Summary of Papers

Sreevatsa Nukala

June 2020

Summaries

1. Berland et al. [1] investigates the development of biomarkers based on the analysis of the TCRα repertoire to assist patients with primary immunodeficiencies with V(D)J recombination. This study finds that sub-optimal V(D)J recombination activity can cause partial immune defects and/or DNA repair defects. The analysis of the TCRα repertoire enables them to reveal a possibility of early diagnosis of patients presenting with hypomorphic DNA repair defects inclined to experience acute toxicity during prehematopoietic stem cell transplantation conditioning.

2. Bolland et al. [2] successfully develops a method to measure antigen receptor diversity. The study achieves this through discovering the underlying logic of the recombination rates of V gene segments, chromatin states. This paper finds that chromatin states were based on clan evolution and not geographical location, which they discover because of the ability of VDJ-seq [3] to report on DNA rather than downstream RNA expression.

3. In this paper, Dash et al. [4] introduce new analytical tools to characterize epitope-specific TCR repertoires. The analysis demonstrates that each epitope-specific repertoire contains a group of receptors that share core sequence similarities. Based on the similarities in core sequences in a cluster of TCRs, they highlight key conserved residues that drive TCR recognition.

4. Freeman et al. [5] uses direct sequence-based immunoprofiling to understand repertoire dynamics in the immune response. TCRβ subunits can be identified by their hypervariable $CDR3$ sequence, which encodes the principal site of antigen contact. This study identifies 33,664 TCRβ clonotypes and retrieve precise measurements of $CDR3_{\beta}$ length diversity, usage of nontemplated bases, sequence convergence, and gene usage and pairing.

5. In this paper, Gellert et al.[6] discusses the role of enhancers, histone acetylation, and chromatin remodeling factors in controlling accessibility. This paper explains how RAG proteins, repair factors, and regulation affect V(D)J Recombination.

6. Livak and Schatz [7] analyze V(D)J Recombination by-products by using murine TCRα locus as a model system. This analysis reveals many DNA sequences, which were previously thought to have been lost during intrathymic T-cell development, are actually retained.They

also discover that strict regulation of V(D)J recombination is required to prevent the loss of functionally selected, assembled antigen receptor genes. Their findings raise questions regarding the mechanism of V(D)J recombination and the maintenance of genome integrity during lymphoid development.

7. This paper by Yu Ping et al. [8] focuses on how to further enhance the function of TCR-engineered T cells and their longevity in tumor areas. TCR-engineered T cells, T cells using combined recognition pathways, showed greater efficacy by by-passing the mechanisms by which tumor cells escape immune recognition. TCR-engineered T cells cells can mediate tumor lysis and eradication. This paper finds that in combination with drugs that target chemokines, cytokines, and immune checkpoint proteins, TCR-engineered T cells can obtain better clinical response in future treatments with some action taken to prolong their usefulness.

8. Ramesh et al. [9] discovers an inherent T cell defect in Common Variable Immune Deficiency(CVID), which displays unique V gene usage. They utilize high throughput sequencing to examine the structure and composition of the T cell receptor β chain in CVID to find that the CVID $CDR3$ repertoire is strikingly deficient in junctional modifications in V–D and D–J segments. Because TCR abnormalities like this in CVID didn't seem to be associated with specific clinical issues, they concluded that there must be inherent defects in T cells.

9. Samy at al. [10] finds that bladder cancer exomes with productive TCRβ recombinations in tumor resident T cells showed a positive response to drug treatments. They validate the approach for using exome files to assess the immune status of tumor samples by searching tumor specimen exome files for TCR-β, TCR-γ, and TCR-δ recombinations, for bladder and stomach cancer. This paper discovers the detection of these recombinations to be useful for prognosis in bladder cancer.

10. Sethna et al. [11] utilizes sequence repertoire analysis to underline the impact of selection on the V(D)J recombination process. Using data from mice of different ages, they quantify the changes with time in the way receptors are generated and selected for function. This research finds a strong increase in repertoire diversity, occurring shortly after birth. They also find that selection is weaker in lab mice than in humans and it doesn't affect the diversity of the repertoire.

11. Gomez-Tourino [12] shows that short $CDR3s$ increase risk of autoimmune disease. This paper finds that early events in thymic cell development and repertoire generation are abnormal in type 1 diabetes because a high frequency of $CDR3s$ are found in type 1 diabetes patients. Random VDJ gene rearrangement typically yields a pre-selection repertoire of TCRB $CDR3s$ across a range of lengths, but shorter lengths are favored in type 1 Diabetes.These findings are consistent with the idea that antigen-receptor repertoires should be included as a major contributor to disease risk.

12. Zhao et al. [13] used a linear-amplification VDJ-seq method to measure T cell receptor diversity. This paper used linear-amplification because it reduces the bias in the PCR process.This method contributes to further understanding of the antigen receptor rearrangement process because they are able to obtain millions of clean sequence reads efficiently. They use this same method to quantify the usage of Jα within the TCRα gene.

