HIV: Current Research

Extended Abstract

B cell exhaustion in HIV: A role for programmed death receptor 1 (PD-1) immune checkpoint

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Abstract

Immune checkpoints are several co-stimulatory and inhibitory pathways that regulate T cell immune responses. Most of the discoveries about immune checkpoints were made in cancer research where inhibitory immune checkpoints cause immune exhaustion and down-regulate anti-tumor responses. In addition to cancer, immune checkpoints are exploited in chronic infectious diseases. In human immunodeficiency virus (HIV) infection, the immune checkpoint molecule called programmed cell death protein 1 (PD-1) has been determined as being a major regulatory factor for T cell exhaustion. Recent studies with antibodies blocking either PD-1 ligand 1 (PD-L1) or PD-1 show not only promising results in the enhancement of HIV-specific immune responses but even in reducing the latent HIV reservoir. Apart from the therapeutic target for a functional cure of HIV-1, immune checkpoint molecules might be used as biomarkers for monitoring disease progression and therapeutic response. In this review, we will summarize and discuss the inhibitory immune checkpoint molecules PD-1, cytotoxic T-lymphocyte-associated protein 4 (CTLA4), lymphocyte-activation gene 3 (LAG3), and T cell immunoglobulin and mucin-domain-containing-3 (TIM3) as well as the co-stimulatory molecules CD40L and CD70, including their role in immunity, with a particular focus on HIV infection, and being potential targets for a functional HIV cure.

An estimated 33.2 million people are infected worldwide with human immunodeficiency virus (HIV), the etiologic cause of acquired immunodeficiency syndrome (AIDS). In 2007, 2.5 million people were newly infected with the virus, and 2.1 million people died of AIDS-related illnesses,1 making this pandemic the fourth leading cause of mortality globally. The successful development of a safe and effective HIV vaccine is still in the future.2 Therefore, research continues to focus on disease treatment by chemical anti-HIV agents.

Significant progress has been made in the development of antiretroviral therapy (ART). ART can successfully delay destruction of the immune system, reduce severity and frequency of opportunistic infections, and consequently delay AIDS progression. Introduction of highly active antiretroviral therapy (HAART), which employs a combination of nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and/or protease inhibitors (PIs), can reduce viral load to below detectable levels in patient plasma, resulting in improved patient health and life span.3–6 However, the virus is suppressed rather than eradicated by HAART.7–9 On HAART regimens, multiple drug therapies can lead to increased adverse effects and toxicities due to long-term use and drug–drug interactions.10,11 Moreover, inadequate clinical viral suppression of HIV-1 due to various reasons and the high error rate of the reverse transcriptase lead to the emergence of drug-resistant and multi-drug-resistant viral strains.12 Drug-resistant virus is then involved in HIV transmission, and more than 25% of newly infected individuals harbor HIV-1 isolates that are resistant to at least one ART.13,14 Therefore, novel potent antiretroviral agents, which have simplified treatment regimens (fewer pills and less-frequent administration), and target not only reverse transcriptase and protease but also other viral targets, may hold particular promise in addressing issues of current therapies.

Down-Regulation of CD4 Expression :

CADA analogs (cyclotriazadisulfonamide) (12) (Fig. 2) have been distinguished as powerful enemy of HIV mixes with novel component of action.53 Binding investigations with HIV-1 uncovered that CADA didn't straightforwardly connect with the CD4 receptor and additionally popular envelope glycoproteins. Further examination found that CADA analogs work by a particular CD4 down-adjusting potency.54 Analysis of CD4 mRNA levels recommended that CADA guideline isn't required at the transcriptional level yet most likely communicates at a (post)translational level.55 Vermeire et al. further showed that the antiviral intensity of the CADA analogs relied essentially upon the down-guideline of CD4 receptor articulation. Expulsion of CADA mixes from the cell culture medium brought about complete reclamation of CD4 articulation. This classification of mixes indicated against HIV section movement at micromolar or sub-micromolar concentrations.56,57 Most as of late, this equivalent gathering announced that they have effectively coordinated a dansyl fluorophore into the synthetic structure of some CADA mixes, and demonstrated the possibility of following a receptor and its down-modulator simultaneously.58 These fluorescent CADA analogs would now be able to be applied in further investigation on receptor tweak.

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Co-Receptor Binding Inhibitors :

Chemokine receptors have a place with the seven transmembrane G protein coupled receptor family. They are associated with the movement of numerous infections, including rheumatoid joint inflammation, transplant dismissal, asthma, disease, HIV, and others. CCR5 and CXCR4 are the primary chemokine receptors engaged with the HIV passage process.59 Based on their chemokine receptor use, HIV separates might be partitioned into R5, X4, and R5/X4 strains.60 R5 detaches are the overwhelming infection strains, which are specially transmitted between HIV-tainted patients.61 However, R5 variations will in the long run develop into X4 segregates or R5/X4 secludes in around half of HIV-1 positive people, bringing about expanded viral replication rate, quicker sickness movement, and the beginning of AIDS.62

During the HIV section process, the CD4-gp120 complex should additionally tie to chemokine co-receptors so as to enter the objective cells.63 The third factor locale, V3, of gp120 is the significant district ensnared in co-receptor associations. It is an around 35-buildup long, as often as possible glycosylated, exceptionally factor, disulfide-reinforced structure that impacts HIV-1 tropism.64 The amino-corrosive arrangements of V-3 can decide the use of CCR5 or CXCR4.65 Besides V3, a moderately all around saved structure found halfway on the spanning sheet is likewise significant for authoritative to both CCR5 and CXCR4 co-receptors.64 Epidemiology information shows that people homozygous for δ32 CCR5 allele (no statement of CCR5 on cell surface) are profoundly impervious to HIV infection66,67 and clearly solid. This reality features the benefits of focusing on co-receptor authoritative to repress HIV section.