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Comprehensive Reanalysis of Some Data in the Reports Relate to the TCR Vβ Repertoire of Peripheral Blood in the Patients with Different Diseases

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Abstract

Eighteen reports related to Variable region of Beta Chain (Vβ) of T cell Receptors (TCR) of the patients with leukemia were reanalyzed. In the results, Vβ3 and Vβ9 were the usually predominantly used genes in all the diseases, which including infectious disease, cancers and leukemia. There were common characteristic of TCR Vβ usage in the same kind of disease; while there were specific characters in the different individuals with the same disease. This finding indicated that it may be helpful for the mechanism study or diagnosis of the diseases according to the specific or common features of TCR Vβ usage.

Keywords: T cell receptor; Beta chain; Peripheral blood; Leukemia; Cancer; Infectious diseases

Introduction

In the past fifteen years, there were some studies related to the clonalities of TCR α and β heterodimer, especially the clonal expression of Vβ genes. In these reports, the predominant usage TCR Vβ gene families usually were shown, and these genes were considered as the factors associated with the corresponding diseases by the authors. However, there was no report about an overview aiming at these reports till now. This paper just focused on the reanalysis of the data in the reports. Through this comprehensive analysis, we attempt to find some new ideas which were different from the original authors, and exhibited some novel indications for the researchers of this filed.

Literature Review

Eighteen reports (1-18) were selected as references to reanalyze, and the inclusion criteria was that the specific predominant usage TCR Vβ genes were clearly listed; if not, it would be excluded. The relative diseases involved Hepatitis Virus B (HBV) infection, *Human Immunodeficiency Virus* (HIV) infection, *Pemphigus vulgaris (PV),* Colorectal Cancer (CC), Lung Cancer (LC) and leukemia. Leukemia mainly included Acute Promyelocytic Leukemia (APL), T cell-Acute Lymphoblastic Leukemia (T-ALL), B cell-Acute Lymphoblastic Leukemia (B-ALL), Acute Monoblastic Leukemia (AMoL), Acute Myelogenous Leukemia (AML) and Chronic Myeloid Leukemia (CML). The details of the useful information extracted from the reports were listed in Table 1.

Generally, there were two Vβ genes which further divided into two subfamilies in the family of 24 TCR Vβ genes: Vβ5 and Vβ13. The former contained Vβ5.1 and Vβ5.2; the later had Vβ13.1 and Vβ13.2. In some references of this study, there were some Vβ genes else which held subfamilies, for example, Vβ7 contained Vβ7.1, Vβ7.2 and Vβ7.3. These differences probably lied on the different classification standards for the subfamilies. However, the main Vβ gene families' classification was consistent with each other. In order to unify the classification standard and make the data convenient for counting the predominant usage, the numbers of Vβ subfamilies were counted as the total of the corresponding main Vβ gene family. Besides, a concept of Predominant Usage Frequency (Frequencies) (PUF or PUFs) was applied, and its calculation formula was as following:

$$PUF\ (\%) = \Sigma n / \Sigma p \times 100$$

Σn: the summary of the times for certain a Vβ gene which was predominantly used; Σp: the summary of the patients with certain disease or all the patients in the study.

Comprehensive Reanalysis

In the predominant usage Vβ genes of all the patients, Vβ3 were the highest usage genes, the PUF was 18% (36/200); Vβ9 was next to it with the PUF of 17% (34/200), which was followed by Vβ5 with the PUF of 13% (26/200). Both PUFs of Vβ13 and Vβ21 were 11.5% (23/200). In all of the 24 Vβ genes, the lowest usage gene was Vβ4 with PUF of 1.5% (3/200); Vβ16 and Vβ24 were second to it and which PUFs were all 2.5% (5/200) (Figure 1).

As shown in Figure 2, in HBV infection, the gene with highest PUF was Vβ11 (28%), Vβ12 was next to it with PUF of 22%. The PUFs of Vβ8, Vβ9 and Vβ10 were all 16%; in HIV infection, the gene with highest PUF was Vβ5 (37%), Vβ7 was next to it in which PUF was 32%. The PUFs of Vβ9 and Vβ20 were both 26%. According to the predominant usage frequencies of TCR Vβ specific to different diseases, the features of Complementarity

Determining Region 3 (CDR3) of TCR Vβ were reanalyzed with histograms.

