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Exosomal PD-L1 and lactate versus tissue PD-L1 as biomarkers for clinical outcomes of PD-1 Blockade plus chemotherapy in metastatic esophagogastric signet ring cell carcinoma

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Abstract

In this investigator-initiated, prospective, exploratory study, biomarkers predictive of clinical outcomes of first-line immune checkpoint inhibitor (ICI, nivolumab or pembrolizumab) plus XELOX(oxaliplatin and capecitabine) were identified in human epidermal growth factor receptor 2 (HER2)–negative patients with metastatic esophagogastric signet ring cell carcinoma. The findings showed an objective response rate (ORR) of 51.5% and a disease control rate of 86.8%, the median progression-free survival (PFS) for the entire cohort was 6.63 months. PD-L1 expression level in tumor tissues could not identify a high PD-L1 group that significantly benefited from ICI plus XELOX in terms of the ORR and PFS. By contrast, the patients expressing low exosomal PD-L1 or lactate in peripheral blood plasma before treatment initiation demonstrated a significantly increased ORR and prolonged PFS compared to that with high exosomal PD-L1 or lactate, patients with combining predictor of exosomal PD-L1 and lactate lower than −0.249 was associated with a better ORR (82.1% vs. 30.0%, $P<0.001$) and a longer median PFS (13.83 vs. 5.50 months, $P<0.001$) compared to those with combining predictor ≥−0.249. The results also revealed that exosomal PD-L1 levels in peripheral blood plasma before the treatment were significantly correlated with the frequency of $CD8^+$ T cells ($P=0.007$), and in patients after receiving ICI plus XELOX, high exosomal PD-L1 level was associated with more $PD\text{-}1^+$ Treg cells, high exosomal lactate level was associated with less $CD8^+$ T cells and more Treg cells. Thus, the levels of PD-L1 and lactate in exosomes may affect the balance between Treg cells and $CD8^+$T cells, leading to treatment resistance to ICI plus XELOX. Compared to PD-L1 expression level in tumor tissues, exosomal PD-L1 and lactate levels could more accurately predict clinical outcomes of HER2–negative patients with metastatic esophagogastric signet ring cell carcinoma receiving first-line PD-1 blockade plus chemotherapy.

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To the editor,

Signet ring cell carcinoma (SRCC) is a specific type accounting for 8–30% of esophagogastric cancer patients, and advanced SRCC has a worse prognosis [1, 2]. PD-1 antibodies have shown encouraging anti-tumor activity and acceptable safety in all types of esophagogastric cancer [3–5]. Given the lack of prospective data evaluating predictive factors that are associated with the therapeutic efficacy of anti-PD-1 on SRCC, we aimed to compare exosomal PD-L1 and lactate versus tissue PD-L1 and assess if either provided utility as a predictive biomarker in HER2–negative patients with metastatic esophagogastric SRCC receiving first-line PD-1 blockade plus chemotherapy. Additionally, we sought to explore the correlation between PD-L1 and lactate levels in exosomes and peripheral blood T cells subsets.

From January 2022 to March 2023, 68 HER2–negative patients with metastatic esophagogastric SRCC were included, the median age was 63 years old, 67.6% patients were male, ECOG PS of 1 score (72.1%), HER2(0) (57.4%), microsatellite instability status (stable) (98.5%) and metastatic disease of the stomach (66.2%). As of the cut-off date (June 1, 2024), the median follow-up time was 14.2 months. The efficacy noted an objective response rate (ORR: CR + PR) of 51.5% and a disease control rate of 86.8% (Fig. 1, supplementary Tables 1, 2). Materials and methods of this study can be found in the supplementary data.

