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Porto Biomed. J. 2017;2(5):150–152

PORTO BIOMEDICAL JOURNAL
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Porto Biomedical Journal

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Rostrum

The path toward an HIV-1 vaccine☆

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ARTICLE INFO

Article history:
Received 10 June 2017
Accepted 15 June 2017
Available online 31 August 2017

Keywords:
HIV-1 virus
Vaccine
HIV-1 trimer structures
Immunogen design
HIV-1 antibodies

ABSTRACT

HIV is responsible for millions of deaths around the world and in the absence of available treatment capable of a cure, only the vaccine can offer protection against this virus. However, and after three decades of research, such a vaccine remains elusive. Here, I attempt to explain the major challenges on the development of an anti-HIV immunogen, and how the three-dimensional pictures of antibodies interacting with this virus can guide us to the design of a successful vaccine.

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Background

According to the World Health Organization (WHO), the Human Immunodeficiency Virus (HIV), has taken 39 million lives since the beginning of the epidemic to 2015; and with over 2 million new cases of HIV-1 infection reported in 2015 (http://www.unaids.org/en/resources/fact-sheet), this global epidemic does not show signs of remission. The HIV-1 virus replicates by infecting T cells, which are an essential component of our immune system.[1] HIV-1 infection, therefore, compromises the host's immune system eventually leading to its absolute dysfunction. Individuals suffering from untreated HIV-1 infection will ultimately develop the acquired immune deficiency syndrome (AIDS)[2] and will see their survival threatened by otherwise harmless viral or bacterial pathogens. Although there are groups in the population under a higher risk of HIV-1 infection, the epidemic affects people of all ethnic groups, genders and conditions. Current treatments limit viral replication and progression to AIDS in infected patients, however no curative treatment or vaccine is available to date. Thus, finding a cure or designing an efficacious vaccine against HIV-1 infection is undoubtedly a question of great public interest.

The need for a vaccine

Shortly after infection, HIV-1 integrates its genetic material in the host's DNA, an event currently impossible to revert. Therefore, the design of a vaccine against HIV-1 is paramount in order to prepare the immune system to act promptly and neutralize this pathogen before the establishment of a permanent infection.[1] Indeed, the scientific community understood the challenge early on and has dedicated tremendous efforts to obtain immunogens capable of triggering a protective immune response against HIV-1. However, after over three decades of intensive research and 6 unsuccessful HIV-1 vaccine efficacy trials,[1] we still lack an efficacious vaccine. Surprisingly, 20% of the HIV-1 infected individuals develop antibodies (Abs) of extraordinarily broad and potent neutralization activity against nearly all of the 4000 different HIV-1 strains represents that the diversity of circulating viral isolates.[3] Also, some of these Abs isolated from HIV-1 infected patients show protective effects in non-human primates when passively administered before viral challenge. Understanding the conditions in which humans can develop this type of immune response could pave the way for the design of a successful and universal HIV-1 vaccine.

Why have we failed?

The only viral component capable of inducing a protective antibody immune response in humans is the envelope glycoprotein (Env) located on the exposed viral surface.[1] This protein is comprised of two subunits, the surface unit gp120 and the transmembrane subunit gp41, that associate non-covalently to form a trimer of hetero-dimers. Env plays a key role in the viral life cycle by mediating viral entry into the host cell through the interaction with the CD4 and CCR5/CXCR4 receptors on the surface of the target T cells. Such an infection mechanism requires Env conformational changes between two main Env states: the pre-fusion and post-fusion, with remarkable structural differences between

☆ Essay for YES meeting.

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http://dx.doi.org/10.1016/j.pbj.2017.06.002
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these two. Naturally, for its immunogenic properties, the structure of the pre-fusion state is of major importance for the scientists because neutralizing Abs recognize this Env state. However, a clear picture of the three-dimensional structure of HIV-1 Env protein remained elusive for decades. In the past 5 years we have achieved notable breakthroughs in the field of HIV structural biology leading to the determination of several high-resolution crystal and cryo-EM (electron microscopy) structures of the HIV pre-fusion Env.[4–7] The laboratory of Professor Ian Wilson, at the Scripps Research Institute, spearheaded most of the effort that lead to the successful determination of the first crystal structure for an HIV-1 Env protein. Wilson and colleagues engineered a soluble HIV-1 trimer platform where the conformation of this extremely flexible and unstable protein is locked in the pre-fusion state, enhancing the conditions to grow Env protein crystals.[8–10] The outcome of this outstanding research is reported in top scientific journals and unveils the atomic details of this long sought-after protein structure, offering a plausible explanation as to why previous attempts to produce a vaccine may have failed.

