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Review

AIDS DESTROYS IMMUNE DEFENSES: HYPOTHESIS

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ABSTRACT

In a hypothesis, the immune-system devastation that performs acquired immunodeficiency syndrome (AIDS) arises from the permanent evolution of human immunodeficiency virus (HIV) in humans. After the initial rapid proliferation of HIV in humans the infection remains controlled for a certain period by a strong immune response, in which affected people do not show AIDS symptoms. However, after some years HIV ends to defeat the defence system and AIDS is manifested. In order to explain the progression an evolutionary hypothesis was proposed: HIV experiences mutations, which cause variants. After a certain number of variants the immune system collapses.

Keywords: human immunodeficiency virus type 1, acquired immunodeficiency syndrome, evolutionary hypothesis, mathematical model, human immune response.

1. INTRODUCTION

Escultura reviewed qualitative mathematics and modelling [1]. Barillot *et al*. examined the computational systems biology of cancer [2]. Wang analyzed complex diseases with a mathematical perspective [3]. Simonyi revised the cultural history of physics [4]. Although viruses be not metabolizing cells and considered forced cell parasites, they played an important role in life evolution since its emergence. The human diseases of human immunodeficiency virus type 1 (HIV-1) and hepatitis C virus cannot be understood without the evolutionary framework. Developments in theory, technology, medicine and study of human disease with respect to virus evolution occurred. Reverse transcription broke the

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molecular genetics central hypothesis (*The Central Dogma*), *i.e*., deoxyribonucleic acid (DNA) makes ribonucleic acid (RNA) makes protein, was established *via* retroviruses.

The HIV presents a health, social and economic impact. Current therapies control infection but neither healer treatment nor effective vaccine. In order to achieve the objectives, one should take into account HIV genetic variability and rapid evolution associated (*e.g*., with the appearance of drug-resistance variants, antigenic changes). The HIV-1 represents a real-time bioevent in human evolution that confirms the importance of quasispecies and retroviruses to human biology. Human and primate evolution was significantly affected by earlier, prevalent primate retroviruses. From the earliest events in evolution of prebiotic replicators to recent ones in human evolution, *e.g*., emergence in human-specific HIV, viral evolution is expected to show profound effects on the evolution of life. A question follows. How do HIV variation and adaptation lead to a collapse of the human immune system?

In an earlier publication the phylogeny of anthropoid apes was reported [5]. Fractal [6] and hybrid-orbital [7,8] analyses of protein tertiary structure were informed. Complex multicellular systems and tumour–immune cells competition were modelled [9]. Structural classification of complex molecules by information entropy and equipartition conjecture was published [10-12]. Molecular classification, diversity, complexity and emergence were informed [13-15]. The periodic classification of HIV inhibitors was reported [16]. The molecular classifications of thiocarbamates with cytoprotection activity *vs*. HIV [17], styrylquinolines as HIV integrase inhibitors [18] and *N*-aryloxazolidinone-5-carboxamides as HIV protease inhibitors [19] were informed. Current study of molecular evolution benefits from structural data [20]. Mucoadhesive polymer hyaluronan was published as drug delivery vehicle [21]. Reflections on the nature of the periodic table of the elements were informed [22]. In the present report, the basic model of virus dynamics and HIV–evolution relationship are reviewed with the aim to provide a broad sketch of the fundamental human–HIV biophysical forces that enable and constrain HIV evolution and disease. Despite the importance of biomacromolecule's structures and conformational dynamics to their functions and fitnesses, phylogenetic methods embody their minimal biophysical knowledge. The following section presents the computational model. In the next section, some themes are reviewed and discussed. Finally, the last section summarizes our remarks.

