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Review Article

CD8 T cells in HIV Infection: A Review

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Abstract

CD stands for clusters of differentiation used to classify monoclonal antibodies that recognised identical subgroups from a panel of leukocyte cell lines and is now used almost exclusively to refer to the leukocyte antigens themselves.CD8 and CD4 are among the most well known and intensively studied of the CD antigens. CD8 is glycoprotein expressed on thymus derived lymphocytes (T-cells) and contains immunoglobulin-like (ig-like) extracellular domains, a membrane- spanning segment, and a short cytoplasmic tail that interacts with $P56^{lck}$ a sre-like tyrosine kinase. The CD8 exists as a disulfide-linked dimer of either one α- and one β- chain of 34kDa each or of two α- chains. CD8 T cells play an important role in the control of HIV replication during the early phase of infection. These HIV-specific CD8 T cells are targeted at the dominant viral variant and their emergence is usually associated with a rapid fall in viral load before the development of an antibody response. HIV infection is characterized by CD4 T cell depletion, CD8 T cell expansion, and chronic immune activation that leads to immune dysfunction

Keywords: CD8 T Cells,CD,HIV,AIDS

Introduction

The term CD stands for clusters of differentiation used to classify monoclonal antibodies that recognised identical subgroups from a panel of leukocyte cell lines and is now used almost exclusively to refer to the leukocyte antigens themselves.CD8 and CD4 are among the most well known and intensively studied of the CD antigens.

CD8 is glycoprotein expressed on thymus derived lymphocytes (T-cells) and contains immunoglobulin-like (ig-like) extracellular domains, a membrane- spanning segment, and a short cytoplasmic tail that interacts with $P56^{lck}$ a sre-like tyrosine kinase. The CD8 exists as a disulfide-linked dimer of either one α- and one β- chain of 34kDa each or of two α- chains. The extracellular regions of the α- and β- chains of CD8 are homologous to one another and consist of a single NH_2 terminal ig-like domain and a 50-(α) or 30-(β) amino acid hinge region (Leahy,1995). In humans, both genes are located on chromosome 2 in position 2p12. The CD8 co-receptor is predominantly expressed on the surface of cytotoxic T cells, but can also be found on natural killer cells, cortical thymocytes, and dendritic cells. It is expressed in T cell lymphoblastic lymphoma and hypo-pigmented mycosis fungoides, but is frequently lost in other T-cell neoplasms (Leong *et al.*, 2003).

CD8 Structure

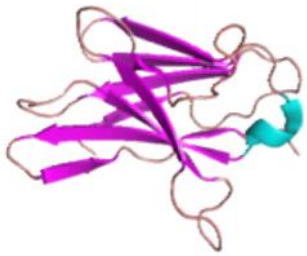

Fig 2.10: Crystallographic structure of the CD8 molecule (Leahy *et al*., 1992).

The cDNA sequence of the α, and β subunits of CD8 revealed them both to consist of an NH_2 terminal domain homologous to Ig variable domains and a short hinge region connecting the ig-like domain to a putative membrane- spanning region. E.g., the alignment of the NH_2 terminal ig-like domains of the α- and β- chains results in 17% of the residues matching, and 30 amino acid long hinge region of the β- chain is 20 amino acids shorter than that of the α- chain. Also the cytoplasmic region of the β- chain does not contain the pattern of cysteine residues identified in the α- chain. Although the differences in the expression and function of α/α α/β dimmers have also been detected but the significance of these differences remains uncertain. The α- chain of CD8 alone has shown to be sufficient for at least some of CD8 function through the transfection of α- chain of CD8 with a TCR which was sufficient to reconstitute MHC (Major histocompatibility complex) restricted recognition of antigen. The crystal structure of the NH_2 terminal 113 amino acids of human CD8 showed the expected NH_2 terminal domain homologous to Ig variable domains with 9 beta-strands divided into 2 beta sheets, one of 4 and the other of 5 strands (Leahy *et al*.,1995). The C-C and F-G loops that in CD4 were truncated form part of the dimer interface in immunoglobulins and immunoglobulin –like in CD8 in both length and function. In the CD8α structure there is an immunoglobulin-like intersheet disulfide bridge from the B-strand to the F-strand with another cysteine conserved in the C-strand which closely apposed to the B-F disulfide bridge suggesting that either the B-F or B-C disulfide could form without gross rearrangements of CD8 structure. The hinge region that connects the NH_2 terminal Ig –like domain to the transmembrane segment consists of 50 residues in the α- chain and 30 residues in the β- chain. This hinge region has O-linked glycosylation which correlates with extended structure for the CD8 hinge region necessary to allow the NH_2terminal of CD8 to span the length of a TCR (T-cell receptor) and MHC molecule to interact with the α3 domain of class 1 MHC molecule. This O-linked glycosylation is heavily sialiated leading to several negative charges in the region. Also the glycosylation in the hinge region extends the extracellular portion of CD8 away from the negatively charged cell membrane or modulates intermolecular interactions with other T-cell membrane proteins. In β chain hinge region of CD8, the level of sialiation has been shown to vary with activation state of the T-cell and this modulation of glycosylation may reflect a regulated charge in CD8 properties.

