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Technological Advances in the Design of Biological Cell Robot as an HIV Vaccine

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Abstract

High genetic variability of HIV has been a major intractable challenge to the effective design of vaccines. However, a recent pioneer study published in PNAS Xenobots, is likely to revolutionize the field of HIV prevention as it presented the world's first living robot made of cells. In the advent of this discovery, we herein discuss the possibility of using living biological cell robots to target HIV-infected T lymphocytes and the prospects of this approach being a new HIV vaccine. We capture the current research status and trend of advances in the design of biological cell robots as a new HIV vaccine. The key differences between this novel vaccine and other HIV vaccines are highlighted.

Keywords: HIV; The new vaccine; Biologically inspired micro robots; HIV target cell surrogate

Introduction

While preventive HIV vaccine development has been a constant goal since the discovery of HIV, interest in a therapeutic vaccine for HIV-infected people has fluctuated. Many have felt that a therapeutic vaccine is not possible as until recently there were no examples of such vaccines for other diseases. Moreover, with the advent of increasingly effective, simple to take and relatively nontoxic combination drug therapies there has been less call for immune therapies to substitute for or augment drug therapy. However, The world's first living somatic cell robot has rekindled interest in a therapeutic vaccine, the vaccine can be used as a stand-in for HIV target cells, through alternative ways to protect the body's normal immune cells, but also can enhance immune-mediated clearance of virus-producing cells and/or assist in the destruction of the reservoir of latently infected cells that drug therapy alone does not seem to be able to eliminate [1].

The Status of HIV Vaccines

Since the discovery of AIDS in 1981, massive resources have been directed at research aimed at developing preventive and curative agents for affected patients. Nearly 40 years later, AIDS has become a global public health threat claiming many lives. A few years ago, a meeting was held in Bethesda, Maryland (September 19 20, 2013) to reinvigorate therapeutic HIV vaccine development. Recent therapeutic HIV vaccine trials were described and there was a discussion of results of therapeutic vaccine studies in nonhuman primate models. It was readily apparent that therapeutic vaccine development trials and studies are following the standard preventive vaccine development path. After conceptualizing a product, 5 to 10 years of animal model testing are performed before 2 to 5 years of GMP product development to enable another 10 to 15 years of phase I then phase II then phase III clinical trials of a specific candidate vaccine product before licensure and distribution will occur. This path is depressingly slow and may not be an optimal way to deal with the multiple critical issues to be addressed in therapeutic vaccine development. Attempting to design a vaccine to address such a complexity of issues by reasoning out all the multiple aspects of the final product before testing is very risky. There is a strong possibility of total failure at the end of a prolonged period of testing because of failure to include one essential component, or the inclusion of unnecessary components that detract from overall efficacy. We have long believed that it is postulated that HIV vaccine is the most effective approach to control AIDS pandemic. Although much progress has been made to achieve this goal [1,2] no licensed HIV vaccine has been put on the market to prevent HIV infections. It was clear that therapeutic HIV vaccine development requires addressing several very different issues. These include the following: (1) How to correctly understand the mechanism of HIV infection? (2) How does the vaccine respond to HIV mutations? (3) How to choose the optimal way to block HIV infection?

The Mechanism by Which HIV Infects Host Cells

Human Immunodeficiency Virus (HIV) selectively infects helper T lymphocytes, dendritic cells and macrophages because these cells express CD4 molecules. The HIV infection process is very complex, with several stages including, adsorption, entry, uncrating, reverse transcription, integration, replication, transcription, translation, assembly and maturation (Figure 1). Prevailing research provide evidence that HIV infection requires not only CD4 molecules and helper receptors (CXCR4, CCR5), but also proteins encoded by HIV genes, such as gp120 and gp41. A detailed list of proteins encoded by genes associated with HIV infection in host cells is provided in (Table 1) [3]. When HIV enters human blood stream, it selectively invades host cells expressing CD4 molecules on their cell surface. HIV binds to the CD4 receptor on the surface of the host cell via its surface envelope protein gp120 [4]. Upon binding, gp120 protein undergoes structural alterations exposing another envelope protein gp41. Meanwhile, the gp120-CD4 dimers formed interact with the host's cell surface auxiliary receptor CXCR4/CCR5 to create three molecular complexes constituting gp120-CD4-CXCR4/CCR5. These complexes expose the host cell membrane and the envelope protein gp41, which is hydrophobic, enabling the HIV to be coated with the

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Table 1: HIV-related genes and their coding proteins, specific functions and host-cell related proteins.