2. MODEL

Basic model of virus dynamics considers uninfected target cells T, productively infected cells I and virus particles V [23]. Uninfected cells are produced at a constant rate σ and die at rate $\delta_T T$. Virus particles infect uninfected cells at a rate proportional to the product of their abundances βTV, and infected cells die at rate δI. Virus is produced from infected cells at rate pI and is cleared at rate cV, which causes system of ordinary differential equations (ODEs):

$$dT/dt = \sigma - \delta_T T - \beta TV \quad (1)$$

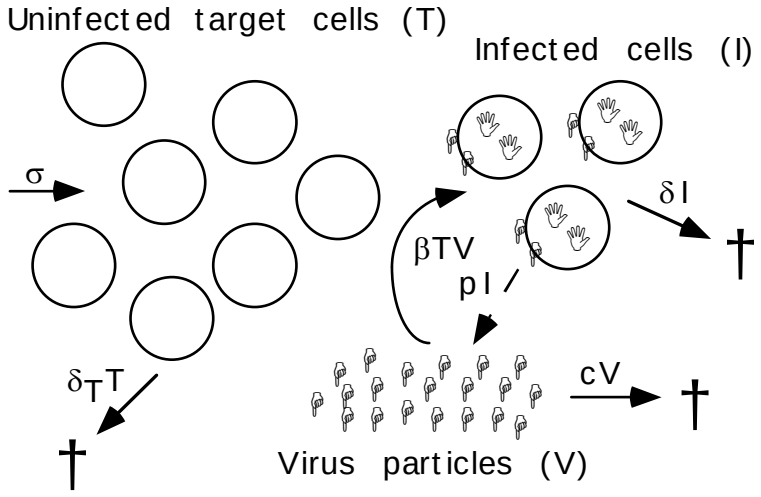
$$dI/dt = \beta TV - \delta I \quad (2)$$

$$dV/dt = pI - cV \quad (3)$$

The model (*cf*. Fig. 1) was used as a starting point for explaining HIV dynamics. It describes quantities in the whole body or in a given volume of blood plasma/tissue depending on scaling. The ODEs define change rate of every quantity and every term corresponds to a

production/decay process. Decay-rate reciprocal defines the average lifespan, which results $1/\delta_T$, $1/\delta$ and $1/c$ for uninfected and infected cells, and virus particles, respectively. The model captures the dynamics of a single mixed compartment with large homogeneous populations of cells and viruses that undergo asynchronous infection and cell cycles. Full HIV complexity is not captured by the model. However, the model is used as a consensus starting point and extended to more complexity. Building a single *full model* of HIV dynamics that describe all biosystem details is not feasible. A complex model becomes intractable making it impossible to dissect individual-processes roles in the system. Complexity implementation needs to be guided by the particular research question and kept at the minimum possible level. The model is nonlinear and a general solution for the time course of its variables cannot be derived. Its analysis provides insight. In the absence of virus the model attains an uninfected equilibrium with $\hat{T}_U = \sigma/\delta_T$, $I = 0$, $V = 0$. If virus is added to the system the infection takes hold or peters out depending on the parameters. The conditions for successful infection are summarized in the basic reproductive ratio R_0, which describes the number of cells infected by a single infected cell that is added to an uninfected equilibrium. If $R_0 < 1$, infected cells cannot replace themselves during their lifetime and their numbers dwindle steadily towards zero. If $R_0 > 1$, the number of infected cells rises to a transient peak and the system settles to an infected equilibrium. In the model it results: $R_0 = \beta\sigma p/\delta\delta_T c$. The infected equilibrium is at $\hat{T} = \delta c/\beta p$, $\hat{I} = \sigma/\delta - \delta_T c/\beta p$, $\hat{V} = p\hat{I}/c$. An established infection indicates $R_0 > 1$. Lack of infection may indicate viral-invasion failure but also lack of real exposure. Highly exposed uninfected individuals present $R_0 < 1$, which would indicate HIV systemic resistance. Alternatively, an efficient innate immune response or a lack of appropriate target cells at the entry site may block virus access to the main target cell population in the individuals. Homozygous carriers of C-C chemokine receptor type 5 (CCR5)Δ32 deletion mutant lack susceptible target cells at the entry sites important in sexual transmission and are apparently resistant to infection by the route. However, the infection resistance is breached if viruses able to infect target cells that reside in the systemic circulation are transmitted directly into blood.