Molecular Basis of the Peptide Major Histocompatibility Complex 1 (PMHC1)–CD8 Interaction

The interaction of CD8 with MHC 1 molecule during both T- cell development and response to antigen are central to T- cell function. The molecular nature of these interactions and the signals arising from them are thus of considerable interest. The CD8 co-receptor binds to a largely invariant region of MHC1 that is spatially distinct from the TCR binding platform, allowing the potential for tripartite (TCR–pMHC1–CD8) complex formation.The CD8- binding site on MHC 1 had been identified as a region of highly negative charge, and so a surface of complementary positive charge was sought on CD8 and the only surface of CD8 with a uniformly positive electrostatic potential is the surface containing the complementarity-determining region-like (CDR-like) loops. In an analogous fashion to the TCR, the soluble domain of CD8 contains a number of flexible complementarity-determining region-like (CDR) loops that are involved in MHC1 binding. The interaction between the CDR-like loops of human CD8αα (residues 51–55) and a finger-like loop in the α3 domain of HLA-A*0201 (residues 223–229) forms the main contact zone of the complex. The CDR-like loops of CD8αα ‘clamp’ onto this flexible finger-like loop asymmetrically, with each molecule in the dimer contributing differently to the overall binding. Additionally,

CD8αα contacts the α2 and β2m domains of HLA-A*0201, compounding the overall stability of the complex . These findings have been confirmed recently by another study that reported the co-crystal structure of CD8αα in complex with HLA-A*2402 in which, CD8αα bound primarily to the flexible α3 domain of HLA-*2402 in a virtually identical conformation to that observed with HLA-A*0201 (Shi *et al.,* 2011). Although murine CD8αα bound to H2-K^b in a similar fashion compared with the human HLA-A*0201-CD8αα complex, there were some key differences in fine specificity between these two interactions. For example, in the murine system, more contacts were made between CD8 and the MHCI α3 domain, fewer contacts existed between CD8 and the MHC1 α2 domain, and a number of unique bonds were formed at the interface between CD8 and β2m. These differences probably explain the higher binding affinity of murine CD8 compared with human CD8 for their corresponding species-specific MHC1s.

Until recently, the orientation of the CD8αβ heterodimer in complex with pMHCI was still speculated and the atomic structure of murine CD8αβ in complex with H-$2D^d$, at 2.6 Å resolution (Wang *et al.,* 2009) revealed that the binding mode of the CD8αβ heterodimer was largely homologous to that of the CD8αα homodimer. Accordingly, the CDR-like loops of CD8αβ bound predominantly to the conserved finger-like loop in the H-$2D^d$ α3 domain. Moreover, CD8αβ adopted a single orientation in the H-$2D^d$–CD8αβ co-complex, with the β-chain in the equivalent position to the CD8 α1-chain in the pMHCI–CD8αα complex, proximal to the T-cell membrane, in opposition to the original structural conformation predicted previously. Nonetheless, there were also some notable differences between the murine pMHCI–CD8αα and pMHCI–CD8αβ complex structures. For example, CD8αβ did not contact the α2 and β2m domains of H-$2D^d$, which reduced the buried surface area of this complex compared with murine pMHCI–CD8αα.

