

Immune Checkpoints of CD8⁺ T Cells in Acute Myeloid Leukemia

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Abstract

Acute myeloid leukemia (AML) is one of the most common types of hematopoietic malignancy in the adults. Induction chemotherapy followed by post-remission is the general treatment for AML patients with high relapse rate and poor prognosis, which is often related to the CD8⁺ T cell immune status of the AML patients. Herein, we will make a mini review of phenotype-immune checkpoints expression and function of CD8⁺ T cells in AML based on our data and other groups, and this might indicate the application of immune checkpoints blockade alone or in combination in AML treatment.

Keywords: Immune checkpoints; CD8⁺ T cells; AML

Introduction

Acute myeloid leukemia (AML) is one of the most common types of hematopoietic malignancy in the adults. Induction chemotherapy followed by post-remission is the general treatment for AML patients with high relapse rate and poor prognosis, which is often related to the CD8⁺ T cell immune status of the AML patients [1-4]. Herein, we will make a mini review of phenotype-immune checkpoints expression and function of CD8⁺ T cells in AML based on our data and other groups, and this might indicate the application of immune checkpoints blockade alone or in combination in AML treatment.

Immune checkpoints, which are divided into co-stimulatory and co-inhibitory, are regarded as new targets for control of immune surveillance in AML. With immune checkpoints in clinical cancer immunotherapy have made a breakthrough, such as PD-1/PD-L1 and CTLA-4 blockade [5], blockade of the immune checkpoint has generated promising results of preclinical studies and has emerged as one as the novel anti-tumor immunotherapy [6], which prevents negative signals from entering immune cells, releasing them to attack the tumor. Blockade of PD-1/PD-L1 and CTLA-4/CD28 pathways have already demonstrated improved clinical response rates and prolonged survival in solid tumors such as melanoma, bladder cancer and non-small cell carcinoma, which enhanced anti-tumor T cell response [7-9]. Although the progress of the study of immune checkpoints in solid tumors has been promising, the research in hematological malignancies such as AML is not yet clear. About AML, impressive results have been obtained with PD-1 alone or in combination with other immune checkpoint blockade in mouse AML models, by improving anti-leukemia CD8⁺ T cell function. This suggests that blockade of the immune checkpoint has the role of anti-leukemic effect in AML [10,11].

The leukemic environment in AML patients is highly immunosuppressive [12]. For example, PD-1 and PD-L1 were up-regulated in CD8⁺ T cells and AML blasts, respectively, especially from the patients with AML relapse [11]. Blocking the PD-1/PD-L1 axis enhanced activation of CD8⁺ T cells to result in the lysis of AML cells by reversing the T cell-induced immune evasion mechanism [13]. Moreover, TIGIT contributes to functional T-cell impairment. CD8⁺ T cells expressed high TIGIT in AML patients, which was associated with relapse of leukemia after allogeneic stem cell transplantation (ASCT). TIGIT⁺ CD8⁺ T cells displayed a phenotypic characteristic of exhaustion, such as decreasing cytokine production and increasing sensitivity to apoptosis. Importantly, knockdown of TIGIT restore the dysfunction of TIGIT⁺CD8⁺T cells [14].

However, dysfunctional CD8⁺ T cells do not simply express a single inhibitory receptor, but often express multiple inhibitory receptors simultaneously. Immunosuppressive receptors such as CD244 (2B4), CD160, PD-1, BTLA, TIM-3 and LAG-3 are over-expressed by the CD8⁺T cells in AML patients [15]. For example, CD8⁺ T cells co-expressing PD-1 and TIM-3 were increased during the progression of AML [11,16]. The accumulation of PD-1^{hi} TIM-3⁺ CD8⁺ T cells in AML patients correlated with relapse and might be used to predict recurrence relapse after ASCT [17]. In addition, co-expression of PD-1 and TIM-3 on CD8⁺ T cells were observed in mouse acute myeloid leukemia with dual blockade of PD-1 and TIM-3 has been used to reduce the burden of AML on the recovery of CD8⁺ T cell function. Also, co-expression of PD-1, TIGIT and KLRG-1 were increased on CD8⁺ T cells during relapse after ASCT [18]. Blockade of TIGIT and PD-L1 synergistically enhanced CD8⁺ T cell function and resulted in tumor rejection [19]. These data show that AML patients had increased immune checkpoints expression, whereas blocking these checkpoints can exert anti-leukemic effects.

Discussion

In our recent publication [20], a unique subset of CD8⁺ T cells, PD-1⁺ TIGIT⁺ CD226⁻ CD8⁺ T cell subsets, associated with dysfunction in leukemia milieu and with poor prognosis. Increased frequency of PD-1⁺ and TIGIT⁺ expressing CD8⁺ T cells was observed in the peripheral blood of newly diagnosed AML patients, but the percentage of CD226⁻ expressing CD8⁺ T cells was reduced in AML patients. Moreover, these dysfunctional CD8⁺ T cells expressed low IFN- γ and TNF- α . Furthermore, PD-1⁺ TIGIT⁺ CD226⁻ CD8⁺ T cells were associated with non-remission after induction to chemotherapy, and T-cell exhaustion may be related to the presence of the FLT3-ITD mutation and the expression of CD112 and CD155 in leukemia blasts [20].