Discussion

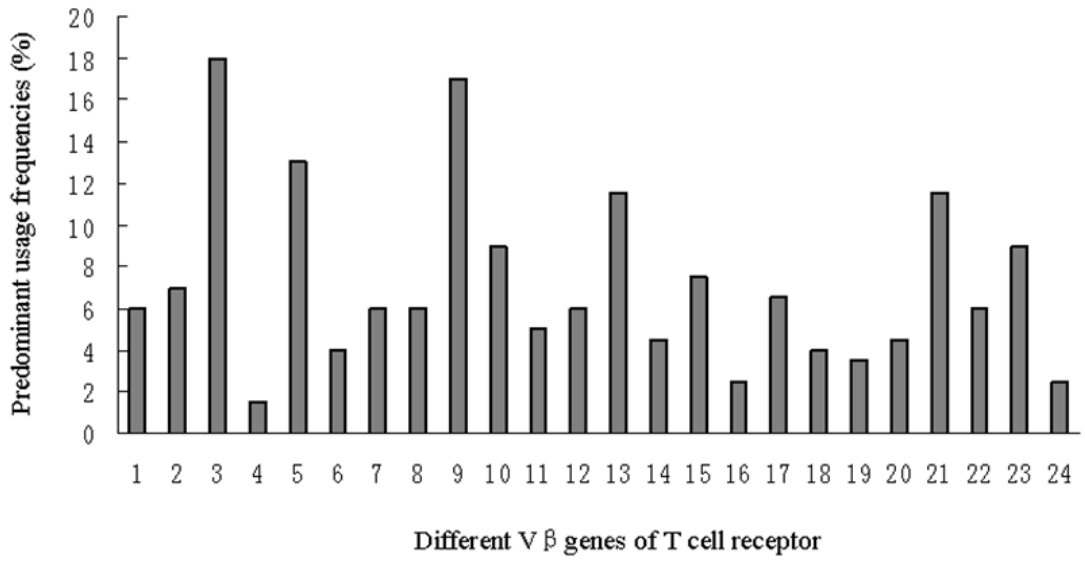
As the authors shown, there were different predominant usage gene families in different diseases. For example, Vβ11 and Vβ12 expressed in HBV infection; Vβ3 and Vβ13 in CC; Vβ12, Vβ21 and Vβ23 in APL; and so on. In most viewpoints of the researchers, these different predominant usage genes were just specific to the different diseases and probably represent the different features of the corresponding diseases. However, in our opinion, there were some insufficiencies in the perfect analysis for every report, and there would be more meaning to comprehensively analyze these research results.

In 24 Vβ gene families of all the cases, TCR Vβ3 was the most advantageous usage gene in the diseases except HBV and HIV infections. This probably indicated that Vβ3 always was the predominantly used in most of diseases beside virus infections. Vβ9 and Vβ13 even existed in all the diseases which except for APL and AML, respectively. This result showed that there were no specificities for their expression to the diseases; but if the expression absence of the two genes could indicate the occurrence of APL or AML needed for further study. As the gene families of low PUFs, Vβ4 was predominantly used in HBV infection, CC and APL; while Vβ16 was the advantageous expression gene for HBV infection, AML and CML. These results showed that Vβ4 and Vβ16 probably were the diagnosis indices for HBV, CC, APL, AML and CML; especially, Vβ4 plus Vβ16 may be more helpful for the diagnosis of HBV infection because both had relative high PUFs in this disease.

According to different PUFs of TCR Vβ in different diseases, the histograms were designed. As Figure 2 shown, the columns of different heights in the histogram represented the predominant usage frequencies of Vβ subfamilies. Obviously, the panorama of each histogram looked like a key, and the prominent columns were as same as the kits of the key. There were different kits in different diseases, for example, the components of the kits for HBV infection were Vβ2-Vβ4-Vβ5-Vβ8-Vβ9-Vβ10-Vβ11-Vβ12-Vβ13-Vβ15-Vβ16-Vβ17- Vβ18-Vβ21-Vβ22-Vβ23-Vβ24; those were Vβ5-Vβ7-Vβ9-Vβ13-Vβ20 in HIV infection; while those were Vβ2-Vβ7-Vβ9-Vβ21 in AMOL. Except for the components, and the height of the column determined by PUF was also the factor which determined the key's feature. The higher the frequency of the TCR Vβ gene family was, the higher the kit of the key would be. Therefore, to some extent, the key presented the total characterization of TCR Vβ skewness of the patients with certain a disease. As we known, the skewness of TCR Vβ specific to the associated antigen of the corresponding disease, so the key formed with the predominant usage genes could be taken as the whole skewness of TCR Vβ; in another words, it was a specific key to the certain a disease. There is a proverb in China which says that 'Open different locks with different keys'. Accordingly, there should be a key specific to every disease, such as various pathogen infections, colorectal cancer, leukemia, and so on.

