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Variable density of CD8+ and CD25+ programmed cell death-1 (PD-1) ligand (PD-L1) CD4+ T cells within the tumor microenvironment causes differential responses to the PD-1/PD-L1 blockade

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The programmed cell death-1 (PD-1)/programmed cell death-1 ligand (PD-L1) pathway has been shown to play a pivotal role in tumor evasion. Inhibition of PD-1 and its ligand PD-L1 using an immune checkpoint inhibitor has emerged as a promising immunotherapy for the treatment of various types of cancer. The expression of PD-L1 in tumor cells and tumor-infiltrating lymphocytes (TILs) has been shown to be correlated with improved efficacy of antibodies against PD-1 or PD-L1. Moreover, the density of $CD8^+$ TILs has been shown to be correlated with the response to immunotherapy. In this study, we examined the expression of PD-L1, CD25, PD-1, FoxP3, CD4, CD8, and EpCAM in 42 peripheral blood samples and fresh tumor specimens using multiparametric flow cytometry. Our results showed that the percentages of PD-L1-expressing $CD25^+$ $CD4^+$ T cells were significantly higher in TILs than in peripheral blood lymphocytes (PBLs; TILs: mean, 48.6%; range, 23.6–81.5% versus PBLs: mean, 35.4%; range, 16.8–64.3%; $P < 0.001$). The density of $CD25^+$ PD-$L1^+$ $CD4^+$ TILs positively correlated with that of PD-1^+ $CD8^+$ TILs but negatively correlated with interferon (IFN)-γ^+ and tumor necrosis factor (TNF)-β^+ $CD8^+$ TILs. However, the high ratio of $CD8^+$ TILs to that of $CD25^+$ PD-$L1^+$ $CD4^+$ TILs or to $EpCAM^+$ tumor cells were associated with high percentages of IFN-γ^+ and TNF-β^+ $CD8^+$ TILs. Moreover, inhibition of PD-L1 and PD-1 decreased the density of $CD25^+$ PD-$L1^+$ $CD4^+$ cells and PD-1^+ $CD8^+$ TILs but increased the percentage of IFN-γ^+ and TNF-β^+ $CD8^+$ cells. High ratios of $CD8^+$ TILs to $CD25^+$ PD-$L1^+$ $CD4^+$ TILs or to $EpCAM^+$ tumor cells enhanced the activity of tumor-specific $CD8^+$ T cells after PD-1/PD-L1 blockade therapy. Taken together, our results highlighted the importance of $CD25^+$ PD-$L1^+$ $CD4^+$ TILs in mediating the tumor microenvironment immune response. Our findings also indicated that high ratios of $CD8^+$ TILs to $CD25^+$ PD-$L1^+$ $CD4^+$ TILs or to $EpCAM^+$ tumor cells in patients may be more effective after PD-1/PD-L1 blockade therapy. Thus, the variable density of $CD8^+$ and $CD25^+$ PD-$L1^+$ $CD4^+$ T cells within the tumor microenvironment caused differential responses to PD-1/PD-L1 blockade.