Figure 1: The scheme of the basic model of human immunodeficiency virus infection



3. APPLICATION

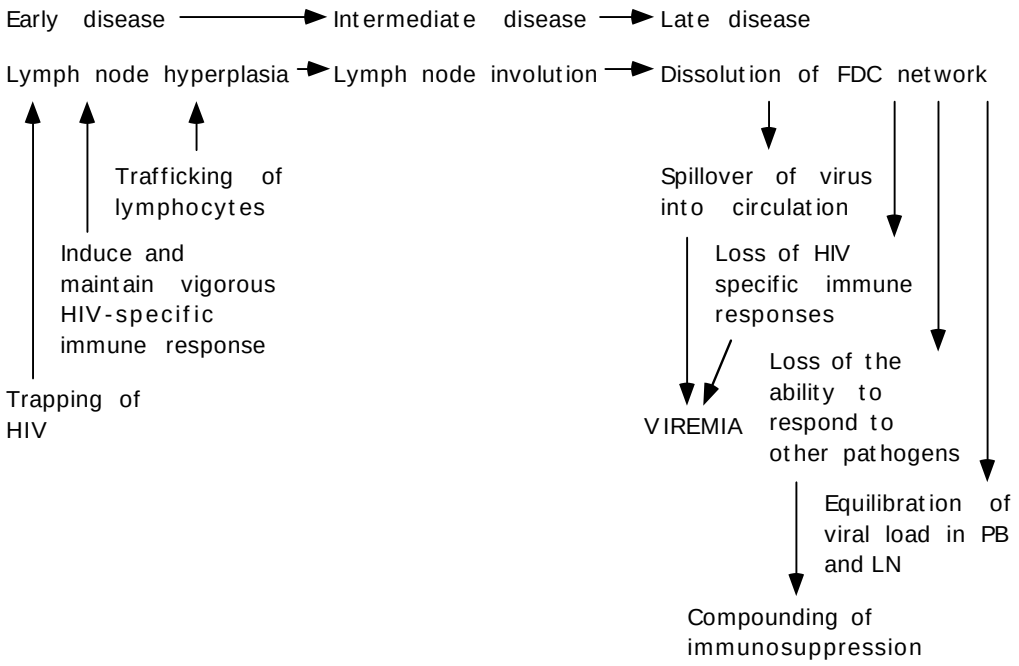
3.1. Results

Longitudinal studies of patients, infected with HIV-1, revealed a long and variable incubation period between infection and development of acquired immunodeficiency syndrome (AIDS). Data from a small number of infected patients showed temporal changes in number of genetically distinct strains of HIV throughout incubation period, with a slow but steady rise in diversity. A dynamic-interaction model between HIV diversity and human immune system showed an antigen diversity threshold, below which the immune system regulates HIV population, but above which HIV inhabitants induce collapse of cluster of differentiation of T_4-receptor subtype (CD_4^+) of thymus (T)-dependent lymphocyte populace [24]. It showed that antigenic diversity is AIDS cause, not consequence. Its comparison with data assessed how timing of chemo/immunotherapy application influences AIDS progress.

In a longitudinal study of HIV patients, fluctuations in specificity of cytotoxic T-lymphocytes (CTLs) were matched by variability in proviral group-specific antigen (*gag*) DNA epitope sequences [25]. Variants of HIV are unrecognized by autologous T-cells. Mutations accumulation in T-cell antigenic targets provides an immune-escape mechanism.

Theories of HIV pathogenesis explain the long and variable infection–AIDS delay. McLean reviewed the theories in the context of a simple model of HIV–immune system interactions from which a theoretical progression index was derived [26].