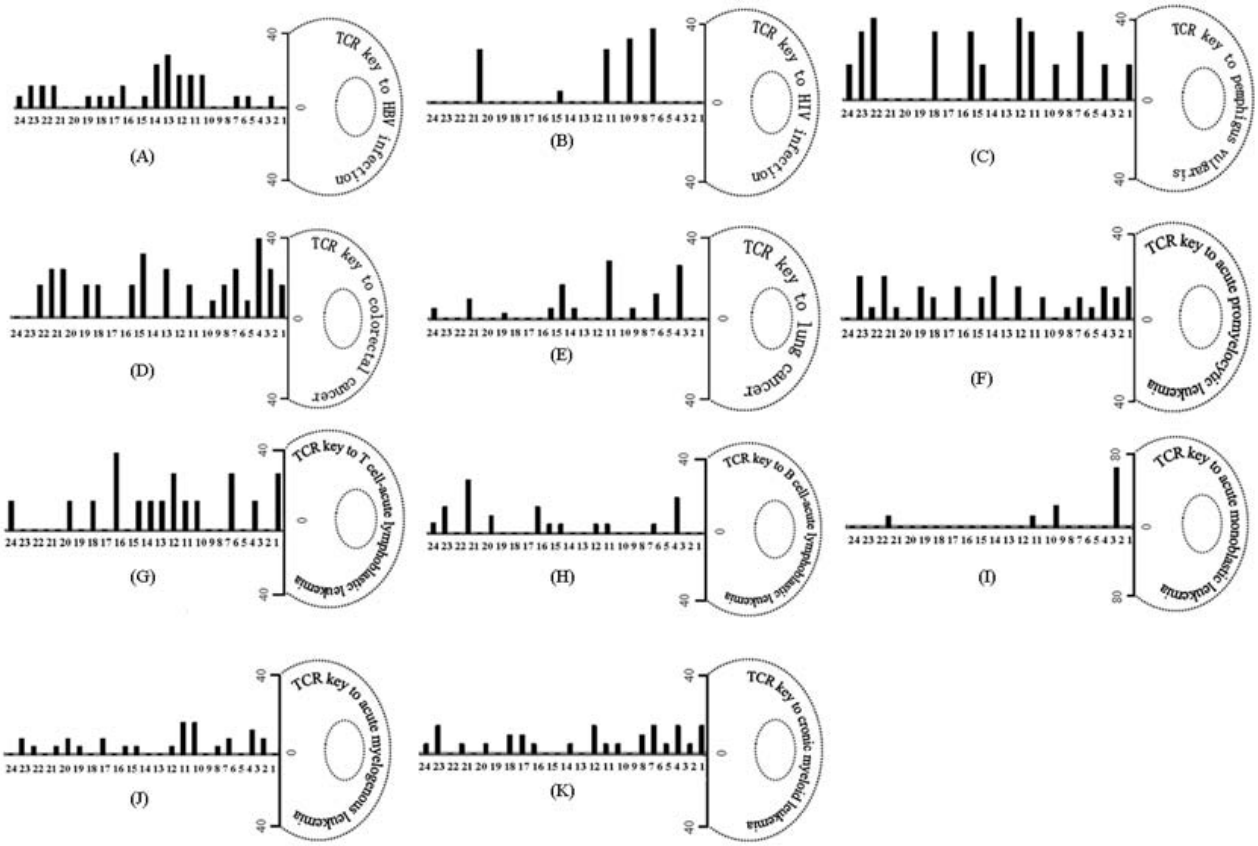
Conclusion

Through the reanalysis of the data in the articles related to TCR Vβ predominant usage, we found the total usage characteristics of 24 Vβ gene families in the different diseases, and the individual features of the gene usage in each of the disease. To our understanding, these results probably pose a new idea or a novel viewpoint for analyzing and using the skewness of TCR for the researchers. For example, if the histogram of TCR



In all the patients, Vβ3 were the highest usage genes, the PUF was 18% (36/200); Vβ9 was next to it with the PUF of 17% (34/200), which was followed by Vβ5 with the PUF of 13% (26/200). Both PUFs of Vβ13 and Vβ21 were 11.5% (23/200). In all of the 24 Vβ genes, the lowest usage gene was Vβ4 with PUF of 1.5% (3/200); Vβ16 and Vβ24 were second to it and which PUFs were both 2.5% (5/200).

Figure 1: The total predominant usage frequencies of TCR Vβ genes summed from the patients with different diseases.



