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Distinct Immune Signatures in Chronic Lymphocytic Leukemia and Richter Syndrome

Yucai Wang,[1] Sutapa Sinha,[1] Charla Secreto,[1] Karen L. Rech,[2] Timothy G. Call,[1] Sameer A. Parikh,[1] Daniel L. Van Dyke,[3] Jose F. Leis,[4] Saad J. Kenderian,[1] Amber B. Koehler,[1] Susan L. Slager,[5] Haidong Dong,[6] Stephen M. Ansell,[1] Neil E. Kay,[1] Rong He,[1] Wei Ding[1]

[1]Division of Hematology, [2]Division of Hematopathology, [3]Division of Laboratory Genetics and Genomics, [5]Division of Biomedical Statistics and Informatics, [6]Department of Immunology, Mayo Clinic, Rochester, MN, USA; [4]Division of Hematology and Medical Oncology, Mayo Clinic, Phoenix, AZ, USA

Disclosures

- None

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Introduction

- Richter syndrome (RS) is associated with a number of genetic alterations including *TP53*, *NOTCH1*, *CDKN2A* and *MYC* mutations. It is unclear whether RS is also associated with immune microenvironment changes.
- Immune checkpoint inhibitors pembrolizumab and nivolumab were shown to be effective in RS, particularly in patients with prior exposure with ibrutinib or when used in combination with ibrutinib. In contrast, no objective response to pembrolizumab was seen in patients with progressive CLL, suggesting that the immune microenvironment may be different in CLL and RS.
- In this study, we sought to define the immune signatures in CLL and RS as well as the potential effect of ibrutinib on the immune microenvironment (immune checkpoint molecule expression, immune cell infiltration, T-cell diversity).

1. *Rossi D, et al. Blood, 2011, 117(12):3391-401.*
2. *Chigrinova E, et al. Blood, 2013, 122(15):2673-82.*
3. *Ding W, et al. Blood, 2017, 129(26):3419-3427.*
4. *Jain N, et al, Blood, 2018, 132(Suppl 1):296.*

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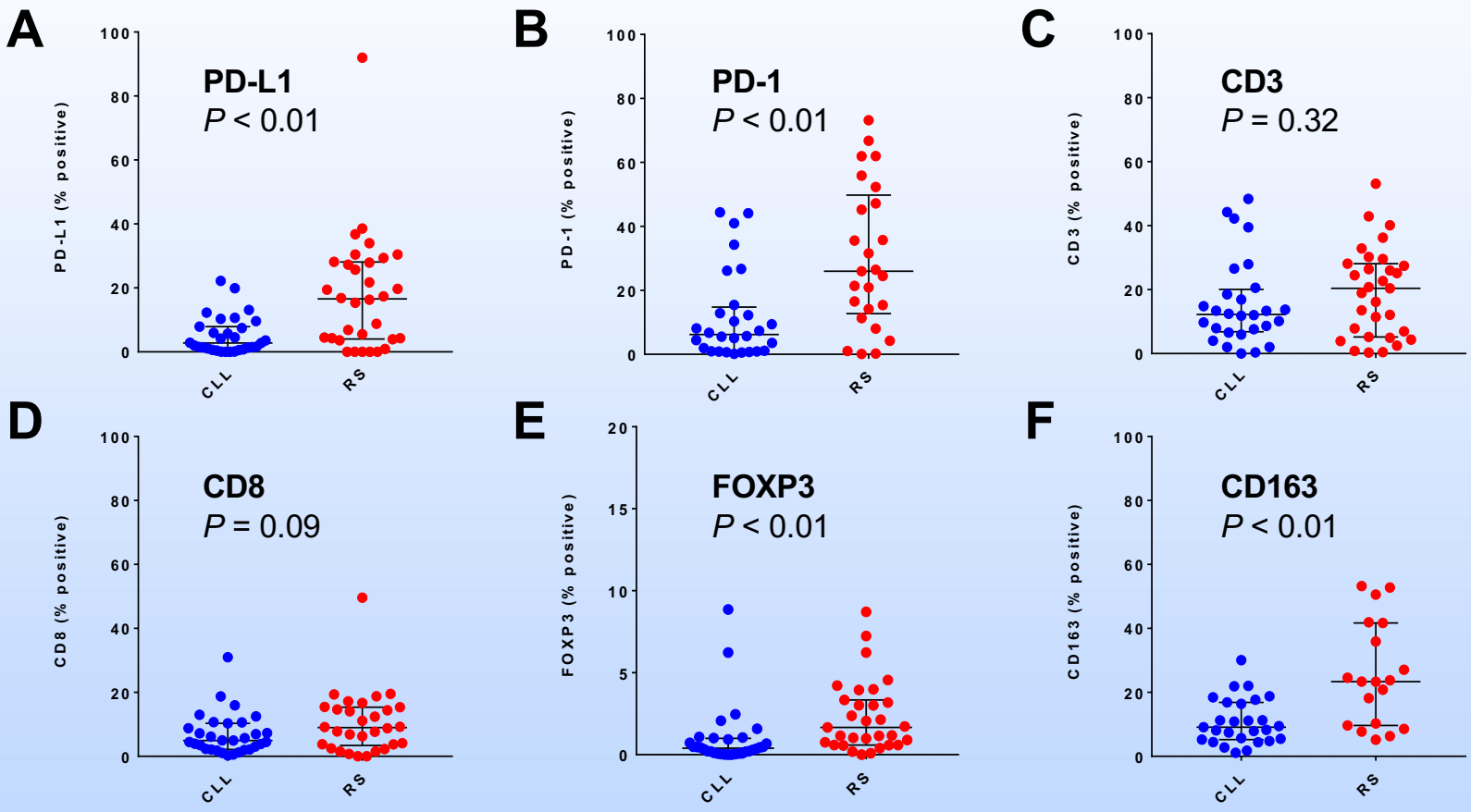
PD-L1/PD-1 expression and immune cell infiltration



