Modeling of the A6 T Cell Receptor Interacting with the Viral Tax Peptide

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Abstract

T-cell receptors (TCR) on cytotoxic T lymphocytes (CTL) detect the presence of intracellular infections by binding specifically to foreign peptides bound to class I major histocompatibility complex (MHC) on infected cells. TCRs are heterodimers consisting of alpha and beta chains found on the surface of T lymphocytes. The extracellular portions of these chains contain two domains, a constant and variable region. A constant transmembrane region found in both chains anchors the TCR to the T cell membrane. The variable domain contains complementarity determining regions (CDRs) composed of short stretches of amino acids that differ among TCRs. Each chain contains three CDRs that form a unique antigen binding site, which determines the specificity of the TCR to foreign peptides. The antigen binding site is created by random rearrangements of multiple, short gene fragments in the DNA. The modeled A6 TCR is specific for the Tax peptide of the human T-cell lymphotrophic virus type 1 (HTLV-1). The Tax peptide is composed of nine amino acids which interacts with the flat surface of the TCR. When the TCR binds the class I MHC-peptide complex, the CTL is activated. Activated CTLs eliminate intracellular infections by releasing substances which lyse the infected cell. Interaction between the TCR and class I MHC-peptide: complex is critical for eliminating the infection.

Introduction

- CTLs express TCRs that recognize the presence of a specific infectious agent by binding to a peptide derived from a protein of the intracellular pathogen (Fig. 1).
- In the absence of TCRs, intracellular pathogens are not detected by the CTLs and survive in the host.

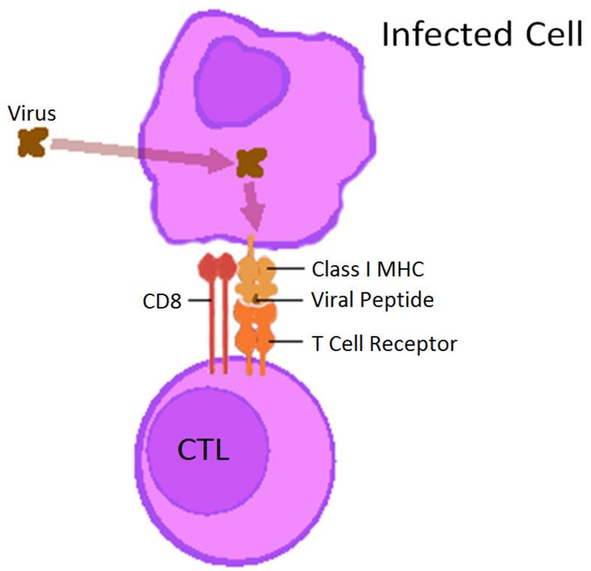

Fig 1. A viral peptide binding to a TCR. The virus infecting the cell gets broken down into small viral peptides, which are presented on class I MHCs. A TCR, specific for the viral peptide, binds to the MHC-peptide:complex; activating the CTL to kill the infected cell. (http://www.mcld.co.uk)

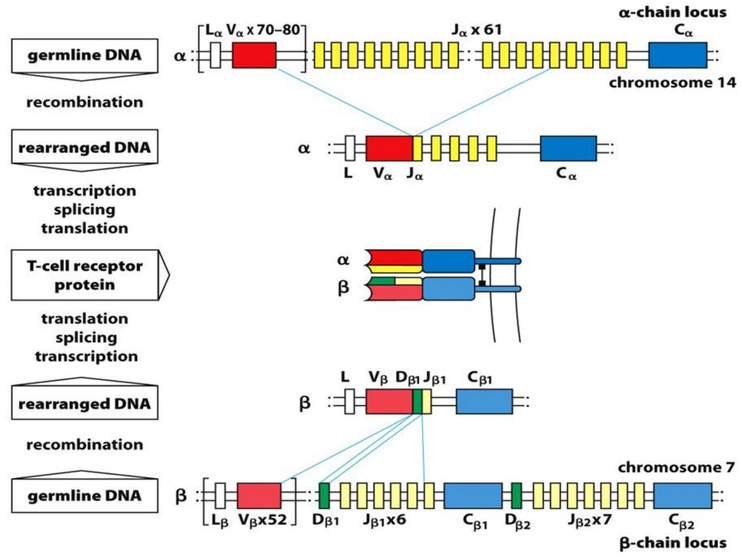

Fig 2. Somatic recombination of alpha and beta chains on the TCR. Functional antigen receptor genes are created in T lymphocytes following DNA rearrangements, which bring together randomly chosen V, D, and J gene segments in the beta chain and V and J gene segments in the alpha chain. Together the Va and Vb domains create the variable portion /antigen binding site of the TCR. (Janeway, 2005)