13. Carter et al. [14] reveals that while α and β chains are only weakly associated with lineage, $\alpha\beta$ pairings appear to synergistically drive TCR-MHC interactions and are significant in accurately inferring repertoire functionality. This paper analyzed paired TCR sequences from T cells captured using single-cell sequencing methods. They further utilized tools from information theory and machine learning to show the statistical significance of $\alpha\beta$ pairings in TCR interaction. These findings provide insight into the functional implications of $\alpha\beta$ pairing and the utility of single-cell sequencing.

14. Priel et al. [15] presents a network-based view of the dynamics of the T cell repertoire to observe cancer progression via the perspective of the immune system. Based on this view of the repertoire, they apply a network analysis of the TCR repertoire and a machine learning classifier to demonstrate its effectiveness in identifying changes in the repertoire that correlate with changes in the phenotype.

15. Greiff et al.[16] differentiates between private and public/shared antibody repertoires in order to gain insight into the shaping of the immune system. By utilizing a machine learning approach capable of capturing the high-dimensional compositional information of each clonal sequence($CDR3$), they predicted the public and private status of antibody repertoires with 80% accuracy in humans and mice, which demonstrates that public and private sequences possess predictable high-dimensional immunogenomic features. These findings uncover the existence of predictable rules that shape immune repertoire diversity.

16. DG Schatz [17] explains the process of V(D)J Recombination and its regulation. This paper is describes the fundamental process of V(D)J Recombination, its effect in immune system development, and the factors such as RAG that regulate it. This paper is commonly cited as a source of backing for the complex process of V(D)J Recombination and its role in antibody repertoire diversity.

17. MP Lefranc et al. [18] uses this paper to highlight the properties of the IMGT database for immunoglobulin and TCR variable domains. This paper goes through the usefulness of IMGT for comparative analysis and evolution studies in immunoglobulin and TCR research. This paper serves as a guide to using the IMGT database in aiding TCR research and is commonly cited by many research papers regarding analysis of the TCR repertoire.

References

[1] A. Berland, J. Rosain, S. Kaltenbach, V. Allain, N. Mahlaoui, I. Melki, A. Fievet, C. Dubois d'Enghien, M. Ouachée-Chardin, L. Perrin, N. Auger, F. E. Cipe, A. Finocchi, F. Dogu, F. Suarez, D. Moshous, T. Leblanc, A. Belot, C. Fieschi, D. Boutboul, M. Malphettes, L. Galicier, E. Oksenhendler, S. Blanche, A. Fischer, P. Revy, D. Stoppa-Lyonnet, C. Picard, and J.-P. de Villartay, "Promidisα: A t-cell receptor α; signature associated with immunodeficiencies caused by v(d)j recombination defects," *Journal of Allergy and Clinical Immunology*, vol. 143, no. 1, pp. 325–334.e2, Jan 2019. [Online]. Available: https://doi.org/10.1016/j.jaci.2018.05.028

[2] D. J. Bolland, H. Koohy, A. L. Wood, L. S. Matheson, F. Krueger, M. J. Stubbington, A. Baizan-Edge, P. Chovanec, B. A. Stubbs, K. Tabbada, S. R. Andrews, M. Spivakov, and A. E. Corcoran, "Two mutually exclusive local chromatin states drive efficient v(d)j

recombination," *Cell Reports*, vol. 15, no. 11, pp. 2475–2487, Jun 2016. [Online]. Available: https://doi.org/10.1016/j.celrep.2016.05.020

[3] Y. Jiang, K. Nie, D. Redmond, A. M. Melnick, W. Tam, and O. Elemento, "Vdj-seq: Deep sequencing analysis of rearranged immunoglobulin heavy chain gene to reveal clonal evolution patterns of b cell lymphoma," *Journal of visualized experiments : JoVE*, no. 106, pp. e53 215–e53 215, Dec 2015, 26780364[pmid]. [Online]. Available: https://pubmed.ncbi.nlm.nih.gov/26780364

[4] P. Dash, A. J. Fiore-Gartland, T. Hertz, G. C. Wang, S. Sharma, A. Souquette, J. C. Crawford, E. B. Clemens, T. H. O. Nguyen, K. Kedzierska, N. L. La Gruta, P. Bradley, and P. G. Thomas, "Quantifiable predictive features define epitope-specific t cell receptor repertoires," *Nature*, vol. 547, no. 7661, pp. 89–93, Jul 2017. [Online]. Available: https://doi.org/10.1038/nature22383

[5] J. D. Freeman, R. L. Warren, J. R. Webb, B. H. Nelson, and R. A. Holt, "Profiling the T-cell receptor beta-chain repertoire by massively parallel sequencing," *Genome Res.*, vol. 19, no. 10, pp. 1817–1824, Oct 2009, [PubMed Central:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2765271PMC2765271] [DOI:https://dx.doi.org/10.1101/gr.092924.10910.1101/gr.092924.109] [PubMed:https://www.ncbi.nlm.nih.gov/pubmed/13112631311263].