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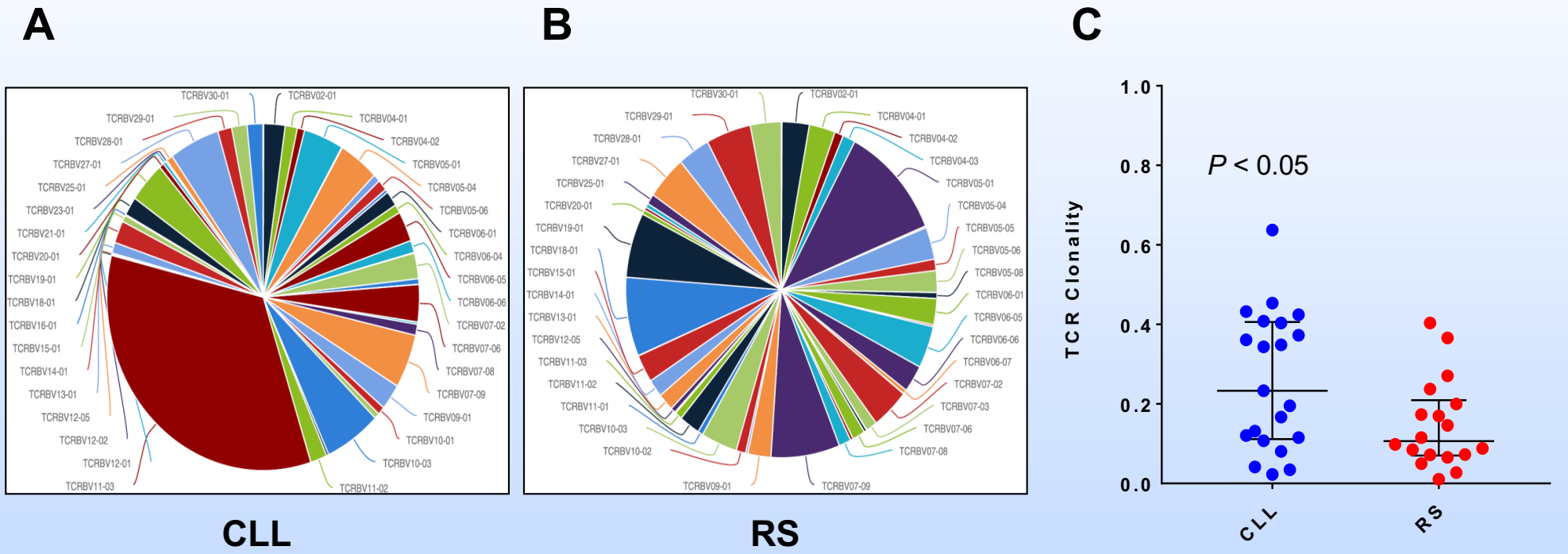
Peripheral blood T-cell TCR clonality



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Post-chemo vs post-ibrutinib immune microenvironment

	CLL Post-Chemo		CLL Post-Ibrutinib		
	N	**Median (25th, 75th)**	**N**	**Median (25th, 75th)**	***P***
PD-L1 (% positive)	18	1.6 (0.4, 6.9)	13	4.5 (1.5, 8.8)	0.21
PD1 (% positive)	16	5.4 (0.9, 10.1)	12	10.2 (1.9, 39.3)	0.16
CD3 (% positive)	16	10.8 (6.1, 14.4)	12	15.3 (8.2, 41.6)	0.12
CD8 (% positive)	18	4.7 (2.2, 9.2)	13	5.0 (2.3, 11.6)	0.77
FOXP3 (% positive)	19	0.3 (0.1, 0.7)	13	0.4 (0.2, 1.6)	0.18
CD163 (% positive)	16	7.8 (4.5, 11.2)	11	11.2 (7.9, 18.8)	0.09
TCR clonality	10	0.181 (0.071-0.386)	11	0.343 (0.115-0.408)	0.56

	RS Post-Chemo		RS Post-Ibrutinib		
	N	**Median (25th, 75th)**	**N**	**Median (25th, 75th)**	***P***
PD-L1 (% positive)	15	16.8 (4.3, 28.2)	17	15.4 (1.8, 28.6)	0.68
PD1 (% positive)	11	15.4 (8.0, 26.5)	14	35.6 (20.2, 57.4)	**0.07**
CD3 (% positive)	14	22.6 (7.1, 28.5)	17	16.2 (4.5, 29.6)	0.68
CD8 (% positive)	14	9.0 (5.6, 14.2)	16	8.5 (2.3, 16.8)	0.93
FOXP3 (% positive)	16	1.7 (0.7, 3.8)	15	1.2 (0.6, 3.3)	0.89
CD163 (% positive)	11	23.8 (10.3, 41.9)	8	20.7 (7.1, 33.7)	0.35
TCR clonality	11	0.146 (0.072-0.200)	7	0.098 (0.066-0.237)	0.93

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Conclusions

- CLL and RS have distinct immune signatures in both the lymph nodes and peripheral blood.
- Expression of PD-L1 and PD1 and infiltration of FOXP3-positive T-cells and CD163-positive macrophages were increased in RS compared to CLL lymph node samples.
- RS patients had a lower peripheral blood TCR clonality (i.e., more diverse T-cells) compared to CLL patients.
- The different immune microenvironments in CLL and RS may partially explain the different responses to therapy with immune checkpoint inhibitors.

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