The levels of exosomal PD-L1 or lactate in plasma before treatment initiation in responders (CR + PR) were much lower than that in non-responders (SD + PD) ($P < 0.05$), while no significant correlation was observed between tissue PD-L1 CPS and tumor response ($P = 0.103$) (supplementary Fig. 1). Exosomal PD-L1 < 55.237 pg/ml or exosomal lactate < 3.681 ng/ug before treatment associated with a better response to first-line PD-1 blockade plus XELOX by ORR ($P < 0.01$), the combining predictor of exosomal PD-L1 and lactate lower than − 0.249 was associated with a better response to the treatment by ORR (82.1% vs. 30.0%, $P < 0.001$). The median PFS for the entire cohort was 6.63 months, patients with a PD-L1 CPS ≥ 1 or ≥ 10 achieved a longer PFS compared to those with PD-L1 CPS < 1 or < 10, but there was not statistically different. However, compared to those with high level of exosomal PD-L1 or exosomal lactate, patients presented with exosomal PD-L1 < 55.237 pg/ml or exosomal lactate < 3.681 ng/ug before treatment achieved a prolonged mPFS ($P < 0.01$), patients with the combining predictor of exosomal PD-L1 and lactate lower than − 0.249 achieved a much longer mPFS when compared to that with high level of the combining predictor (13.83 vs. 5.50 months, $P < 0.001$) (Fig. 2). The same trend was observed in 92 patients used for external validation (supplementary Fig. 2). We investigated whether T cells and their co-expressed PD-1 in the blood can predict response to treatment, and found that the frequency of $CD8^+$ T cells of the responders was significantly higher than that of the non-responders ($P = 0.002$), while the frequency of $CD4^+$ T cells ($P = 0.001$), Treg cells ($P = 0.002$), PD-1^+ $CD8^+$ cells ($P = 0.030$) and PD-1^+ Treg cells ($P < 0.001$) of the responders were significantly lower than that of the non-responders. After treatment, the ratio of $CD8^+$ T cells significantly increased in responders ($P = 0.049$), while the ratio of Treg cells significantly increased in non responders ($P = 0.049$) (supplementary Fig. 3). Exosomal PD-L1 level was negatively correlated with the frequency of $CD8^+$T cells ($P = 0.007$) and positively correlated with the frequency of $CD4^+$T cells ($P = 0.008$) and the rate of $CD4^+$T cells/$CD8^+$T cells ($P = 0.010$), exosomal lactate level was positively correlated with the rate of Treg cells/$CD8^+$T cells ($P = 0.036$). Correlation analysis shows that high exosomal PD-L1 level was associated with more PD-1^+ Treg cells ($P = 0.005$) and more Treg cells ($P = 0.041$), while high exosomal lactate level was significantly associated with an increase in the ratio of Treg cells/$CD8^+$ T cells ($P = 0.034$), associated with more Treg cells and fewer $CD8^+$T cells after treatment, the combination of exosomal PD-L1 and lactate best distinguished responders from non-responders, and correlation analysis shows that high combining predictor was associated with more Treg cells ($P = 0.009$) (supplementary Fig. 4).

Exosomes were involved in the immune escape and exosomes highly expressing PD-L1 could inhibit antitumor immune responses by inactivating T lymphocytes [6–10]. Our study showed that high exosomal PD-L1 level in plasma was associated with an increase in peripheral blood PD-1^+ Treg cells in advanced metastatic esophagogastric cancer patients, and compared with PD-1^- Treg cells, PD-1^+ Treg cells proliferate more actively and exhibit strong immunosuppressive effects, resulting in inferior clinical outcomes after first-line PD-1 blockade plus chemotherapy [11]. In tumor immunity, Treg cells can inhibit $CD8^+$T cells and the balance between Treg cells and $CD8^+$T cells is crucial for achieving superior antitumor efficacy [12–14]. In our study, exosomal lactate level in plasma before treatment was positively correlated with the rate of Treg cells/$CD8^+$T cells, and the Treg cell/$CD8^+$T cell ratio of responders was significantly lower than that of non-responders, the combination of exosomal PD-L1 and lactate best stratified clinical responders from non-responders. Thus, we speculate that exosomal PD-L1 and lactate have a synergistic effect on the proliferation and activation of Treg cells, exosomal PD-L1 promote the expression of PD-1 in Treg cells, exosomal lactate can provide metabolic support for Treg cells, further promoting immunosuppressive effects