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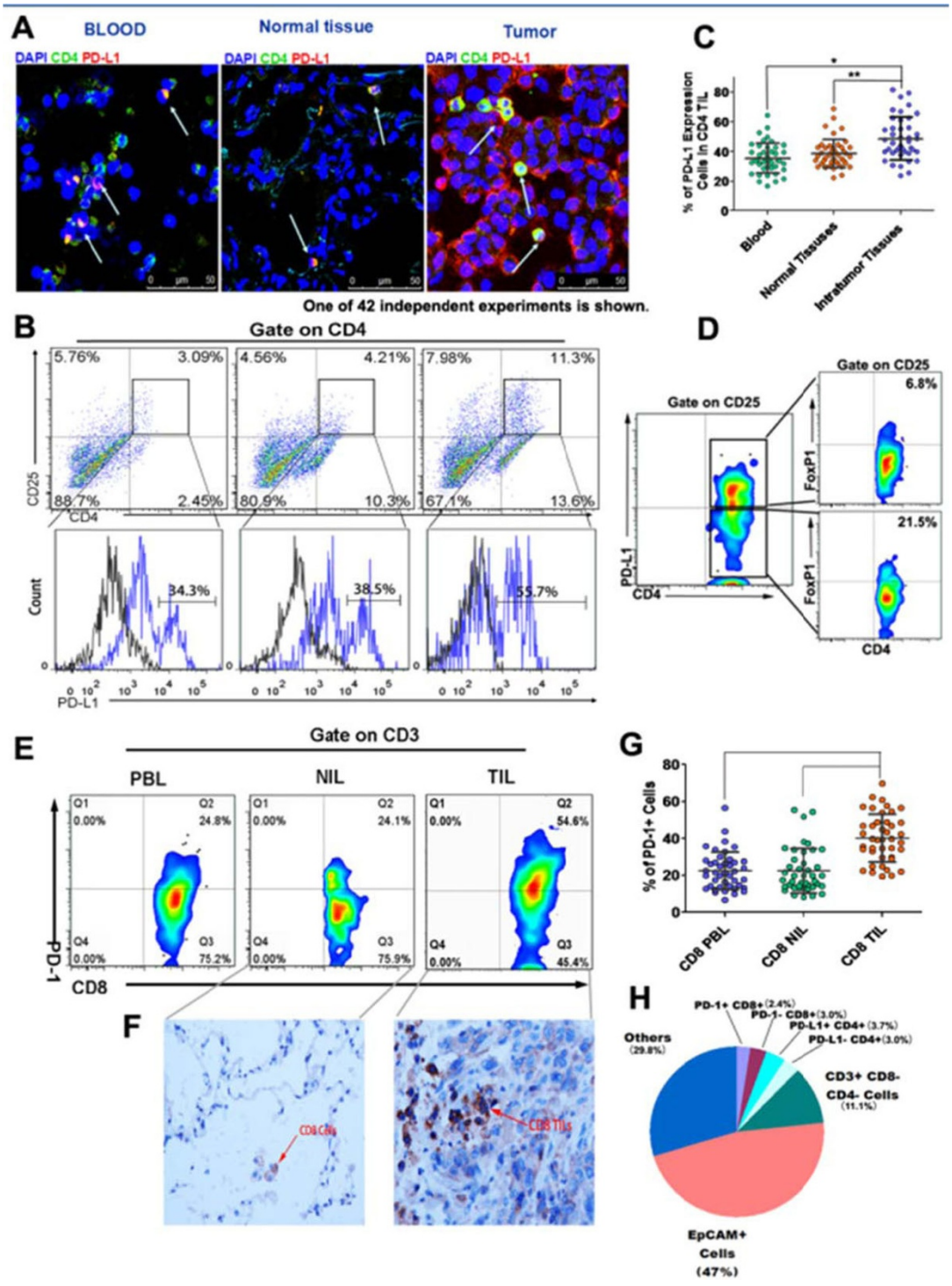
A
BLOOD
Normal tissue
Tumor
DAPI CD4 PD-L1
One of 42 independent experiments is shown.
B
Gate on CD4
5.76%
3.09%
88.7%
2.45%
4.56%
4.21%
80.9%
10.3%
7.98%
11.3%
67.1%
13.6%
CD25
CD4
Count
34.3%
38.5%
55.7%
PD-L1
C
% of PD-L1 Expression Cells in CD4 TIL
Blood
Normal Tissues
Intratumor Tissues
D
Gate on CD25
6.8%
21.5%
FoxP1
PD-L1
CD4
E
Gate on CD3
PBL
NIL
TIL
Q1
Q2
Q3
Q4
0.00%
24.8%
75.2%
24.1%
75.9%
54.6%
45.4%
PD-1
CD8
F
CD8 CTLs
CD8 TILs
G
% of PD-1+ Cells
CD8 PBL
CD8 NIL
CD8 TIL
H
PD-1+ CD8+(2.4%)
PD-1- CD8+(3.0%)
PD-L1+ CD4+(3.7%)
PD-L1- CD4+(3.0%)
Others
(29.8%)
CD3+ CD8-
CD4- Cells
(11.1%)
EpCAM+
Cells
(47%)

Figure 1

Factor	All patients (n = 42)	% PD-1 expressing CD8 TILs		*P*	% PD-L1 expressing CD4 TILs		*P*
		Low density	High density		Low density	High density	
Age							
<60	16	9(56.3)	7(43.8)	0.8	9(56.3)	7(43.8)	0.9
⩾60	26	14(53.8)	12(46.2)	79	15(57.7)	11(42.3)	27
Gender							
Male	27	16(59.3)	11(40.7)	0.4	18(66.7)	9(33.3)	0.0
Famale	15	7(46.7)	8(53.3)	32	6(40.0)	9(60.0)	94
Smoking							
Yes	17	11(64.7)	6(35.3)	0.2	10(58.8)	7(41.2)	0.8
No	25	12(48.0)	13(52.0)	86	14(56.0)	11(44.0)	56
Stage of disease							
I- II	24	14(58.3)	10(41.7)	0.5	12(50.0)	12(50.0)	0.2
III- IV	18	9(50.0)	9(50.0)	91	12(66.7)	6(33.3)	80
Histological type							
ADC	22	14(63.6)	8(36.4)	0.3	9(40.9)	13(59.1)	0.0
SCC	15	6(40.0)	9(60.0)	54	11(73.3)	4(26.7)	80
Other	5	3(60.0)	2(40.0)		4(80.0)	1(20.0)	
ECOG PS							
0	17	9(52.9)	8(47.1)	0.8	9(52.9)	8(47.1)	0.6
1	25	14(56.0)	11(44.0)	45	15(60.0)	10(40.0)	50
EGFR status							
Wild type	25	14(56.0)	11(44.0)	0.4	13(52.0)	12(48.0)	0.2
mutation	11	7(63.6)	4(36.4)	78	8(72.7)	3(27.3)	70
Unknown	6	2(33.3)	4(66.7)		2(33.3)	4(66.7)	

Figure 2 Correlation between the clinicopathologic characteristics and PD-1+CD8 TIL or PD-L1+CD4 TIL in 42 lung cancer patients.