Figure 2: Lymph node (LN) germinal centres during HIV. FDC: follicular dendritic cell; PB: peripheral blood



Is HIV necessary and sufficient to cause AIDS? Is AIDS an autoimmune disease triggering apoptosis? Is HIV infection cause of T-helper lymphocyte depletion? What are HIV-tropism significance and macrophages/dendritic cells role in AIDS? Is there HIV latency? Why is there a long infection–AIDS period? Is HIV variation an aspect of pathogenesis? Do virulent strains emerge? Although Weiss provided answers he focussed on salient points [27]. Tropism and burden of HIV infection correlate with AIDS manifestations.

Immunopathogenic mechanisms underlying HIV AIDS are complex; AIDS is multifactorial with multiple overlapping phases (*cf*. Fig. 2) [28]. Viral burden is substantial and HIV replication occurs throughout entire infection. Inappropriate immune activation and elevated secretion of certain cytokines compose pathogenesis. Immunosuppression occurs together with a disruption of immune-system microenvironment, which is unable to regenerate spontaneously. Therapeutic strategies in HIV AIDS should not be one-dimensional, but rather linked to complex pathogenic components of AIDS and should address every recognized pathogenic process for therapeutic intervention possibility.

A protein antigen contains epitopes, which is recognized by CTLs, but in a characteristic antiviral immune response *in vivo*, CTLs recognize a small number of potential epitopes (*immunodominance*). Antigenic variation in CTL epitopes was shown for HIV-1 and other viruses, and *antigenic escape* is responsible for persistence. Nowak group developed a model, which dealt with interaction between CTLs and multiple epitopes of a genetically variable pathogen, and showed that nonlinear competition among CTL responses *vs*. different epitopes explains immunodominance [29]. Their model showed that an antigenically homogeneous pathogen population induces a dominant response *vs*. a single epitope, whereas a heterogeneous pathogen population stimulates fluctuating responses *vs*. multiple epitopes. Antigenic variations in immunodominant epitope shift responses to weaker epitopes and reduce immunological control of pathogen population, which is consistent with longitudinal studies on CTL responses in HIV-1 infected patients. For vaccine design, their model showed that major response should be directed *vs*. conserved epitopes even subdominant.

Evolutionary theory stands by that random mutation in the genetic material of an organism results in a characteristic, which provides it an advantage; *i.e*., the mutated organism can surpass better than its equals the obstacles to survive and is improved, gifted for reproducing prolifically. In generations, the lineage that shares the same feature predominates among population components, showing preferred *vs*. other members. Environmental pressure determines which features are selected for its propagation in a population. When Nowak group faced HIV vital cycle, it was evident that HIV was especially equipped to evolve enjoying the protection of the characteristics of the pressure with which it was faced. Its genetic constitution changes continually. It is known that a high mutation rate increases the probability that some genetic change cause an advantage. Genetic variability of HIV is because of an own enzyme: reverse transcriptase (RT). In cell inside, HIV resorts to RT to copy its genome from RNA to double-stranded (ds)DNA, which is inserted in a host chromosome from where it directs the production of more HIV RNA/proteins which, in turn, are assembled to give HIV particles, which escape the cell. The HIV mutates because RT is prone to make errors. Every time RT copies RNA into DNA the new DNA differs from the preceding generation in one site. Such a behaviour converts HIV in the most variable virus. The high replicative rate of HIV redoubles the probability that arise a mutation useful for it. In order to esteem HIV multiplication, notice the findings of Shaw and Ho groups (1995). In an infected patient, every day $>10^9$ new HIV particles are produced. In immune-activity

absence, HIV population is doubled every two days. From original HIV to every HIV particle that be in the organism ten years after the infection, thousands of generations will come up.

