BL- 1A, 5A, 17A, NE3A, NW12A/ 2010G659

Crystal structure analysis of HLA-B*52 in complex with peptide derived from HIV

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1 Introduction

It was shown that Pol283-8-specific, HLA-B*52:01-restricted cytotoxic T cells (CTLs) were elicited predominantly in chronically HIV-1-infected individuals. These CTLs had a strong ability to suppress the replication of wild-type HIV-1, though this ability was weaker than that of HLA-B*51:01-restricted CTLs. The crystal structure of the HLA-B*52:01-Pol283-8 peptide complex provided clear evidence that HLA-B*52:01 presents the peptide similarly to HLA-B*51:01, ensuring the cross-presentation of this epitope by both alleles [1]. Population level analyses revealed a strong association of HLA-B*51:01 with the I135T mutant and a relatively weaker association of HLA-B*52:01 with several I135X mutants in both Japanese and predominantly Caucasian cohorts.

2 Experiment

Soluble HLA-B*52:01 (with beta-2 microglobulin and peptide TAFTIPSI) was prepared and crystallized. Prior to crystallization trials, HLA-B*52:01 was concentrated to final concentration of 20 mg ml^{-1} in the buffer containing 20mM Tris-HCl (pH 8.0), 250 mM NaCl.

Data sets were collected at beamlines BL-5A, NE-3A of PF and BL41XU of SPring-8. The data sets were integrated with XDS, merged and scaled using Scala. HLA-B*52:01 crystal belonged to space group $P2_12_12_1$, with unit-cell parameters a = 69.0, b = 83.3, c = 170.3 Å. Based on the values of the Matthews coefficient (V_M) of 1.37 A^3/Da, it was estimated that there are two protomers in the asymmetric (V_{solv} = 10.5%).

Details of the data collection and refinement statistics are summarized in Table 1.

The structure was solved by the molecular replacement method using the Molrep. The crystal structure of HLA-B*51:01 (PDB ID: 1E28) was used as a search model. Structure refinement was carried out using Refmac5 and Phenix. The final model was refined to an R_{free} factor of 30.1 % and R_{work} of 26.0% with root mean square deviations of 0.005Å and 0.836° in bond length and angle, respectively.

3 Results and Discussion

The data and refinement statistics is summarized in Table 1. The overall structure and peptide binding mode were similar to that of HLA-B*51:01 complexed with the same Pol283-8 peptide, which we previously reported (Fig.1). This explains the cross presentation for this peptide of both HLA allele. On the other hand, notably, there exists the conformational difference in the N-terminal region of the peptide (Fig. 1). The substitution of Phe67 with Ser makes the local space, causing the N-terminal region of the peptide (T1 and A2) deeply lied into the peptide-binding groove. Furthermore, the Gln63Glu mutation makes new interaction with T1 residue of the peptide. These changes would to some extent hide the side chains of T1 and A2 (flat surface) to T cell receptors, which may reduce their interactions to TCRs on the HLA-B*52:01-restricted CTLs. On the other hand, the C-terminal region of the peptide onto HLA-B*51:01 and HLA-B*52:01 was similar to each other, even though the C-terminal Ile8 of the peptide exhibits more shallow recognition to the hydrophobic groove of HLA-B*52:01 than HLA-B*51:01 (Fig. 1). These results may indicate that the relatively flat surface of the N-terminal side of bound peptide on HLA-B*52:01 contributes to lower affinity to TCRs than HLA-B*51:01.

Table 1: Data statistics

	HLA-B*52:01
Wavelength(Å)	1.000
Resolution range (Å)	46.9-3.10 (3.27-3.10)
Space group	$P2_12_12_1$
Unit-cell parameters (Å)	a = 69.0, b = 83.3, c = 170.3
No. of observations	165816
No. of unique reflections	18422 (2584)
Completeness (%)	99.6 (98.2)
Multiplicity	9.0 (7.1)
Averaged $I/\sigma(I)$	2.8(1.2)
R_{merge}	0.241 (0.596)
Refinement	
Protein atoms	6312
Resolution range (Å)	38.8 - 3.10 (3.26-3.10)
R_{work}	0.260 (0.355)
R_{free}	0.301 (0.454)
R. m. s. deviation	
Bond lengths (Å)	0.005
Bond angles (°)	0.836

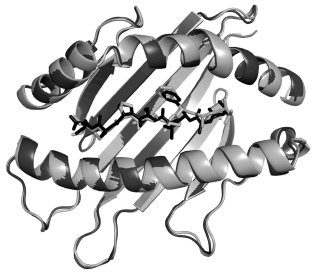

Fig. 1: Crystal structures of HLA α1-α2 domains complexed with the Pol283-8 peptide (stick model) on the HLA-B*52:01 black) and HLA-B*51:01 (light gray).

References

[1] Y. Yagita *et al*., *J. Virology* **87**, 2253-63 (2013).

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