According to the reports relates to the predominant usage frequencies of TCR Vβ specific to different diseases, the features of Complementarity Determining Region 3 (CDR3) of TCR Vβ were reanalyzed with histograms respectively. The columns with different heights represent different predominant usage frequencies of Vβ subfamilies (including the monoclonal, biclonal and oligoclonal gene families), and the polyclonal and low-expression genes are ignored in this analysis. It is easy to see that each merged gram likes a big key, which probably reflects the characteristics of the skewness of T Cell Receptor (TCR) specific to the corresponding disease. (A) The TCR key to Hepatitis Virus B (HBV) infection; (B) The TCR key to Human Immunodeficiency Virus (HIV) infection; (C) The TCR key to *Pemphigus vulgaris*; (D) The TCR key to colorectal cancer; (E) The TCR key to lung cancer; (F) The TCR key to acute promyelocytic leukemia; (G) The TCR key to T cell-acute lymphoblastic leukemia; (H) The TCR key to B cell-acute lymphoblastic leukemia ; (I) The TCR key to acute monoblastic leukemia; (J) The TCR key to acute myelogenous leukemia; (K) The TCR key to chronic myeloid leukemia.

Figure 2: The different "keys" specific to different disease formed with the predominant usage frequencies of TCR Vβ genes in PBMC of the corresponding patients.

Table 1: The summary of the predominant usage TCR Vβ genes in PBMC of all the patients with different diseases extracted from the references.

Diseases	Reference Number	Predominant usage Vβgenes from the corresponding reference	Total of cases
HBV infection	[1]	**P1:** Vβ8, Vβ24, Vβ10; **P2:** Vβ12, Vβ11, Vβ15, Vβ22, Vβ23	18
	[2]	**P1:** Vβ9; **P2:** Vβ5, Vβ9, Vβ13, Vβ11, Vβ15; **P3:** Vβ12, Vβ11, Vβ16; **P4:** Vβ10, Vβ17, Vβ18, Vβ21; **P5:** Vβ4; **P6:** none; **P7:** Vβ22; **P8:** none	
	[3]	**P1:** Vβ11, Vβ23; **P2:** Vβ12; **P3:** Vβ8; **P4:** Vβ2, Vβ8; **P5:** Vβ11; **P6:** Vβ9; **P7:** Vβ10, Vβ22; **P8:** Vβ12	
HIV Infection	[4]	**P1:** Vβ9; **P2:** none; **P3:** Vβ7; **P4:** Vβ9; **P5:** none; **P6:** Vβ5, Vβ7, Vβ20; **P7:** none; **P8:** Vβ5, Vβ20; **P9:** Vβ20; **P10:** Vβ5, Vβ7, Vβ9, Vβ20; **P11:** Vβ5, Vβ7, Vβ9, Vβ20; **P12:** none; **P13:** Vβ7; **P14:** Vβ5, Vβ13.1; **P15:** Vβ7; **P16:** Vβ5; **P17:** none; **P18:** Vβ9; **P19:** Vβ5	19
PV	[5]	**P1:** Vβ1, Vβ3, Vβ7, Vβ17; **P2:** Vβ10, Vβ13, Vβ14; **P3:** Vβ10, Vβ14, Vβ22, Vβ23; **P4:** Vβ5, Vβ9, Vβ22, Vβ23; **P5:** Vβ9, Vβ10, Vβ22, Vβ24; **P6:** Vβ5, Vβ17	6
CC	[6]	**P1:** Vβ5; **P2:** none; **P3:** Vβ2, Vβ3; **P4:** Vβ3; **P5:** none; **P6:** Vβ2, Vβ3	13
	[7]	**P1:** Vβ1, Vβ7, Vβ9, Vβ11, Vβ22; **P2:** Vβ2, Vβ3, Vβ4, Vβ5.2, Vβ13.1, Vβ13.2, Vβ17, Vβ18, Vβ20, Vβ21; **P3:** Vβ1, Vβ3, Vβ5.2, Vβ6, Vβ9, Vβ11; **P4:** Vβ20; **P5:** Vβ6, Vβ14, Vβ17, Vβ21; **P6:** Vβ13.1, Vβ14, Vβ22; **P7:** Vβ11, Vβ13.2, Vβ18, Vβ20, Vβ21	

