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Escape of pathogens from the host immune response by mutations and mimicry. Possible means to improve vaccine performance

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ABSTRACT

The ability of certain pathogens, such as human immunodeficiency, hepatitis C, herpes simplex, influenza viruses, *Plasmodium falciparum*, etc., to escape from host immune response is generally ascribed to high mutation rate of their genome. We challenge this assumption and propose that molecular mimicry of host antigens by these pathogens could also participate to this resistance. Several studies show that there is no correlation between the mutation rate value of a pathogen and the possibility to develop an effective vaccine. On the other hand, pathogens which do not respond to vaccine are usually reported to display host protein mimicry.

We propose to suppress in the thymus the epitopes of the self which are in common with the pathogen. This could be achieved by intrathymic injection of antibodies against this microorganism. These antibodies would be obtained by vaccination of a foreign animal species. It is expected that the negative selection of the $CD4^+$ and $CD8^+$ T lymphocytes specific for these epitopes would be prevented, that the number of epitopes recognized as foreign to the host would be increased and that the immune response diversity would be enhanced.

Introduction

To date, no effective vaccine has been developed against human immunodeficiency virus (HIV 1), Herpes simplex virus (HSV), Hepatitis C virus (HCV) or *Plasmodium falciparum*. The vaccine strains of influenza A virus have to be changed yearly to protect against the ever evolving virus population. In contrast, vaccines against most other RNA viruses (poliovirus, measles virus, Hepatitis A and B viruses, smallpox virus, etc.), which are based on strains used for decades, show no loss of efficacy. A high rate of genetic variation (mutations and recombinations) is generally suggested to account for the escape of certain pathogens from host immune response and to be the major obstacle to the development of effective vaccine [1]. However, this commonly accepted assumption is at odds with the mutation rate data expressed per genome and per duplication. Genetic variation alone does not explain resistance of certain pathogens to vaccination. We suggest that this resistance would be due to the combination of the mutations of the pathogen genome and of the mimicry of the host proteins by a great part of the pathogen epitopes.

Comparison of the mutation rates of pathogen organisms

The high mutation rates of RNA viruses are due to the deficiencies in the mechanisms of proofreading, leading to high error rate of both the RNA dependent polymerase of the lytic viruses (riboviruses) and the reverse transcriptase of the retroviruses. The mutation rate values are scattered over a relatively large range, due to non-standardized methods of measurement, and to experimental and theoretical inadequacies. Indeed, the mutational targets studied are sometimes too small to be correct sampling of the whole genome, or the process of replication is not known. However, it seems that the RNA viruses have evolved so that their mutation rates, expressed by the number of modifications per genome and per replication, have roughly similar values, varying over an order of magnitude, approximately 0.8 for the riboviruses and 0.2 for the retroviruses [2]. The mutation rate of viral and cellular microbes whose genetic information resides in DNA has been estimated, with good accuracy and on a large range of molecular weight, to 0.0034 per genome per replication. This value is far lower than the mutation rate of RNA viruses [2], and thus cannot account for an escape strategy. The mutation rates of eukaryotes are around 0.01 when expressed per effective genome (fraction of the genome in which most mutations are likely to have a deleterious effect) and per replication [2]. Table 1 [1–21] shows the rates of mutation measured for influenza A, human

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Table 1
Mutation rates per replication of some pathogens. μ_S: mutation rate per base pairs, G: number of nucleotides, μ_G: mutation rate per genome.

Viruses	Mutation rates			
	μ_S	G	μ_G	Ref.
Influenza		13,558		
	$4.5\ 10^{-5}$			[1]
	$1.5\ 10^{-5}$		0.203	[3]
	$>7.3\ 10^{-5}$		>0.99	[2,10]
	$7.1\ 10^{-6}$		0.092	[1]
	$3.9\ 10^{-5}$		0.52	[1,12]
	$2.3\ 10^{-5}$			[1,11]
Human immunodeficiency virus 1		9200		
			0.22	[2]
	$3\ 10^{-5}$		0.255	[6]
	$4.9\ 10^{-5}$			[1]
	$1\ 10^{-4}$		0.92	[1,9,13]
	$3.4\ 10^{-5}$			[14]
	$2.2\ 10^{-5}$			[15]
	$7.3\ 10^{-7}$			[16]
Hepatitis C		9600		
	$1.2\ 10^{-4}$			[17]
Herpes simplex		152,000		
			0.003	[18]
	$5.9\ 10^{-8}$			[19]
Plasmodium falciparum	$<2.5\ 10^{-9}$			[20]
Polio		7440		
	$<2.1\ 10^{-6}$		0.156	[3]
			0.132	[4]
			0.177	[4]
	$4.5\ 10^{-4}$		3.35	[7]
			0.8	[2]
Measles		15,894		
	$9\ 10^{-5}$		1.43	[5]
			1.0	[4]
Hepatitis A		7500		
	$1–10\ 10^{-4}$		0.75–7.5	[8]
Hepatitis B		3200		
	$5.1\ 10^{-4}$			[21]

