts [67-75].

6 Conclusions

The present study marks the need of revising the mechanisms that govern the immune responses in light of the vast inter- and intra- proteomic peptide sharing among microbial entities and the human proteins. In this author's opinion, these data indicate that not the Burnet's *a priori* 'negative selection of self-reactive lymphocytes', but rather an *a posteriori* 'positive selection of reactive lymphocytes' is the memory-driven mechanism at the basis of the immune system maturation and activity.

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