APL	[8,9]	**P1:** Vβ1, Vβ21; **P2:** Vβ12, Vβ18, Vβ21; **P3:** Vβ8, Vβ10, Vβ13, Vβ21; **P4:** Vβ21; **P5:** Vβ2; **P6:** Vβ22, Vβ23; **P7:** Vβ23; **P8:** Vβ23; **P9:** Vβ1, Vβ3, Vβ10, Vβ12, Vβ15, Vβ23; **P10:** Vβ8, Vβ12; **P11:** Vβ2, Vβ3, Vβ10, Vβ15; **P12:** Vβ3; **P13:** Vβ5, Vβ15; **P14:** Vβ5; **P15:** Vβ18, Vβ20; **P16:** Vβ6, Vβ12, Vβ13, Vβ17; **P17:** Vβ1, Vβ17; **P18:** Vβ4; **P19:** Vβ18; **P20:** none; **P21:** none	21
T-ALL	[10]	**P1:** Vβ10, Vβ11, Vβ15; **P2:** Vβ1, Vβ9; **P3:** Vβ1, Vβ10, Vβ15; **P4:** none; **P5:** Vβ3; **P6:** Vβ5	7
	[11]	**P1:** Vβ5.1, Vβ8, Vβ12, Vβ13.1, Vβ15, Vβ17, Vβ19, Vβ24	
B-ALL	[12]	**P1:** Vβ21; **P2:** Vβ15, Vβ21; **P3:** Vβ13; **P4:** Vβ19, Vβ21, Vβ23; **P5:** Vβ9; **P6:** Vβ15, Vβ21; **P7:** none; **P8:** Vβ3, Vβ21; **P9:** Vβ15, Vβ23; **P10:** Vβ10, Vβ23; **P11:** Vβ3; **P12:** Vβ21; **P13:** none	17
	[11]	**P1:** Vβ3; **P2:** Vβ3, Vβ14, Vβ19, Vβ24; **P3:** Vβ5.2; **P4:** none	
AML	[13]	**P1:** Vβ7; **P2:** Vβ2; **P3:** Vβ2; **P4:** Vβ2, Vβ7; **P5:** Vβ2, Vβ21; **P6:** none; **P7:** Vβ2; **P8:** Vβ2; **P9:** Vβ9	9
AMoL	[14]	**P1:** Vβ5, Vβ8; **P2:** none; **P3:** none; **P4:** Vβ9, Vβ19; **P5:** Vβ19; **P6:** none; **P7:** Vβ2; **P8:** Vβ3; **P9:** none	25
	[15]	**P1:** Vβ5; **P2:** Vβ8; **P3:** Vβ6; **P4:** Vβ23; **P5:** Vβ10; **P6:** Vβ16; **P7:** Vβ18; **P8:** Vβ8, Vβ14; **P9:** Vβ9, Vβ22; **P10:** Vβ9; **P11:** Vβ8, Vβ10, Vβ23; **P12:** Vβ16; **P13:** none; **P14:** Vβ	
	[11]	**P1:** Vβ3, Vβ13.1; **P2:** Vβ3, Vβ9	
	[16]	**P1:** Vβ9, Vβ16; **P2:** none; **P3:** Vβ1, Vβ23; **P4:** Vβ3, Vβ5, Vβ6, Vβ15, Vβ17, Vβ24; **P5:** Vβ3, Vβ10; **P6:** Vβ23; **P7:** Vβ3; **P8:** Vβ17; **P9:** none; **P10:** Vβ1, Vβ23; **P11:** Vβ5, Vβ6	
CML	[17]	**P1:** Vβ3, Vβ19; **P2:** Vβ3, Vβ6, Vβ10; **P3:** Vβ3, Vβ6, Vβ10; **P4:** Vβ3, Vβ11; **P5:** Vβ3, Vβ21, Vβ22; **P6:** Vβ17, Vβ21; **P7:** Vβ21; **P8:** Vβ13, Vβ17, Vβ21 ; **P9:** Vβ13, Vβ15; **P10:** Vβ13; **P11:** Vβ13, Vβ15; **P12:** Vβ17; **P13:** Vβ1, Vβ9; **P14:** Vβ1; **P15:** Vβ1, Vβ8; **P16:** Vβ8, Vβ16; **P17:** Vβ10, Vβ22; **P18:** Vβ9; **P19:** Vβ14, Vβ15; **P20:** Vβ12; **P21:** Vβ19; **P22:** none; **P23:** none; **P24:** none; **P25:** none; **P26:** none; **P27:** none	22
LC	[18]	**Vβ3:** 11; **Vβ5.2:** 2; **Vβ5.3:** 2; **Vβ7.2:** 2; **Vβ9:** 12; **Vβ12:** 2; **Vβ13.2:** 7; **Vβ14:** 2; **Vβ18:**1; **Vβ21:** 4; **Vβ23:** 2	43

Vβ of a patient looks like that of AMoL, this may be helpful for the physician to make a diagnosis; and if the heights of predominant columns decrease, this may, indicate that the treatment is proper for the patient in clinic. Of course, this hypothesis needs lots of studies to prove by the researchers in future.

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