immunodeficiency, polio, measles, hepatitis A, B and C, herpes simplex viruses and *P. falciparum*. It can be seen that fluA, HCV and HIV 1, for which vaccines are either non-existent or ineffective, are not distinguishable, on the basis of their mutation rates per genome per replication, from the other examples (polio, measles and hepatitis A), against which highly effective vaccines have been developed.

In the case of HSV, a DNA based virus, and of *P. falciparum*, parasite of the malaria, the low values of their mutation rates cannot explain the escape from human immune response and the difficulties encountered in the development of effective vaccine.

In other respects, the mutation rates measured per year in natural virus populations [22] cannot be compared with the mutation rates per replication. A multitude of factors, such as the immune pressure of the different hosts or prevailing ecological conditions may have a larger impact on the genetic variability than the polymerase error rate itself.

Host protein mimicry by some pathogen organisms

In the case of pathogens against which no effective vaccines have been developed, some proteins show sequence homologies with those of the host. This phenomenon, called molecular mimicry, allows these pathogens to evade host immune recognition, by eluding it when the molecules of the immune system are mimicked, or by making some of their proteins indistinguishable from those of the self. In addition, these pathogen antigens may induce autoantibodies and trigger autoimmune diseases that damage host tissues [23,24], when genetic, hormonal or environmental factors are met [25].

- gp 41 of human immunodeficiency presents in its carboxy terminus highly conserved homologous regions with the aminoterminal part of the β chain of all human HLA class II antigens [26]. Mimicry by gp 41 of proteins of astrocytes in human brain tissue is a probable cause of autoimmune pathogenesis [27]. Autoantibodies cross-reacting with this trans membrane protein and human IL2 [28] or human platelet glycoprotein gp IIIa (integrin β3) [29] have been found in sera of HIV 1 infected individuals. HIV 1 gp 41 shares also regions of homology with complement factor H [30] and membrane proteins of human T, B and monocyte cells [31]. Production of cross-reactive antibodies between HIV 1 gp 120 and platelet glycoproteins gp IIb/gp IIIa [32], human T cell proteins [33–35] and human brain proteins [36] have been ascribed to molecular mimicry. Similar aminoacid sequence motifs have been found on gp 120 and on the antigen recognition site of most HLA class I C [37] or on the CD4 binding site of the class II major histocompatibility complex proteins [38]. Molecular mimicry between an epitope of nef, protein encoded by the HIV 1 genome, and the glycoprotein IIIa has been reported [39]. More recently, high sequence similarity was found between EL9 epitope and the human nucleolar protein 6 (NOL6) [40], extensive viral mimicry of 22 AIDS related autoantigens by HIV 1 proteins was noted [41] and exclusion of HIV epitopes shared with human proteins was recognized as prerequisite for designing safer AIDS vaccines [42].
- The N-terminal region of the viral glycoprotein E2 of the Hepatitis C virus is antigenical and structurally similar to human immunoglobulin variable domains, the degree of similarity to immunoglobulin types being correlated with the virus immune escape and persistence in humans [43]. Homologies between the non-structural 5 (NS5) region of HCV and the human protein nitrogen oxide synthases type III have been reported [44]. Similarities between NS3 and NS5A HCV proteins and cytochrome P450 2D6 have been ascribed to be the cause of anti liver–kidney microsome type 1 autoantibodies [45]. HCV core 178–187 shows also sequence homology with cytochrome and may lead to autoreactive $CD8^+$ CTLs by molecular mimicry [46]. In chronic HCV infections, autoantibodies to smooth muscles and nuclear components may arise as a consequence of molecular mimicry [47]. In contrast, according to other authors, the high rate of variability of the hypervariable region 1 of the virus envelope protein E2 would play a major role in the mechanism of escape from host immune response and would represent a major obstacle to developing an HCV vaccine [48]. To date, the link between HCV and autoreactivity is tentatively explained on the basis of sequence homologies shared by the HCV polyprotein and the "self" proteins (such as CYP2D6, target of anti LKM1) [49].
- Influenza A virus mimics cytoplastic dynein, and an anti-virus antibody is used to localize this protein in the central nervous system [50]. A $CD4^+$ T-cell clone, specific for an immunodominant influenza hemagglutinin peptide, cross-reacts with a human myelin derived peptide [51]. Antibodies formed after influenza A or hepatitis C virus infections react with antigenic targets present on platelets and induce idiopathic thrombocytopenic purpura [52]. Human autoantibodies from patients with systemic rheumatic disease recognize epitopes shared by influenza B virus and by p68 associated with small nuclear ribonucleoprotein particles [53]. Molecular mimicry is also suspected to be the cause of the Guillain Barre syndrome by an inactivated flu vaccine [54].