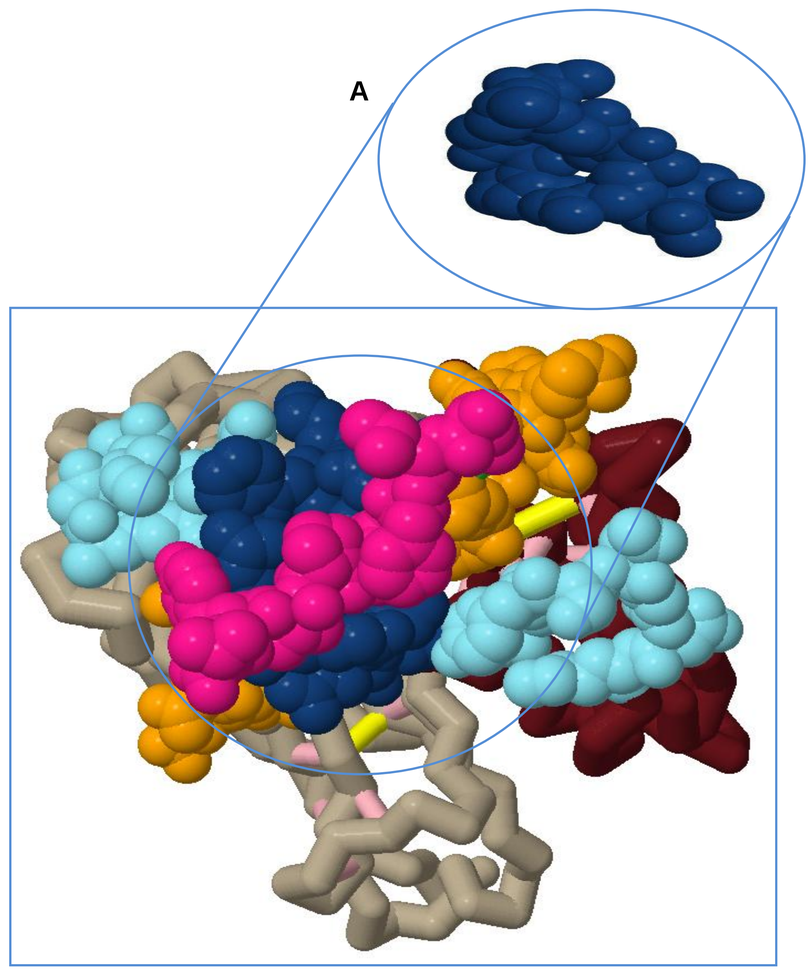

Fig 3. Tax peptide bound to TCR. CDR1 (orange), CDR2 (light blue), CDR3 (dark blue), alpha domain (brown), beta domain (grey). The CDRs contact the peptide on a flat surface. As a result, the TCR has a diagonal orientation allowing it to better interact with the peptide. **A.** The CDR3 region binds the peptide with the greatest affinity. Shown without the peptide. Based on 1AO7.pdb.

Molecular Story

- CTLs arise in the bone marrow but mature in the thymus.
- During maturation, the alpha and beta chains of the TCR undergo somatic cell recombination (Fig. 2).
- Once the variable regions of both chains of the TCR are rearranged, the TCR peptide-binding site undergoes a selection process.
- Positively selected TCRs are released into the bloodstream and migrate to secondary lymphoid organs.
- When the TCR binds a specific peptide-MHC complex on an infected cell, the CTL is activated to kill the infected cell.

Experimental Evidence

Sequencing Studies by Jores et al. (1990) revealed the presence of hypervariable regions in TCRs which correspond with the peptide binding domain. A variability plot of the variable region on the TCR was used to identify the hypervariable regions.

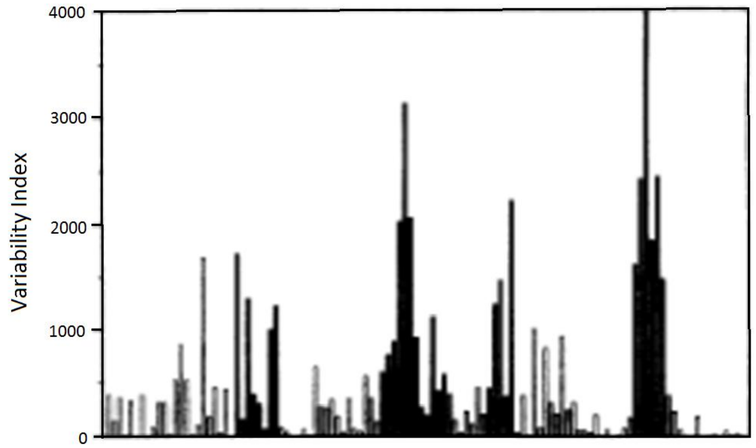

Fig 4. Variability plot of 159 TCR beta chains. Each TCR beta chain was sequenced and examined for differences. The area of the chart with a high variability index indicates a hypervariable region. These regions are unique to each TCR. (Jores et al., 1990)

Conclusion

CTLs develop unique TCRs through somatic recombination. Positively selected TCRs are released from the thymus where the CDRs in the variable domain are responsible for binding the peptide. The CDR3 portion binds the peptide with the highest affinity.

References

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