Gene	Encoding protein	Protein function	Host cell related proteins
Structural genes	MA	Matrix proteins	Karyopherins, H03, Calmodulin, VAN/NAF1, cyclophilinA, TRIM5α, CyPA
	CA	Capsid protein	HP68/RNaseL Inhibitor, Actin gag
	NC	Nucleocapsid protein	ESCRT, Tsg-101, AIP-1, Nedd4, Ubiquitin
	p6	Nucleocapsid protein	
	RT	A viral genome that can be transcribed and copied pol	
	PR	Cut polymerized protein	
The necessary regulatory genes	IN	Integrate viral DNA with cellular DNA	INI1/hSNF5, LEDGF/p75, BAF, HMGal, ATR, ATM, Karyopherins, XRCC5 env
	gp120	They attach the virus to the surface of the cell	CD4, CCR5. CXCR4, DC-SIGN, DC-SIGNR, MR, CD207
	gp41	Fusion with host cells	
	Tat	Trans-activated proteins that activate HIV gene transcription	NF-κB, cyclin T, CDK9, Med28
	Rev	A regulator of viral protein expression that regulates mRNA splicing and promotes mRNA transport to the cytoplasm	TNPO3, importin β, Crm1, Ran GTPase, Sam68, p32
Nonessential regulatory genes	Nef	Negative regulatory factors, which change cell signals, reduce the expression of CD4 and MHC-I molecules and reduce the killing of HIV infected cells by CTL, are important factors in the development of infection into AIDS	PACS-l, ASKl, PAK, PI3-K, Lck, VAN/NAFl
	Vif	Viral infectious factors that promote viral assembly and maturation	APOBEC3G
	Vpr	Viral protein r, which transports viral DMA to the nucleus, inhibits cell growth	Karyopherins, Uracil-DNA glycosylase, Weel
	Vpu	The viral protein, u, promotes the release of the virus	cD317 (Tetherin, BST-2)

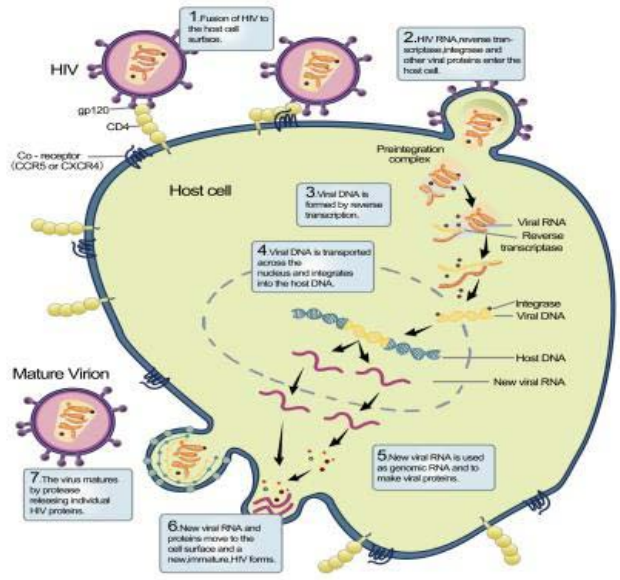

Figure 1: The mechanism by which HIV attacks a target cell.

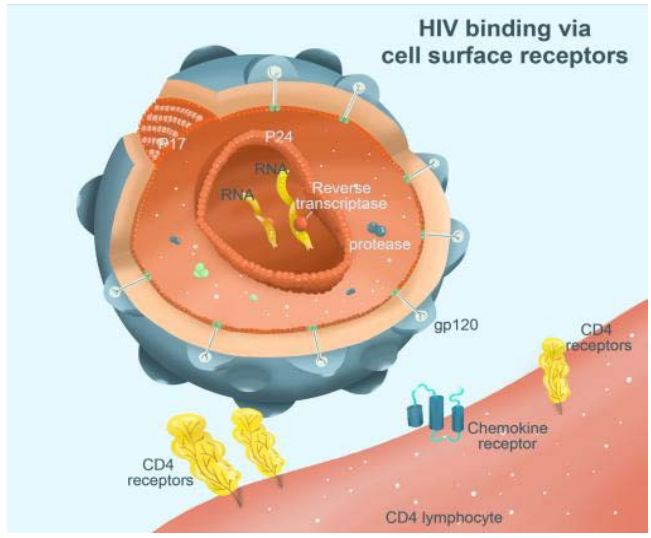

Figure 2: HIV recognizes and binds a CD4 lymphocyte.

host cell membrane followed by HIV and host cell fusion. Finally, the HIV virus nucleic acid is released into the host cell (Figure 2).

