Mini Review

Integrative Immunobiology and Vaccines

Human Immunodeficiency Virus (HIV): Current Research and Therapeutic Approaches

Lauren R. Byrne and Haley O. Tucker*

Department of Molecular Biosciences, the University of Texas at Austin, Austin TX, 1 University Station A5000, Austin TX 78712, USA

*Corresponding: Haley O. Tucker, Molecular Biosciences, Institute for Cellular and Molecular Biology, University of Texas at Austin, 1 University Station A5000, Austin TX 78712, USA, Tel: (512) 475-7706; Fax: (512) 475-7707; E-mail: haleytucker@austin.utexas.edu

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Abstract

This mini-review evaluates the current molecular approaches in preventing infection, inflammation and AIDS progression through structure-based vaccine design, targeted immunotherapy, and antiretroviral drug regimens.

Keywords: Pyroptosis, Caspase-1 inhibitors, Anti-retroviral, Viral therapy

Introduction

The sexually transmitted virus Human Immunodeficiency Virus I (HIV) is a single-stranded RNA retrovirus that infects CD4+ T cells by binding to and cellular entry via T cell CD4 and CCR5 coreceptors [1]. As a retrovirus, HIV reverse transcribes its RNA genome into DNA and then integrates it into the host genome, giving rise to persistent infection. HIV initiates caspase-1 mediated pyroptosis of CD4+ T cells causing the release of pro-inflammatory cytokines such as IL-1beta and IL-18 [2]. These chemical messengers, in conjunction with the release of cellular contents (including newly assembled virions), recruit T cells to the site of infection, creating a cyclic pathway of chronic infection and inflammation.

When blood T-cell counts drop below 200 cells/µl, the patient is said to have progressed to Acquired Immunodeficiency Syndrome (AIDS) [1]. At this stage, the body's immune system is severely hindered and susceptible to opportunistic infections—a syndrome that is typically fatal. In 2017, approximately 36.9 million people worldwide were living with HIV/AIDS [3]. While this epidemic has sparked extensive research in HIV susceptibility and viral pathogenesis, it has cultivated momentum in the field of immunotherapy with growing support and efficacy of anti-retroviral therapies.

Humoral bNAb response to HIV

Understanding the humoral response to HIV infection is critical in the development of new approaches toward limiting its infection. Significant efforts have gone into understanding how HIV is capable of evading antibodies (Abs). Several studies (reviewed in [1]) have indicated that a high mutation rate, dispersed location of envelope glycopolypeptides 120 and 41 (gp120 and gp41), and structural masking of conserved regions from Ab recognition are mechanisms of immune evasion exploited by the virus [4].

Despite neutralization insufficiency of anti-HIV Abs generated by the majority of infected patients, rare HIV+ individuals have been found to produce broadly Neutralizing Abs (bNabs). Typified by VRCO1, which targets HIV's CD4 binding site (CD4bs), bNabs are capable of neutralizing various HIV strains [4].

Very few bNabs had been isolated until recently, with
the advent of single-cell cloning techniques [1]. The number of promising bNAbs now has been expanded significantly to include quaternary-specific Abs, whose epitopes involve the gp120 variable loops and gp120 glycosylation, as well as a series of Abs that recognize the CD4bs on gp120 [4,5]. Despite bNAb isolation from different donors, West and colleagues [3] found that CD4bs Abs arose from two closely related germ-line IgVH genes, V_{H}1-2 and V_{H}1-46. Through sequencing and structural analyses, they identified key residues found in the CD4bs regions of gp120 as well as specific V_{H}1-2 gene family amino acid residues necessary for the production of potent bNAbs [3]. These studies illuminated immunogen targets for vaccine production and identified structural Fab components for improved design of Ab function.

In conjunction with these findings, identification via structure-based analysis of the hydrophobic N-terminal region of the gp41 transmembrane subunit has been carried out. This region is critical for cell entry and has shown susceptibility to neutralization by Abs (e.g., VRC34.01) generated by an HIV+ donor with broadly neutralizing sera [6]. VRC34.01 neutralization was tested against several HIV pseudo strains with induced point mutations within their fusion peptides to elucidate critical residues contributing to neutralization. Figure 1 highlights the crystal structure of HIV fusion peptide interaction with VRC34.01 that identified the dominant fusion-peptide residues. Further studies from this group [6] determined the effects of mutations of these dominant residues upon VRC34.01 neutralization of 206 HIV-1 Env pseudoviruses.

These findings shed light on a new target for Ab neutralization, validated the potential use of fusion peptide sequences for rational Ab design, and highlighted the plausibility of employing such peptides as immunogens for vaccine development.