From HIV evolutionary potential, Nowak group conceived a model to explain in which way HIV resists complete eradication and usually causes AIDS at the end of a long period. Their proposal assumed that the incessant mutation of HIV genes would lead to a continued production of HIV variants able to break, till certain point, the defences of the immune system operative at a given moment. Variants would arise when the genetic mutations would bear changes in the structure of HIV peptides (epitopes) recognized by the immune system. Frequently, the changes cause no effect on the immune activity but sometimes they make that a peptide become invisible to the organism defences. Involved HIV particles, carriers of a lesser number of recognizable epitopes, escape notice more easily from the immune system. The hypothesis proposed that a mutation, able to avoid that an epitope be recognized, lends HIV variant a survival advantage at least till the immune system discover it and react with the altered peptide, response which reduces HIV charge for some time but other *elusive mutants* arise and the cycle continues preventing total infection elimination. Checking a scheme of this nature is difficult resorting exclusively to clinical tests because detailed monitoring of nonlinear HIV–immune system interactions is impossible. They attended a computer simulation in which HIV population evolved in response to immune pressure. They argued that if the model produces the known patterns of HIV progression, evolutionary scene results interesting. Equations that constituted model kernel reflected characteristics that they considered important in HIV-infection progression: HIV alters immune function causing death of co-adjuvant T-cells. Greater HIV levels cause death of more T-cells. The HIV promotes production and release of *elusive mutants*, which avoid the normal attack of the immune system so that the mutants are propagated among HIV population. After a period, however, defences advert the elusive presence and their population decays. Their model distinguished between two types of immune responses: those that recognize epitopes that easily suffer mutations and the ones that know conserved epitopes. The simulation reproduced the characteristic delay between HIV infection and sudden rise of HIV levels that ends present in the organism. It provided an explanation of why the cycle constituted by new *elusive mutant* and repression does not continue in an undefined way but it culminates in an uncontrolled HIV replication: almost complete loss of co-adjuvant T-cell population and AIDS instauration. The model indicated that the immune system could frequently set up a simultaneous defence intense enough *vs.* different HIV variants. Despite that, a moment arrives usually at the end of many years in which multiple HIV alternatives coincide. When threshold is broken the immune system is incapable of controlling HIV. *Diversity threshold* (rupture point) differs from one person to another; *e.g.*, if the immune system is weak from the beginning a relatively low number of variants ruin organism defences.

Why does the presence of multiple HIV variants weaken the immune system yield? Every member of HIV army is a generalist able to attack any enemy cell that it find. Every immune soldier is a specialist able to recognize an HIV soldier only if this carries a flag of a determined colour. Let one accept that both armies present equal power, if every specialist of the immune army recognizes the same flag and every soldier of HIV faction bears such standard. Let one assume that HIV army is constituted by three groups, every one with a different flag, and that in response the immune specialists are split into three groups, every one able to know a different flag, in which conditions the immune army is in disadvantage.

An immune specialist recognizes and attacks only one out of three enemy soldiers that it find. Soldiers of HIV continue attacking any specialist that waylays and end winning the war.

3.2. Discussion

Life emergence on Earth is a unique historical process. Like in a trial, one investigates to establish main facts. Tools should be science and history. Molecular genetics central hypothesis states that DNA is transcribed to RNA, which is then translated into proteins. However, reverse transcription allows RNA to be transcribed back into DNA. *Molecularity* in biology took scientists to recognize RNA role in bioprocesses and that it preceded DNA as genetic material. The success of these approaches shows a deep synergy between biophysics and evolution. As Darwin noted how natural selection enabled simple life to evolve into complex one, Pross evolution theory hinted how simple but fragile replicators complexified into intricate life chemical systems. A reorientation of research in translational (marketable) science is necessary. In chemistry and physics the reorientation can be carried out by bench-guided reverse engineering. Ideas in biology should be valued by the number of questions that they generate. On one hand, in biology (science) the reorientation can be performed by clinic-guided reverse engineering. The same applies to medicine (the technology of biology). A scheme of the reorientation of research in translational science is in Fig. 3.