HIV is Highly Variable

HIV is the most complex of all retroviruses. Its genetic material ranges between 9.2 and 9.8 KB of RNA. Structurally, it is not very stable and has a high mutation rate. Once HIV is coated and fused with the host cell membrane, it releases its capsid protein HIV p24, which is gradually degraded within the host cell to release HIV RNA and reverse transcriptase [5]. The reverse transcriptase uses the RNA as a template to synthesize viral DNA. The HIV DNA is integrated into the host cell nucleus chromosome by the integrase enzyme. Subsequently, the viral DNA uses existing host cell gene copies and protein replication machinery to synthesize its own proteins. Activation of HIV-infected cells triggers the transcription of pre-viral DNA into viral RNA, which is further translated into structural proteins of HIV. These proteins assemble in the cytoplasm, forming several new viral particles. Eventually, viral particles are exported to the cell surface in form of buds, which then recognize and attack other target cells. Currently, it is known that HIV exhibits high RNA variability, but more importantly, the reverse transcriptase of HIV is prone to the problem of base mismatch in the reverse transcriptase synthesis of DNA using RNA as a template, because the reverse transcriptase lacks the function of base proofreading. This leads

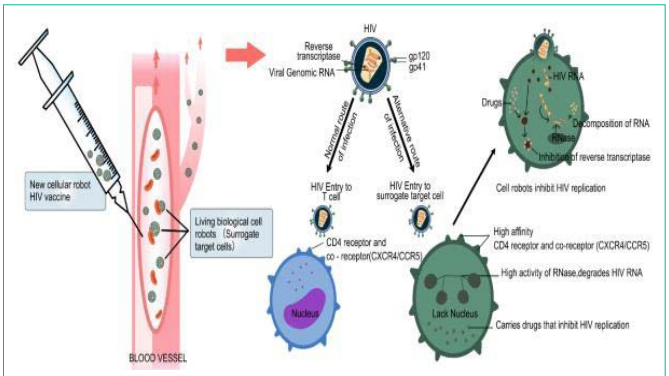

Figure 3: Functions of a living biological cell robot.

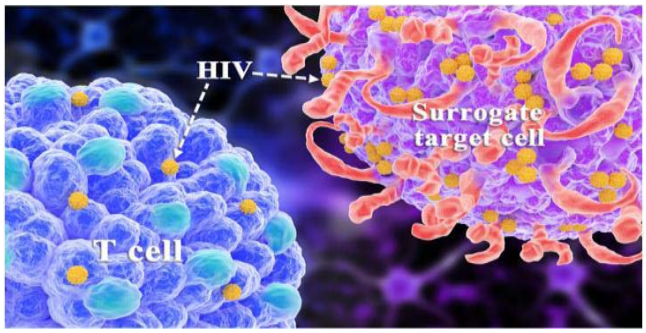

Figure 4: A simulation of HIV infecting a surrogate target cell by the alternative infection.

to a failure to remove the miss-introduced nucleotides in time for replication and an error occurs about once in every replication cycle, causing the virus to replicate with random mutations that are high frequency and non-directional. The high genetic variability translates to high variability in the encoded proteins. A comparison of antigens extracted from wild type strains of HIV with those from AIDS patients in which HIV has already undergone many replications reveal that the structure and amino acid sequence of proteins from these two groups are different. It has been observed that inoculation of vaccines based on HIV antigen into AIDS patients; fail to induce formation of immune cells and antibodies to neutralize HIV. This is because HIV surface antigen molecules undergo rapid mutations, which help HIV-infected cells to escape immune recognition due to decreased affinity of produced antibodies for the mutant HIV antigens.