New path to vaccine: structure-guided immunogen design

These high-resolution Env structures not only shed light on the molecular details of the HIV-1 fusion mechanism but also, and perhaps most importantly, provided us with the clear mapping of the neutralizing antibody epitopes (regions of antibody recognition) of those broadly neutralizing antibodies (bNAbs) isolated from HIV-1 infected patients.[1] Such knowledge is of paramount importance since the immunogens to be used in a potential vaccine regimen must contain all the components required for antibody recognition and binding. Notably, Wilson and colleagues also discovered that the same epitope recognized by a mature anti-HIV-1 antibody is not necessarily the same epitope that a precursor antibody will bind to. Indeed, work published in Cell by Garces, Wilson and colleagues,[11] identified structures within the epitope (i.e. glycans) that partially block the binding of germline Abs, which are the precursors to the bNAbs isolated from infected HIV-1 humans. These observations had a profound impact in the understanding of the many hurdles involved in triggering the right B cells to initiate antibody affinity maturation leading to a bNAb. These observations also led to the design of a sequential set of immunogens to be administrated in a controlled fashion in order to teach the immune system, step by step, how to generate the desired bNAb.[12]

Proof of concept

Although the vast structural information provided us with valuable knowledge of the intimate relationship between the HIV-1 virus and the human immune system, the direct test of a vaccine in humans is beyond consideration. Fortunately, the availability of new animal models (humanized mice) allowed scientists to prove that immunization strategies, using a series of modified Env proteins, can lead to the development of bNAbs. These mice have cells (B cells) that produce antibodies known to be the precursors of broadly neutralizing antibodies against HIV-1.[12–14] The series of Env proteins used to immunize these mice, guided the maturation of the precursor antibodies to become antibodies that could efficiently neutralize HIV-1 viruses.

Is the HIV-1 vaccine within reach?

This billion-dollar question does not have a simple answer. The structure-guided rationale presented above shows promising results in animal models, demonstrating that this approach is indeed capable of eliciting Abs similar to those bNAbs isolated from HIV-1 infected individuals.[1] Similarly, neutralizing antibodies isolated from Ebola patients were used to successfully treat many patients from the latest Ebola outbreak responsible for 11 thousand deaths in West Africa. So does all of this scientific progress indicate that we will, in time, produce a successful vaccine against the HIV-1 virus? Let's go step by step. The HIV-1 virus exhibits an extraordinary mutational rate, higher than the Ebola, Hepatitis-C and Influenza viruses. To better illustrate this difference we could say that the genetic diversity within a single HIV-1 individual is equivalent to the diversity for the Influenza virus globally, and still the flu vaccine does not always show 100% efficacy. Because the HIV infected individual can live for many years as a virus carrier, it would be important to develop an HIV vaccine that is easily administered and available to everyone in the world to maximize protection coverage, since just one infected individual can spread the disease over such a long period of time. Although we do not have an efficacious vaccine today, the research on the HIV vaccine is also helping to overcome some limitations in our understanding of the immune system in humans. How B cells first recognize the antigens and the role of germinal centers is still largely unknown but may be of tremendous importance to develop a vaccine capable of developing bNAbs.[15] It is also possible that in the pursuit of an HIV-1 vaccine, we may well advance our understanding of the Immune system to a point where other vaccines may be developed. An example of this, is the structure-based vaccine recently developed to prevent Respiratory Syncytial Virus (RSV) infection in infants, where high resolution envelop glycoprotein crystal structures were used to generate an immunogen that improved the current RSV vaccine.[16,17]

Acknowledgments

The author would like to thank Dr. Amelia Escolano from the Rockefeller University, in New York, and Dr. Javier Guenaga from The Scripps Research Institute, in San Diego, for helpful discussions that improved the quality of this review.

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