**Preventing host immune response T-cell damage**

Despite growing efforts in developing effective preventative methods, clinical demands have focused current areas of research onto the host immune system and its role in HIV pathogenesis. More specifically, research aimed at understanding the elusive mechanisms by which CD4+ T cells are eradicated during HIV infection has elucidated potential targets for immunotherapeutic interventions.

![Figure 1: Crystal structure space filling model of molecular interface between synthetic fusion-peptide and Fab VRC34.01 illustrating critical interactive residues. HIV fusion peptide, red; VRC34.01 heavy chain, green; VRC34.01 light chain, yellow. Modified and reproduced with permission from Kong et al. [5].](image)

While caspase-3 mediated apoptosis has been identified as a key mechanism, it only accounts for approximately 5% of CD4+ T cell death [2]. The other 95% of T cells die due to caspase-1 mediated pyroptotic cell death. In this highly inflammatory form of programmed death, cytoplasmic contents are released that initiate production of pro-inflammatory cytokines such as IL-1β and IL-18 [2]. This caspase-1 mediated pathway links the two signature events of HIV infection—CD4+ T-cell depletion and chronic inflammation—creating a vicious pathogenic cycle of lysed cells recruiting more cells to enter and die.

Dotish et al. [2] designed a series of experiments to study the role of caspase-1 in CD4 T cell death of HIV infected lymphoid tissue by employing a variety of caspase inhibitors (specifically, against caspases 1, 3 and 6 as well as a “pan”-caspase).

They found that pan-caspase and caspase-1 inhibitors blocked CD4 T cell depletion as efficiently as the viral inhibitors efavirenz and AMD3100 [2]. Inhibitors of caspase-3 and -6 as well as necrostatin-1, a RIP1 inhibitor, were unsuccessful at preventing CD4 T-cell depletion or the release of IL-1beta (Figure 2 and data not shown). This led to the suggestion that cell death did not reflect necroptosis, but rather pyroptosis with release of cellular contents [2].
Figure 2: Caspase 1 inhibitors prevent CD4 T-cell death in HIV-infected human lymphoid aggregate cultures (HLACs). Viable CD4 T cells were assessed by flow cytometry. Supernatants were prepared and then examined for cytoplasmic LDH enzyme release either without virus (gray bar), with drug inhibitors (Efavirenz and MD3100, blue bars) or following 50 or 100 ug addition of Caspases (blue bars). Caspase-1 and Pan-caspase inhibitors exhibited highest level of CD4 T cell count maintained under HIV-1 infection. Modified and reproduced with permission from Doitsh et al. [2].

These findings proposed a different perspective in anti-AIDS treatment by placing focus on preventing host immune response T-cell damage rather than preventing viral replication and transmission.

Combined antiviral therapy (cART)

Targeted immunotherapy shows great promise in the global field of viral therapy. The current most efficacious treatment for HIV/AIDS is combined Anti-Retroviral Therapy (cART), which consists of multiple drugs that inhibit viral genome transcription, integration and viroid assembly [7]. Within the spectrum of antiretroviral drugs, there are several classes that target different enzymes or aspects of the HIV life cycle. Namely, Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs), Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs), Protease Inhibitors (PIs) and Integrase Inhibitors (ITIs) [1,7]. Despite proven effectiveness of these drugs when taken as directed, there are associated toxicities that accompany PIs and nucleoside analog blocking of DNA synthesis due to negative effects on similar host enzymes [7].

Thus, current efforts under development have shifted focus to long-lasting ARTs in order to promote adherence and reduce acquired resistance [8]. In order to relieve damage to the patient, integrase and non-NNRTIs show the greatest selective toxicity, and therefore, the most promise in positive patient outcomes. Margolis et al. [9] performed a clinical trial to test the efficacy and determine dosage regimens for intramuscular cabotegravir and rilpivirine (ITI and NRTI) as compared to daily doses of these drugs administered orally. Their study revealed that viral suppression was significantly more successful in both treatment groups as compared to controls. Despite not exceeding the efficacy of orally administrating current ART drugs, cabotegravir and rilpivirine still proved effective as a long-lasting ART [9].

These findings support further investigation of long-lasting anti-retroviral therapies in an effort to eliminate contributing factors to therapy resistance such as suboptimal patient adherence.

Conclusions

With the HIV epidemic growing more prominently in developed countries, current research has focused on preventative measures, anti-viral therapy, immunotherapy and palliative care. In the absence of a cure, current research described in this review have promoted a variety of new options for treatment and prevention by uncovering “hidden” targets for vaccine development, areas of immune response modulation for immunotherapy, and promising selectively-toxic anti-viral therapies.

References