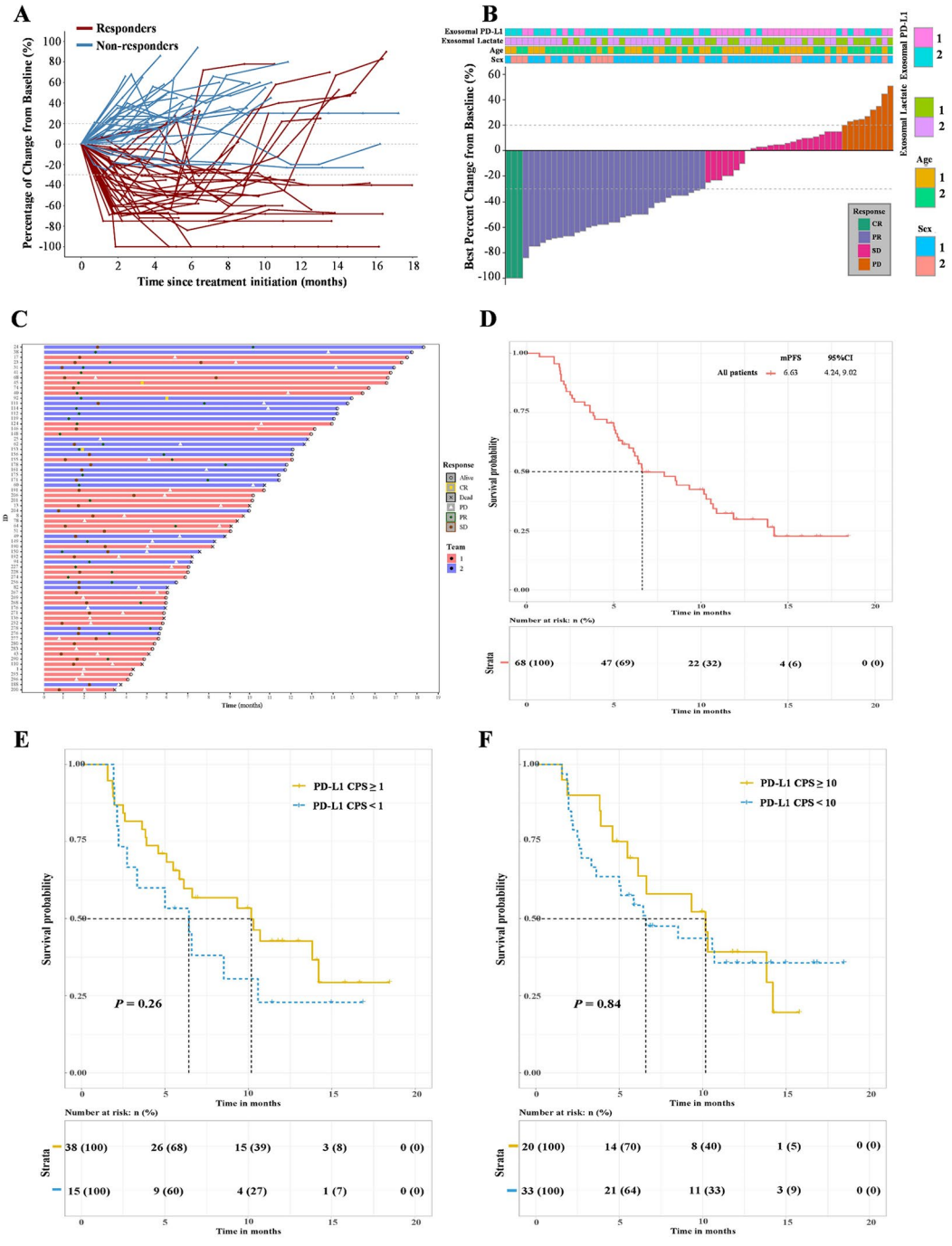

Fig. 1 Treatment efficacy. (**A**) Spider plot of tumor response in target lesions of 68 patients. (**B**) Waterfall plots showing the best change of target lesion from baseline. *Note*: Exosomal PD-L1, 1: high exosomal PD-L1 group (exosomal PD-L1 ≥ 55.237 pg/ml), 2: low exosomal PD-L1 group (exosomal PD-L1 < 55.237 pg/ml); Exosomal lactate, 1: high exosomal lactate group (exosomal lactate ≥ 3.681 ng/ml), 2: low exosomal lactate group (exosomal lactate < 3.681 ng/ml); Age, 1: age < 65 years, 2: age ≥ 65 years; Sex, 1: male, 2: female. (**C**) Swimming chart showing the treatment results of the low combination prediction group ($n = 28$) and the high combination prediction group ($n = 40$). *Note*: 1: combining predictor of exosomal PD-L1 and lactate ≥ −0.249, 2: combining predictor of exosomal PD-L1 and lactate < −0.249. (**D**) Kaplan-Meier estimates of progression-free survival in the entire cohort. (**E**, **F**) Correlations between tumor PD-L1 CPS and progression-free survival. *P*-values were based on a two-sided log rank test for survival analysis