- Following molecular mimicry of host proteins by Herpes simplex virus, a DNA based virus, have been reported: the chemokine receptors [55], interleukin 6 [56], CD200, a protein implicated in preventing macrophage activation [57], a cell surface glycoprotein expressed on monocytes, macrophages and platelets [58], the acetylcholine receptor [59,60], the myelin basic protein [61] and the human intermediate filament protein [62]. Autoimmune diseases such as myasthenia gravis or multiple sclerosis are sometimes associated with the presence of this virus and ascribed to host protein mimicry by the pathogen.
- Some proteins of *P. falciparum*, (pathogen of malaria), present similarities with human homologs: the translationally controlled tumor protein (TCTP), the parasite protein called RESA, the antigen that mediates erythrocyte invasion, show respectively similarities with the mammalian histamine-releasing factor [63], the ovalocyte band 3 protein [64], and the interleukin 8 receptor as well as the macrophage inflammatory protein 1α/RANTES receptor [65]. A common binding motif displaying homology to muscle myosin and neurofilament sequences was also identified [66]. Sequence homologies between parasite and human proteins, due to molecular mimicry, can cause autoimmune responses [23].

Interestingly, this strategy is rarely reported regarding RNA viruses which respond to vaccine: there is no data concerning mumps or rabies viruses. No evidence has been found that measles, mumps and rubella vaccination during adolescence might trigger autoimmunity [67] and no measles virus specific $CD4^+$ T cell showed any reactivity to myelin basic protein [68], however, there is cross-reaction between the phosphoprotein of this virus and an intermediate filament protein of human cells, probably vimentin [62]. Molecular mimicry between viral and host epitopes has been suspected in progressive rubella panencephalitis [69], and demonstrated in autoimmune demyelination, due to homology with myelin oligodendrocyte glycoprotein [70]. Sequence similarities have been found between poliovirus receptor and myelin P0, a major peripheral nerve protein [71]. More data are related to mimicry of host proteins and autoimmune diseases by hepatitis A [72] and B viruses, but several of them conclude to an absence of causal link. No correlation seems to exist between hepatitis B vaccination and multiple sclerosis [73,74], this disease being probably due to contamination with hepatitis B polymerase [75]. No evidence of autoimmunity has been found among 6-year-old children immunized at birth with hepatitis B vaccine [76]. On the other hand, mimicry was suspected to be responsible for multiphasic disseminated encephalomyelitis in a patient infected by hepatitis A virus [77] and in another one, for demyelinating transverse myelitis by hepatitis B virus [78]. Aminoacid sequences similarities have been observed between virus B polymerase and myelin basic protein [79] or nuclear and smooth muscle proteins [80], and also between small hepatitis B virus surface antigen and myelin oligodendrocyte glycoprotein [81]. An antigenic mimicry of an immunoglobulin A epitope was found in a hepatitis B virus cell attachment site [82] and the hepatitis B virus preS1 domain hijacks host trafficking proteins by motif mimicry [83].

Finally, it seems that host protein mimicry by pathogen is less frequently reported when there is an effective vaccine against it, than when there is not.