[6] M. Gellert, "V(d)j recombination: Rag proteins, repair factors, and regulation," *Annual Review of Biochemistry*, vol. 71, no. 1, pp. 101–132, 2002, pMID: 12045092. [Online]. Available: https://doi.org/10.1146/annurev.biochem.71.090501.150203

[7] F. Livak and D. G. Schatz, "T-cell receptor alpha locus v(d)j recombination by-products are abundant in thymocytes and mature t cells." *Molecular and Cellular Biology*, vol. 16, no. 2, pp. 609–618, 1996. [Online]. Available: https://mcb.asm.org/content/16/2/609

[8] Y. Ping, C. Liu, and Y. Zhang, "T-cell receptor-engineered t cells for cancer treatment: current status and future directions," *Protein & Cell*, vol. 9, no. 3, pp. 254–266, Mar 2018. [Online]. Available: https://doi.org/10.1007/s13238-016-0367-1

[9] M. Ramesh, D. Hamm, N. Simchoni, and C. Cunningham-Rundles, "Clonal and constricted t cell repertoire in common variable immune deficiency," *Clinical Immunology*, vol. 178, pp. 1 – 9, 2017. [Online]. Available: http://www.sciencedirect.com/science/article/pii/S1521661615000042

[10] M. D. Samy, W. L. Tong, J. M. Yavorski, W. J. Sexton, and G. Blanck, "T cell receptor gene recombinations in human tumor specimen exome files: detection of t cell receptor-β vdj recombinations associates with a favorable oncologic outcome for bladder cancer," *Cancer Immunology, Immunotherapy*, vol. 66, no. 3, pp. 403–410, Mar 2017. [Online]. Available: https://doi.org/10.1007/s00262-016-1943-1

[11] Z. Sethna, Y. Elhanati, C. R. Dudgeon, C. G. Callan, A. J. Levine, T. Mora, and A. M. Walczak, "Insights into immune system development and function from mouse t-cell repertoires," *Proceedings of the National Academy of Sciences*, vol. 114, no. 9, pp. 2253–2258, 2017. [Online]. Available: https://www.pnas.org/content/114/9/2253

[12] I. Gomez-Tourino, Y. Kamra, R. Baptista, A. Lorenc, and M. Peakman, "T cell receptor β-chains display abnormal shortening and repertoire sharing in type 1 diabetes," *Nature Communications*, vol. 8, no. 1, p. 1792, Nov 2017. [Online]. Available: https://doi.org/10.1038/s41467-017-01925-2

[13] H. Zhao, Z. Li, Y. Zhu, and B. Hao, "A linear-amplification vdj-seq technique for quantification of immunoglobulin and t cell receptor diversity," *Genome*, vol. 63, no. 3, pp. 145–153, Mar 2020. [Online]. Available: https://doi.org/10.1139/gen-2019-0096

[14] J. A. Carter, J. B. Preall, K. Grigaityte, S. J. Goldfless, E. Jeffery, A. W. Briggs, F. Vigneault, and G. S. Atwal, "Single t cell sequencing demonstrates the functional role of $\alpha\beta$ tcr pairing in cell lineage and antigen specificity," *Frontiers in immunology*, vol. 10, pp. 1516–1516, Jul 2019, 31417541[pmid]. [Online]. Available: https://pubmed.ncbi.nlm.nih.gov/31417541

[15] A. Priel, M. Gordin, H. Philip, A. Zilberberg, and S. Efroni, "Network representation of t-cell repertoire- a novel tool to analyze immune response to cancer formation," *Frontiers in immunology*, vol. 9, pp. 2913–2913, Dec 2018, 30619277[pmid]. [Online]. Available: https://pubmed.ncbi.nlm.nih.gov/30619277

[16] V. Greiff, C. R. Weber, J. Palme, U. Bodenhofer, E. Miho, U. Menzel, and S. T. Reddy, "Learning the high-dimensional immunogenomic features that predict public and private antibody repertoires," *The Journal of Immunology*, vol. 199, no. 8, pp. 2985–2997, 2017. [Online]. Available: https://www.jimmunol.org/content/199/8/2985

[17] D. G. Schatz, M. A. Oettinger, and M. S. Schlissel, "V(d)j recombination: Molecular biology and regulation," *Annual Review of Immunology*, vol. 10, no. 1, pp. 359–383, Apr 1992. [Online]. Available: https://doi.org/10.1146/annurev.iy.10.040192.002043

[18] M.-P. Lefranc, C. Pommié, M. Ruiz, V. Giudicelli, E. Foulquier, L. Truong, V. Thouvenin-Contet, and G. Lefranc, "Imgt unique numbering for immunoglobulin and t cell receptor variable domains and ig superfamily v-like domains," *Developmental Comparative Immunology*, vol. 27, no. 1, pp. 55 – 77, 2003. [Online]. Available: http://www.sciencedirect.com/science/article/pii/S0145305X02000393