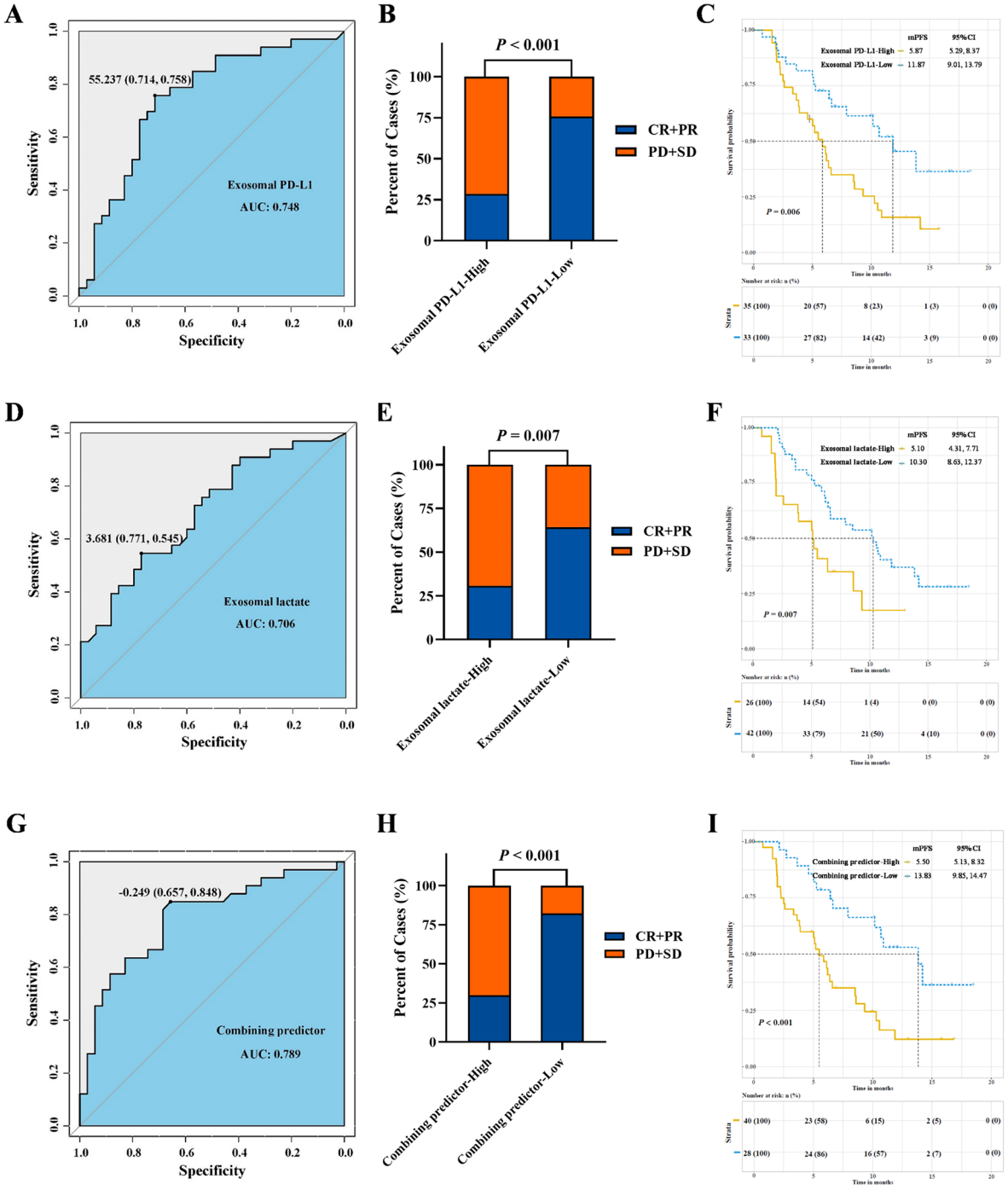

Fig. 2 Levels of exosomal PD-L1 and exosomal lactate and treatment efficacy. (**A**, **B**) ROC curve analysis of exosomal PD-L1 levels in responders (CR+PR) and non-responders (SD+PD) (AUC = 0.748, Sensitivity 0.758, $P < 0.001$), low exosomal PD-L1 group showed a better clinical response vs. high exosomal PD-L1 group (ORR: 75.8% vs. 28.6%). (**D**, **E**) ROC curve analysis of exosomal lactate levels in responders and non-responders (AUC = 0.706, Sensitivity 0.545, $P = 0.004$), low lactate PD-L1 group showed a better clinical response vs. high lactate PD-L1 group (ORR: 64.3% vs. 30.8%). (**G**, **H**) ROC curve analysis of PD-L1 and lactate combination levels in exosomes of responders and non-responders (AUC = 0.789, Sensitivity 0.848, $P < 0.001$), Low combining predictor showed a better clinical response vs. high combining predictor group (ORR: 82.1% vs. 30.0%). Chi-square test was used to determine the statistical significance between the groups. Low exosomal PD-L1 level (**C**), low exosomal lactate level (**F**), low level of combining predictor (**I**) was associated with longer progression-free survival

and inhibiting antitumor immunity, leading to anti-PD-1 therapy failure.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40164-025-00615-w .

Supplementary Material 1

Author contributions

Yuanyuan Tian: Methodology, formal analysis, data curation, writing-original draft and editing.Wei Shi, Jing Wang: Data curation, methodology, writing-review.Wenjie Zhang, Lingling Xia, Lijuan Gao, Hu Qiu: Resource and data curation.Zhenhua Yu, Yongfeng Zhang: Data curation, methodology and investigation.Yongshun Chen: Conceptualization, supervision, funding acquisition and writing-review.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethical approval

This study was reviewed and approved by the ethics committee of Renmin Hospital of Wuhan University, and was conducted in accordance with the Declaration of Helsinki. All the patients provided written informed consent before any procedure.

Competing interests

The authors declare no competing interests.