Proposition of treatment

On Fig. 1, the sets of the antigen epitopes of the different species are represented by the points of the surface of circles. The immune system reacts against the pathogen epitopes which are foreign to the host (which are not included into the host epitope set). When a large proportion of the antigens of a microorganism is shared with the host, only a small number of epitopes can be recognized as foreign by the immune system (Fig. 1a). Some mutations may then shift the virus epitope set and a fraction of antibodies produced by previous infections or vaccination may be inactive against the mutated epitopes. In these conditions, the combined

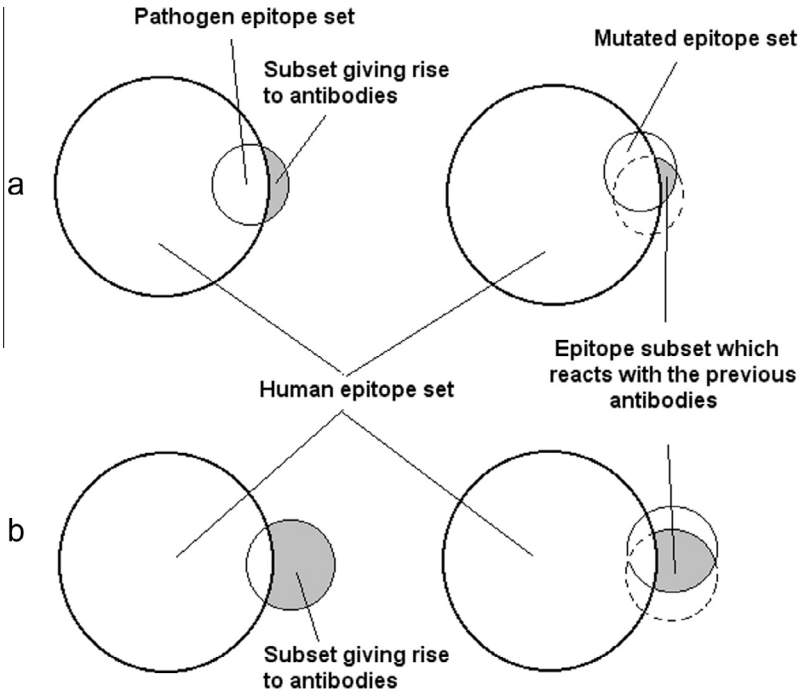

Fig. 1. Influence of mutations on the efficiency of the immune response. The epitope sets are represented by the points of the area of circles. (a) The pathogen shares most of its epitopes (small circle) with the host (large circle). Few antibodies would be produced and a small fraction of them would remain active against the mutated pathogen (in gray). (b) When many pathogen epitopes are foreign to the host, multiple antibodies would be produced and a sufficient part of them would react with the mutated pathogen (in gray).

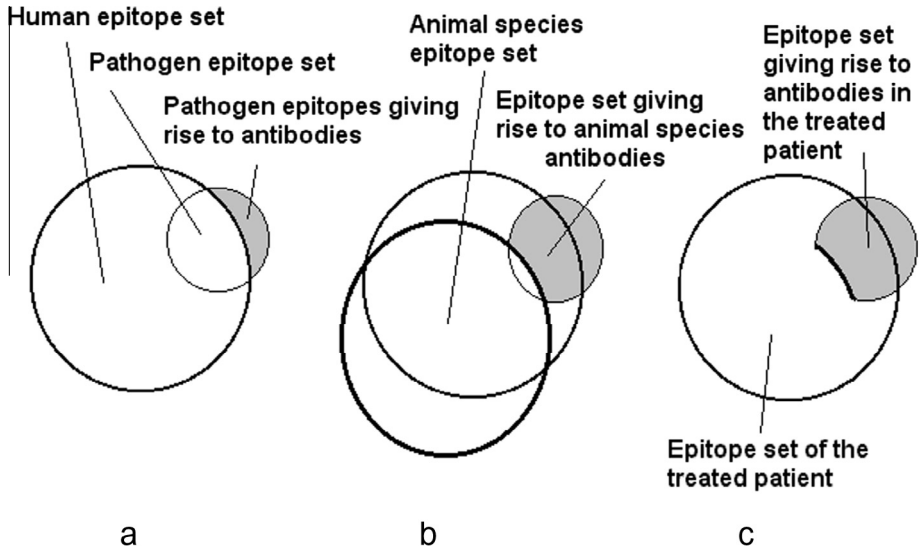

Fig. 2. Proposition to improve the immune response. The epitope sets are represented by the points of the area of circles. (a) The pathogen shares most of its epitopes (small circle) with the host (large circle). Only the small subset outside the human epitope set would give rise to antibodies (in gray). (b) The animal species epitope set (thick lined circle) is different from the human epitope set and more pathogen epitopes would elicit antibodies (in gray). They are purified by affinity and injected into the thymus of the patient. (c) The negative selection of the $CD4^+$ and $CD8^+$ lymphocytes specific of the blocked epitopes would be prevented and a greater number of pathogen epitopes would be recognized as foreign and would induce an immune response (in gray).

effects of host epitope mimicry and mutations would impede the development of an effective vaccine. In case of moderate level of mimicry, the number of mutations being the same, the effect of mutation rate would be reduced as the number of foreign epitopes would be larger (Fig. 1b). It is probably the case for the pathogens against which effective vaccines have been developed, or after the treatment we propose.