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Conclusion

In summary, dysfunctional CD8+ T cells in patients with AML express elevated immune checkpoints and blocking the immune checkpoint is favorable for the anti-leukemic function of T cells. Until now, methods of blocking immune checkpoints, such as CTLA4 or PD-1/PD-L1, are being evaluated in clinical trials in patients with AML [7]. In the future, immune checkpoints may be potentially important diagnostic or prognostic biomarkers for AML patients. Blocking immune checkpoints either alone or in combination will improve clinical remission rates of patients in AML therapy.

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References

1. Dohner H, Weisdorf DJ, Bloomfield CD (2015) Acute myeloid leukemia. *N Engl J Med* 373: 1136-1152.
2. Austin R, Smyth MJ, Lane SW (2016) Harnessing the immune system in acute myeloid leukaemia. *Crit Rev Oncol Hematol* 103: 62-77.
3. Aggarwal N, Swerdlow SH, TenEyck SP, Boyiadzis M, Felgar RE (2016) Natural killer cell (NK) subsets and NK-like T-cell populations in acute myeloid leukemias and myelodysplastic syndromes. *Cytometry B Clin Cytom* 90: 349-357.
4. Zha X, Chen S, Yang L, Shi L, Li B (2015) Upregulated TCR ζ improves cytokine secretion in T-cells from patients with AML. *J Hematol Oncol* 8: 72.
5. Torphy RJ, Schulick RD, Zhu Y (2017) Newly emerging immune checkpoints: Promises for future cancer therapy. *Int J Mol Sci* 18: E2642.
6. Bose CK (2017) Immune checkpoints, their control by immunotherapy and ovarian cancer. *Contemp Oncol* 21: 189-196.
7. Sharma P, Allison JP (2015) Immune checkpoint targeting in cancer therapy: Toward combination strategies with curative potential. *Cell* 161: 205-214.
8. Topalian SL, Sznol M, Dermott DF, Kluger HM, Carvajal RD, et al. (2014) Survival, durable tumor remission and long-term safety in patients with advanced melanoma receiving nivolumab. *J Clin Oncol* 32: 1020-1030.
9. Wang X, Teng F, Kong L (2016) PD-L1 expression in human cancers and its association with clinical outcomes. *Onco Targets Ther* 9: 5023-5039.
10. Masarova L, Kantarjian H, Garcia-Mannero G (2017) Harnessing the immune system against leukemia: Monoclonal antibodies and checkpoint strategies for AML. *Adv Exp Med Biol* 995: 73-95.
11. Assi R, Kantarjian H, Ravandi F (2017) Immune therapies in acute myeloid leukemia: A focus on monoclonal antibodies and immune checkpoint inhibitors. *Curr Opin Hematol*.
12. Teague RM, Kline J (2013) Immune evasion in acute myeloid leukemia: current concepts and future directions. *J Immunother Cancer* 1: 13.
13. Krupka C, Kufer P, Kischel R (2016) Blockade of the PD-1/PD-L1 axis augments lysis of AML cells by the CD33/CD3 BiTE antibody construct AMG 330: Reversing a T-cell-induced immune escape mechanism. *Leukemia* 30: 484-491.
14. Kong Y, Zhu L, Schell TD (2016) T-cell immunoglobulin and ITIM domain (TIGIT) associates with CD8+ T-Cell exhaustion and poor clinical outcome in AML patients. *Clin Cancer Res* 22: 3057-3066.
15. Lichtenegger FS, Schnorfeil FM, Emmerig K (2013) Pseudo-exhaustion of CD8+ T Cells in AML. *Blood* 122: 2615.
16. Zhou Q, Munger ME, Veenstra RG (2011) Coexpression of Tim-3 and PD-1 identifies a CD8+ T-cell exhaustion phenotype in mice with disseminated acute myelogenous leukemia. *Blood* 117: 4501-4510.
17. Kong Y, Zhang J, Claxton DF, Ehmann WC, Rybka WB, et al. (2015) PD-1(hi) TIM-3(+) T cells associate with and predict leukemia relapse in AML patients post allogeneic stem cell transplantation. *Blood Can J* 5: e330.
18. Hutten TJA, Norde WJ, Woestenenk R (2017) Increased co-expression of PD-1, TIGIT and KLRG-1 on tumor-reactive CD8+ T cells during relapse after allo-SCT. *Biol Blood Marrow Transplant* 8791: 30874-30881.
19. Johnston RJ, Comps-Agrar L, Hackney J (2014) The immunoreceptor TIGIT regulates antitumor and antiviral CD8(+) T-cell effector function. *Cancer Cell* 26: 923-937.
20. Wang M, Bu J, Zhou M (2017) CD8+T cells expressing both PD-1 and TIGIT but not CD226 are dysfunctional in acute myeloidleukemia (AML) patients. *Clin Immunol* 6616: 30424-30432.