The T-cell co-receptors govern TCR binding orientation and MHC restriction. According to Bridgeman *et al.*(2012), accumulated structural evidence of TCR–pMHC interactions has shown that the TCR binds with a conserved general topology, with the TCR α-chain positioned over the N-terminus of the peptide and the TCR β-chain over the C-terminus. Also this binding mode is essential to allow co-receptor binding to the same pMHC as the TCR at the cell surface). Hence, the CD8 co-eceptor (and CD4 co-receptor) may have a role in governing the conserved binding mode of the TCR to allow the formation of a functional signalling complex at the T-cell surface,(Yin *et al.,* 2012) Indeed, studies by Kuhns and Davis showed that the ectodomains of CD3εδ and CD3εγ, that constitute an important part of the TCR signalling complex, associate with the Cα DE and Cβ CC' loops, respectively, within the constant domain of the TCR. In this study, mutation of these conserved loops disrupted the formation of the TCR–CD3 signalling domain and subsequent T-cell activation. So it seems that these CD3 subunits, that contain intracellular tyrosine kinase activation motifs and play an important role in providing T-cell activation signals, form specific interactions with the TCR, fixing their position at the cell surface with respect to the TCR. Yin ***et al****.(2012),* showed that the structure of the tripartite TCR–pMHCII–CD4 complex is compatible with this notion. This would position the intracellular signalling domains of CD3 and the co-receptor in close proximity to enable cross-signalling during antigen engagement. If the TCR bound in the reverse polarity, with the TCR β-chain over the peptide N-terminus and the TCR α-chain over the C-terminus, the CD3 complex would lie distal from the co-receptor, and this could presumably reduce the efficiency of the T-cell activation signal between the co-receptor and the CD3 complex. Works have shown that the CD4 and CD8 co-receptors impose MHC-restriction on T cells by preventing Lck availability during TCR interactions with non-MHC antigens. Indeed, in the absence of the co-receptors T cells develop with antibody-like specificities that can respond to other cell surface molecules, such as CD155. It seems probable that the ability of the CD8 co-receptor to interact with the MHCI α3 domain enables the formation of an orientationally correct TCR–CD3 signalling complex essential for positive selection in the thymus, and subsequent efficient recognition of antigen in the periphery.