Alternative Target Cells for HIV Infection

We analyzed the recently reported world's first living bio-robot, which we believe could be a new HIV vaccine. This vaccine differs significantly from conventional vaccines. We know that HIV has a high degree of antigenic variability. For this reason, HIV samples used for vaccine development contain mutated versions of HIV; hence, such vaccines are not effective for controlling AIDS patients. This has been the biggest challenge hindering HIV vaccine research and development. Notably, we have observed that despite its many variants, HIV always targets cells expressing CD4 molecules and the expression of vast majority of CD4 molecules is conserved; variations are rare. This means human CD4 molecules are the main receptors for HIV infection. Based on the recent publication by Joshua Bongard et al [6], we believe that a living biological cell robot can be designed to target CD4 molecules. The surface molecules of this cytbot are highly similar to the target cells, which not only express CD4 molecules but also other helper receptors needed for HIV infection (CXCR4/CCR5). We believe that this somatic cell robot can be an alternative target cell for HIV infection. This robot can be programed using supercomputers and gene recombination technologies, to shorten its lifespan and make it undergo rapid apoptosis after HIV infection. Other cellular robots that are not infected with HIV will also degrade themselves within a short time, to avoid unnecessary immune responses. We can also enzymatically engineer the cell robot to synthesize hiv-rnase in the cell, degrade the hiv-rna that enters the cell, or make the cell robot carry drugs that inhibit HIV replication (Figure 3). In this way, the reproduction of the HIV virus in host cells can be immediately suppressed. To improve the binding rate of HIV to the cell robot, the target cells should be selectively and temporarily sealed with CD4 molecules in the original body using antibodies with radioactive isotopes. Blocking immune cells with CD4 molecules carrying the antibodies may reduce immunity in hiv-infected people, but only temporarily. A recent study showed that the use of live cell robots as alternative target cells for HIV infection, combined with HIV fusion inhibitors, might reduce the use of CD4 blocking antibodies, which will indirectly enhance the effect of the new vaccine without reducing the function of the patient's immune system. In addition, HIV fusion inhibitors can block the entry of HIV virus into human cells. This novel mechanism requires further research. Strategies that inhibit HIV fusion hold huge promise in solving the problem of HIV resistance. Such agents can be used as adjuvant treatments to the new vaccine, given after vaccination to reduce the adverse reactions of the new vaccine (Figure 4). After entering the body, the living cell robot mediates HIV infection by the high affinity receptor expressed on the cell surface and drugs or RNase kills HIV carried by the cell.

By blocking the receptor on the surface of the T cell with the blocking antibody, the probability of HIV infection surrogate target cell will increase.

Results and Discussion

The new live cell robot vaccine is still in the developmental stage and may remain to an idea that require further research. However, we note that it is a better alternative to other HIV vaccines because it overcomes the high variability of HIV. Traditional HIV vaccines currently being studied primarily based on subunit vaccines, live attenuated and inactivated vaccine. However, these approaches are proving difficult due to the high antigenic variability of HIV, which hinders the identification of key representative genotypes or specific protein antigens. Live attenuated vaccines are associated with safety concerns. In the rhesus monkey model, the Simian Immunodeficiency Virus (SIV) mutant strain lacking nef gene prevents attack by pathogenic SIV and protects monkeys from developing AIDS, but it cannot protect vaccinated monkeys against over infection of wild-type virus. Moreover, SIV without nef gene can still cause AIDS, especially when given orally to young monkeys. Of note, genetic mutations or deletions in HIV may attenuate viral reproduction, but at the cost of reducing the effectiveness of the vaccine. For inactivated vaccines, physical or chemical methods are needed to kill the virus, which requires that the antigenic nature of HIV be changed. These inactivated HIV antigens cannot effectively activate the body's

immune system to produce immune responses and the produced antibody titers are very low [7]. This calls for collaborative research between computer science and biological science. In biological sciences, cellular simulations based on the ability of HIV to recognize and bind to CD4 receptors in host cells should be developed. Such simulations should consider some conserved proteins such as gp120 and gp41 to design alternative target cells for HIV infection. In computer science, supercomputers with well-designed evolutionary algorithms, through trial and error approaches, should be employed to program cell robots [5]. Development of "surrogate target cells" for HIV infections will lead to "HIV suicide" because they cannot replicate and reproduce.

Conclusion

We however note that the new cell robot vaccine is still in the early stages of development and many fundamental questions need to be addressed before it can be put into practical use. If cell robots can be made from patients' own cells, the technology could be used to drug delivery in humans. Otherwise, it may ellicit problematic immune responses. The most successful HIV vaccine is still in early trial stages at population level. Although the results are promising, further large-scale clinical trials are needed before it can be deemed suitable for clinical application. The HIV vaccine induces antibody response in the body, but it does not show that the vaccine can effectively fight HIV, prevent AIDS. HIV mainly attacks the body's immune system and the production of antibodies in traditional vaccines is inseparable from the immune system, which often causes failure of vaccination. So far, there has not been a single case of HIV self-healing, suggesting that our immune system alone cannot suppress or eliminate HIV. More importantly, the main defense against HIV in humans relies on Cytotoxic T Lymphocytes (CTL) [8], which secrete a variety of cytokines involved in immune function. In the fight against HIV, the main role of CTL is to kill cells that have been invaded by the virus, thereby halting the reproduction of HIV. However, none of the vaccines developed so far are effective at activating CTL. Another challenge in vaccine development is the long incubation period of HIV/AIDS, which can last for years or decades. As a result, Highly Active Antiretroviral Therapy (HAAT) remains by far the most popular treatment for HIV and we are still a long way from a truly widespread HIV vaccine.

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