The aim of this treatment is to increase the number of pathogen epitopes foreign to the host, in order to enhance the immune response. For this purpose, we have previously proposed [84] to suppress, in the thymus, the part of the epitopes of the self which is in common with the microorganism. Theoretically, this could be achieved by intrathymic injection of antibodies against this pathogen, obtained by vaccination of an animal species. In this way, it is expected that the negative selection of the $CD4^+$ and $CD8^+$ T lymphocytes specific for these epitopes would be prevented and that the diversity of the immune response would be enhanced.

The animal species chosen for the production of antibodies must have an epitope set as different as possible from that of the pathogen (Fig. 2b). These polyclonal antibodies could be purified by affinity chromatography, with the microorganism proteins bound to the matrix of the column. By injecting these antibodies into the thymus, the corresponding subset of the human self epitopes would be blocked, the negative selection of the specific T lymphocytes would be prevented and a greater number of pathogen epitopes would be recognized as foreign by the host immune system (Fig. 2c). Thereby, it is expected that antibodies against many pathogen epitopes, not modified by mutation, would be produced after vaccination. The injection of antibodies ought to be performed into the medullary portion of the thymus, where negative selection takes place, while positive selection is controlled in the cortex [85]. This operation is certainly difficult, but, even if the fixation of antibodies on epitopes of the self is randomly distributed between the compartments, some thymocytes may undergo positive selection by contact with cortical cells not altered by the antibodies. Then, by moving to the next medulla which has received antibodies, they could escape to the negative selection and appear as $CD4^+$ and $CD8^+$ mature cells.

Discussion

Experimental *intrathymic injections of antigens* of all kinds (MHC I or MHC II peptides, cell extracts, bone marrow, splenocytes, islet cells) have been shown to prevent graft rejection, by a mechanism involving the clonal deletion of certain allo and xenoreactive T cells in the thymus [86–89]. On the other hand, blocking antigenic epitopes in the thymus by antibody treatment is possible. In mice injected intraperitoneally, from birth, with antibodies to MHC (class I or II), the development of mature cells of the corresponding specificity is clearly modified [90]. Administration in the same way of anti CD4 monoclonal antibodies differentially affects the intrathymic development of T cell populations [91]. However, surprisingly, *intrathymic injection of antibodies*, as we propose, has not been reported up to now.

This treatment is not exactly a passive immunotherapy, since only the thymus is involved. As the organ is involuted in adults and abnormal in certain diseases such as AIDS [92], one may think that the treatment could not be always applied. However, in the case of young people, it would be easy, and as recent data suggests, the adult thymus can still contribute to cell reconstitution [93].

The choice of the animal species for the antibody production is particularly important: it must be immunologically distant from humans, in order to induce different antibodies against the pathogen, but not too much, to avoid important immune response against them. It is also necessary to choose animals of great size, to obtain sufficient amounts of material. After the end of the treatment, the human circulating antibodies might replace the injected xenoantibodies from their binding sites in the thymus. A constant surveillance of the titer of the antibodies should be ensured over an effective time frame.

After the proposed treatment, the major part of the antibodies produced by the host in previous immunization would remain active against a pathogen having undergone some mutations, while, without this treatment, they would be inactive towards a mutated pathogen sharing a large proportion of its epitopes with the host. By restricting the number of foreign epitopes, molecular mimicry combined with the mutation of the genome are certainly a more efficient mechanism to escape the immune response than

mutability alone. It is probably the major obstacle to the development of some vaccines.

Besides adverse immunological response to allo and xenoproteins (such as urticaria), repeated injections of antibodies may induce the formation of antiidiotypic antibodies. As they bear an internal image of the pathogen epitopes, they could compete with them, displace the injected xenoantibodies from their complexes with the self epitopes in the thymus. However, in the case of dangerous infections and in the absence of an effective vaccine, these drawbacks would be negligible.

On the other hand, blocking with antibodies the epitopes, in the thymus, common to the self and to the pathogen, could modify the production of the autoantibodies responsible of the autoimmune diseases. This issue requires further study.

Finally, the validity of these propositions can be readily evaluated using the appropriate animal model, since the purification of polyclonal antibodies and their injection into the thymus are possible.

Conflict of interest statement

None.

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