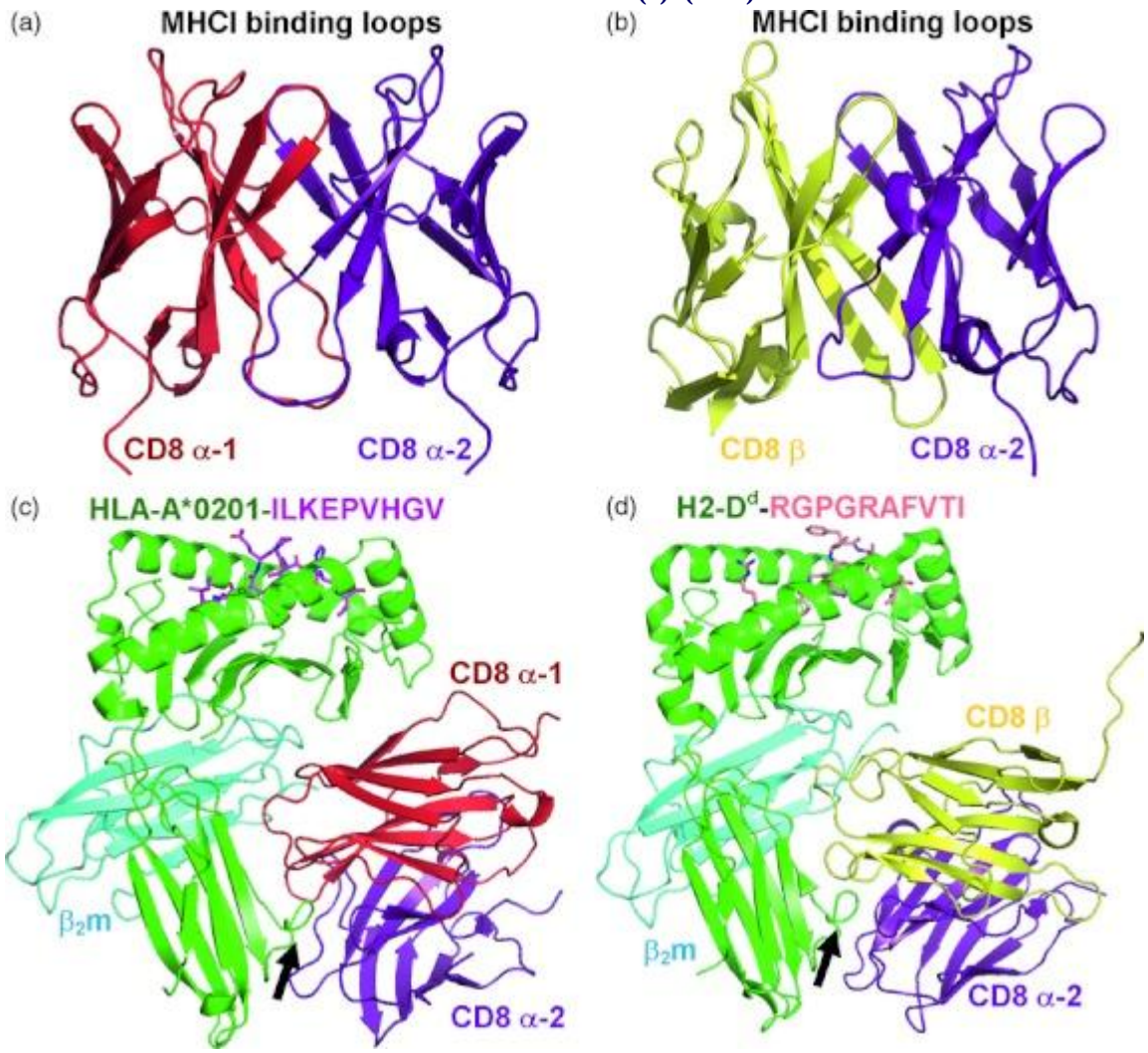

Fig 2.11: Crystal structures of CD8αα and CD8αβ

Fig 2.11: Crystal structures of CD8αα and CD8αβ in complex with peptide–MHC class 1complex (pMHC1). (a a) Crystal structure of the human CD8αα homodimer (PDB: 1CD8) with the α1-chain shown and the α2-chain shown. (b) Crystal structure of the human CD8αβ heterodimer (PDB: 2ATP) with the α-chain shown and the β-chain shown. (c) The co-crystal complex between human CD8αα and HLA-A2*0201-ILKEPVHGV (PDB: 1AKJ). CD8 is shown (α1) and (α2) binding mainly to the α3 domain of MHCI. The complementarity-determining region (CDR)-like loops of the CD8 molecule bind to a finger-like loop formed by residues 223–227 of the MHCI α3 domain; this interaction comprises the main binding interface between CD8 and MHCI (indicated by an arrow). (d) The co-crystal complex between murine CD8αβ and H2-D^d-RGPGRAFVTI (PDB: 3DMM). CD8 is shown (α2) and (β) binding mainly to the α3 domain of MHCI (indicated by an arrow). Although the amino acid sequence of CD8β is distinct from that of CD8α, the CD8αβ heterodimer adopts a virtually identical conformation to that of the CD8αα homodimer and binds to pMHCI in a similar overall manner.

CD8 and Immune System

Immune responses are initiated when resting precursor CD4` T cells are triggered by MHC/peptide complexes in concert with costimulatory molecules on the surface of antigen presenting cells (APCs). As a consequence of this triggering, the CD4` T cells proliferate, begin to secrete cytokines (IL-2, IFN-c, IL-4, etc.) and express important cell surface molecules including the IL-2 receptor (CD25), CTLA-4, and CD40 ligand. In addition to these regulatory pathways, which are intrinsic to CD4 T cells, some studies have suggested that CD8 T cells