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References

1. Kunz PL, Gubens M, Fisher GA, Ford JM, Lichtensztajn DY, Clarke CA. Long-term survivors of gastric cancer: a California population-based study. J Clin Oncol. 2012;30(28):3507–15.
2. Piessen G, Messager M, Leteurtre E, Jean-Pierre T, Mariette C. Signet ring cell histology is an independent predictor of poor prognosis in gastric adenocarcinoma regardless of tumoral clinical presentation. Ann Surg. 2009;250(6):878–87.
3. Janjigian YY, Shitara K, Moehler M, Garrido M, Salman P, Shen L, Wyrwicz L, Yamaguchi K, Skoczylas T, Campos Bragagnoli A, Liu T, Schenker M, Yanez P, Tehfe M, Kowalyszyn R, Karamouzis MV, Bruges R, Zander T, Pazo-Cid R, Hitre E, Feeney K, Cleary JM, Poulart V, Cullen D, Lei M, Xiao H, Kondo K, Li M, Ajani JA. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. Lancet (London England). 2021;398:27–40.
4. Rha SY, Oh DY, Yañez P, Bai Y, Ryu MH, Lee J, Rivera F, Alves GV, Garrido M, Shiu KK, Fernández MG, Li J, Lowery MA, Çil T, Cruz FM, Qin S, Luo S, Pan H, Wainberg ZA, Yin L, Bordia S, Bhagia P, Wyrwicz LS. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for HER2-negative advanced gastric cancer (KEYNOTE-859): a multicentre, randomised, double-blind, phase 3 trial. Lancet Oncol. 2023;24:1181–95.
5. Shitara K, Ajani JA, Moehler M, Garrido M, Gallardo C, Shen L, Yamaguchi K, Wyrwicz L, Skoczylas T, Bragagnoli AC, Liu T, Tehfe M, Elimova E, Bruges R, Zander T, de Azevedo S, Kowalyszyn R, Pazo-Cid R, Schenker M, Cleary JM, Yanez P, Feeney K, Karamouzis MV, Poulart V, Lei M, Xiao H, Kondo K, Li M, Janjigian YY. Nivolumab plus chemotherapy or ipilimumab in gastro-oesophageal cancer. Nature. 2022;603:942–8.
6. Poggio M, Hu T, Pai CC, Chu B, Belair CD, Chang A, Montabana E, Lang UE, Fu Q, Fong L, Blelloch R. Suppression of Exosomal PD-L1 induces systemic Anti-tumor immunity and memory. Cell. 2019;177:414–e427413.
7. Chen G, Huang AC, Zhang W, Zhang G, Wu M, Xu W, Yu Z, Yang J, Wang B, Sun H, Xia H, Man Q, Zhong W, Antelo LF, Wu B, Xiong X, Liu X, Guan L, Li T, Liu S, Yang R, Lu Y, Dong L, McGettigan S, Somasundaram R, Radhakrishnan R, Mills G, Lu Y, Kim J, Chen YH, Dong H, Zhao Y, Karakousis GC, Mitchell TC, Schuchter LM, Herlyn M, Wherry EJ, Xu X, Guo W. Exosomal PD-L1 contributes to immunosuppression and is associated with anti-PD-1 response. Nature. 2018;560:382–6.
8. Theodoraki MN, Yerneni SS, Hoffmann TK, Gooding WE, Whiteside TL. Clinical significance of PD-L1(+) exosomes in plasma of head and neck Cancer patients. Clin cancer Research: Official J Am Association Cancer Res. 2018;24:896–905.
9. Shimada Y, Matsubayashi J, Kudo Y, Maehara S, Takeuchi S, Hagiwara M, Kakihana M, Ohira T, Nagao T, Ikeda N. Serum-derived Exosomal PD-L1 expression to predict anti-PD-1 response and in patients with non-small cell lung cancer. Sci Rep. 2021;11:7830.
10. Li M, Soder R, Abhyankar S, Abdelhakim H, Braun MW, Trinidad CV, Pathak HB, Pessetto Z, Deighan C, Ganguly S, Dawn B, McGuirk J, Dunavin N, Godwin AK. WJMSC-derived small extracellular vesicle enhance T cell suppression through PD-L1. J Extracell Vesicles. 2021;10:e12067.
11. Kamada T, Togashi Y, Tay C, Ha D, Sasaki A, Nakamura Y, Sato E, Fukuoka S, Tada Y, Tanaka A, Morikawa H, Kawazoe A, Kinoshita T, Shitara K, Sakaguchi S, Nishikawa H. PD-1(+) regulatory T cells amplified by PD-1 Blockade promote hyperprogression of cancer. Proc Natl Acad Sci USA. 2019;116:9999–10008.
12. Watson MJ, Vignali PDA, Mullett SJ, Overacre-Delgoffe AE, Peralta RM, Grebinoski S, Menk AV, Rittenhouse NL, DePeaux K, Whetstone RD, Vignali DAA, Hand TW, Poholek AC, Morrison BM, Rothstein JD, Wendell SG, Delgoffe GM. Metabolic support of tumour-infiltrating regulatory T cells by lactic acid. Nature. 2021;591:645–51.
13. Michalek RD, Gerriets VA, Jacobs SR, Macintyre AN, MacIver NJ, Mason EF, Sullivan SA, Nichols AG, Rathmell JC. Cutting edge: distinct glycolytic and lipid oxidative metabolic programs are essential for effector and regulatory CD4 + T cell subsets. J Immunol (Baltimore Md: 1950). 2011;186:3299–303.
14. Wherry EJ, Kurachi M. Molecular and cellular insights into T cell exhaustion. Nat Rev Immunol. 2015;15:486–99.

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