Figure 3: Scheme of the reorientation of research in translational science

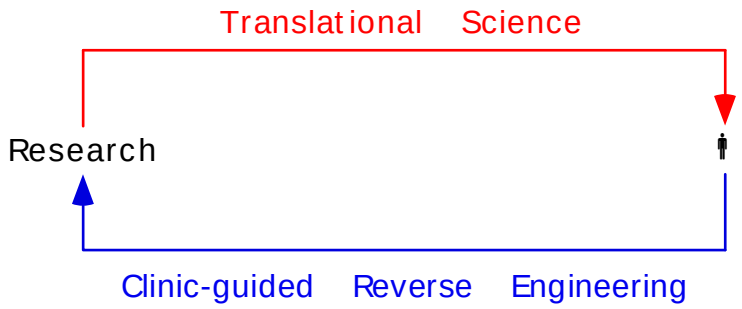
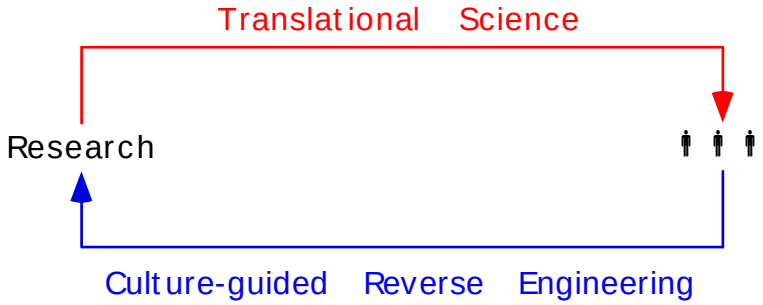


Figure 4: Scheme of the reorientation of research in translational science in a society



On the other hand, in a society the reorientation of research in translational science can be done by culture-guided reverse engineering. A scheme of this reorientation is in Fig. 4.

4. CONCLUDING REMARKS

From the present review and discussion the following remarks can be drawn.

1. It was provided a sketch of the fundamental man–human immunodeficiency virus (HIV) biophysical forces that enable and constrain its evolution and disease. The evolutionary theory turns out to be essential to understand human–HIV relationship and place it in the whole of human diseases. The objective of developing effective antiviral drugs *vs*. HIV was achieved but obtaining a vaccine is distant. Variability of HIV, because of the elevated mutation rate and recombination, together with the latency that characterizes infection, makes it difficult to combat. Knowledge and understanding of the evolutionary mechanisms that govern HIV evolution are key to know not only how it emerged but also how it develops, to treat it, it changes in the future and to eradicate it. An evolutionary scene explained *via* a long way why HIV infection progress slowly and ends destroying the immune system. Advances made *via* computational models were highlighted (basic model of virus dynamics, *etc*.) because discoveries in HIV dynamics, evolution and disease were pioneered *via* simple modelling of biophysical processes that are too complex to be studied in full details.

2. Neglected by modellers, recombination effect in HIV witnessed a rapid interest. The models show that recombination does not facilitate drug-resistance evolution as was frequently assumed. It presents an effect on the expected frequency of combinations of drug resistance mutations, in therapy absence, and rate of fixation of the combinations in the presence of drugs. Whether recombination facilitates or impedes drug-resistance evolution depends on either stochastic effects are the primary force generating statistical associations or epistatic-interactions sign. Recombination-effect understanding in HIV will not only shed light on drug-resistance evolution but also provide insights into other questions of evolutionary biology: what is the benefit of sexual reproduction, *etc*.

3. A current picture of HIV population and evolutionary dynamics was outlined within an infected individual. Progress was made in the area since 2000: clearly no other virus infection exists for which a comparable effort was undertaken to quantify its dynamical behaviour. The quantitative approach led to HIV-infection understanding. However, uncertainty still surrounds many central aspects of viral population dynamics and evolutionary response to changing selection pressures. Quantitative HIV virology was born in 1995 and is still in its childhood. The evolutionary theory turns out to be essential to understand human nature and place it in the whole of living beings. Looking into the future, we expect to witness rising collaboration between the fields of biophysics, biochemistry, cell chemistry, evolution, virology and medicine, as well as between theory/computation and experiment to decipher many aspects of the evolutionary forces that shaped the biological roles of viruses. Further work will be devoted to the reorientation of research in translational science.

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