also interact with CD4 T cells to regulate immune responses in a profound manner. For example, CD8 T cells have been shown to control the physiological outgrowth and function of autoreactive CD4 T cells in vivo (Jiang *et al.*, 2000) .These regulatory interactions between CD4 and CD8 T cells are complex and involve both antigen specific and nonspecific mechanisms. In principle, three distinct but not mutually exclusive models by which CD8 T cells specifically regulate antigen driven CD4 T cells can be enumerated. First, CD8 T cells could be triggered by antigens to secrete lymphokines, which, in turn, control the CD4 T cells activated by the same antigens. Indeed, cytokines including IL-4 and IFN-c secreted by CD8 T cells have been shown in some systems to regulate CD4 T cell function. Because of the potential proximity of CD4 and CD8 T cells at the site of initial antigen activation and because antigen-activated T cells preferentially may express the receptors for these cytokines, the effect of even these antigen nonspecific cytokines will be relatively antigen specific. Second, antigen triggering induces CD4T cells to transiently express non polymorphic membrane activation molecules unrelated either to antigen or TCR that are recognized by regulatory CD8 T cells. The recognition of these activation molecules (sometimes referred to as ergotypic structures) may induce CD8 T cell differentiation into effector cells that have the potential to delete or inactivate antigen-activated CD4 T cells. Third, T cell receptor related structures, including TCR-derived MHC/ peptide complexes expressed on antigen-activated CD4 cells may induce regulatory CD8 T cells. These CD8 T cells could then differentiate and recognize the TCR-derived peptide/MHC class I complexes expressed on the activated CD4 inducer cells. The effector phase of regulation mediated by these putative TCR peptide-recognizing CD8 T cells may involve either conventional cell-mediated cytotoxic (CTL) functions and/or the release of cytokines. This latter view of immune regulation involving recognition of TCR structures was initially suggested, in principle, by Jerne in his idiotype-driven network hypothesis. According to Jiang *et al.*(2000), many of the suppressor cell interaction models proposed during the latter part of the 1970s and early 1980s involved complex interactions between T cell subsets (which now include the CD4 and CD8 subsets) as well as the recognition of TCR related structures by CD8 T cells. It is shown that CD8 T cells are generated during immune responses, in vivo and in vitro, which down regulate CD4 T cells in a TCR Vb–specific manner. This led to two immunological hypotheses generated (i.e. TCR specific network regulation and control of immunity by suppressor T cells) that were more prevalent and/or popular two to three decades ago, at a time when the scientific revolution that has occurred in the molecular characterization of the immune system was in its infancy. During many infections, all T lymphocytes regardless of specificity may undergo cytokine-driven phenotypic changes—so-called bystander activation—but only those T cells that recognize pathogen-encoded antigen go through multiple rounds of replication to generate enormous numbers of CTL effector progeny that are the foot soldiers of the adaptive immune response (Zhang and Beran, 2011).

CD8 T cells in HIV Infection

CD8 T cells play an important role in the control of HIV replication during the early phase of infection. These HIV-specific CD8 T cells are targeted at the dominant viral variant and their emergence is usually associated with a rapid fall in viral load before the development of an antibody response. HIV infection is characterized by CD4 T cell depletion, CD8 T cell expansion, and chronic immune activation that leads to immune dysfunction (Catalfamo *et al*.,2011).

Most of the CD8 T cells generated during primary infection die within a few weeks, leaving a reservoir of HIV-specific CD8 memory T-cells that l persist, regardless of the presence of antigen or CD4 helper T cells. Attempts to account for the gradual failure of CD8 T cells to control HIV replication have been made. The 'viral escape' theory states that the cells begin to lose the ability to recognise HIV's genetic sequences due to the high level of viral turnover and mutation. One study found that CD8 T cells lose their ability to recognise and kill viral variants, even though they may be responsive to normal 'wild type' viruses. CD8 cytotoxic T cells from HIV-infected asymptomatic individuals were compared with

those from symptomatic AIDS patients and it was found that CD8 T cells from asymptomatic individuals could recognise and kill both types of target cells while in contrast, the CD8 T cells from symptomatic patients, while still able to recognise and eliminate the laboratory strain targets, no longer killed target cells infected with their own virus. Additionally, HIV-specific CD8 T cells may fail to produce the cytotoxic molecule, perforin, which CD8 cells use to kill virus-infected cells. The CD8 T cells are unable to keep up with the increasingly diverse population of HIV inside the body without helper T cells that slowly disappear during HIV disease. Also as HIV mutates in the body, due to several factors including pressure from antiretroviral medications, these CD8 T-cells become increasingly irrelevant.CD8 T cells express CD4 receptors on their surface following activation through the T cell receptor, permitting infection by HIV. This suggests that it may be a mechanism through which CD8 T cells become depleted late in infection. The mechanism(s) of HIV-induced immune activation are not completely understood but the dynamics of CD4 and CD8 T cells are altered in many ways during HIV infection. Both show evidence of increased proliferation and preferential loss of the naive subset. Distinct pathways differentially influence proliferation of CD4 and CD8 T cells in patients with HIV infection. Proliferation of CD4 T cells is driven by a combination of the homeostatic response to CD4 T cell depletion (CD4 T cell counts) and viral load (HIV RNA levels) while in contrast, CD8 T cell proliferation is driven mainly by HIV RNA levels (Catalfamo *et al*.,2011). In lymphopenic bone marrow transplant recipients, homeostatic proliferation leads to an accumulation of cells with a highly activated memory phenotype (Boasso *et al*., 2008). During untreated HIV infection, the homeostatic response to CD4 T cell depletion occurs in an Ag-rich inflammatory environment. Together these forces contribute to increased proliferation in both CD4 and CD8T cells (Catalfamo *et al*., 2011).

During HIV infection, HIV replication leads to activation of the innate and adaptive immune systems, generating an inflammatory environment associated with the induction of type I IFN (Boasso and Shearer, 2008). Chronic exposure to type I IFN may have detrimental consequences on T cell homeostasis and survival (Boasso *et al*., 2008). Although type I IFNs exhibit antiviral effects, they also can inhibit thymopoiesis and B cell development and can induce proliferation and exhaustion of hematopoietic stem cells (Sato *et al*.,2009).

CD8+ T Cells in AIDS

The AIDS hallmark is the simultaneous fall in CD4 and rise in CD8 T lymphocytes (Tran *et al*., 2012).

CD8+T lymphocytes (CD8-TLs) play a critical role in control of HIV - infection. There is a strong temporal association between the onset of the initial HIV/SIV-specific CD8-TL response and the decline of peak viremia to the set point, which is maintained into the chronic phase (Borrow *et al*., 1994). There is a close correlation between certain MHC class I (MHC-I) alleles and control of viral replication in HIV-infected humans (Yant *et al*.,2006) implying that certain CD8 T lymphocyte responses are better than others at controlling virus replication, therefore it is important to understand the entire AIDS virus-specific T lymphocyte response particularly in elite controllers, which might represent the rare instances of effective CD8 T lymphocyte responses. In AIDS patients, according to, there exist a population of cells with reduced ability to undergo clonal proliferation (nonclonogenic) which belong to the CD8+ subsets that is phenotypically defined by the surface expression of HLA DR antigens, leading to loss of HIV 1 specific cytotoxicity with CD8+ cells totally retaining their cytotoxic potential as measured in te redirected killing assay. This shows that in AIDS patients, the loss of HIV specific cytolytic activity is in part from a defect in HIV specific ctotoxic T lymphocytes population to expand in vivo and an expansion of CD8+ T subset characterised phenotypically by surface expression of HLA DR Antigens.

Conclusion

The CD8 T cells are unable to keep up with the increasingly diverse population of HIV inside the body without helper T cells that slowly disappear

during HIV disease. Also as HIV mutates in the body, due to several factors including pressure from antiretroviral medications, these CD8 T-cells become increasingly irrelevant.CD8 T cells express CD4 receptors on their surface following activation through the T cell receptor, permitting infection by HIV. This suggests that it may be a mechanism through which CD8 T cells become depleted late in infection.CD8 T cells should be improved to help CD4 T cells in fighting HIV infection.Those infected with HIV infection should eat well to boost the immune level.

In the present study, serum Leptin was found to increase significantly 6 months after insertion of BIB. These results are in agreement with those of Marek Bužga et al in which serum Leptin showed a significant decrease 6 months after the insertion of the balloon which is probably related to the decrease in the amount of adipose tissue after MedSil® balloon application [31].

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