American Journal of
Biomedical Science & Research

www.biomedgrid.com
ISSN: 2642-1747

Mini Review

Beyond CTLA-4 Expression: The CTLA-4/CD80/CD86 Axis in Acute Myeloid Leukemia

Milan Jagurinoski* and Margarita Guenova

Laboratory of Hematopathology and Immunology, National Specialized Hospital for Active Treatment of Hematological Diseases, Sofia, Bulgaria

***Corresponding author:** Milan Jagurinoski, Laboratory of Hematopathology and Immunology, National Specialized Hospital for Active Treatment of Hematological Diseases, Sofia, Bulgaria.

To Cite This article: *Milan Jagurinoski* and Margarita Guenova, Beyond CTLA-4 Expression: The CTLA-4/CD80/CD86 Axis in Acute Myeloid Leukemia. Am J Biomed Sci & Res. 2026 32(1) AJBSR.MS.ID.004128,* **DOI:** 10.34297/AJBSR.2026.32.004128

Received: August 26, 2026 **Published:** September 02, 2026

Abstract

Acute Myeloid Leukemia (AML) induces profound alterations of the immune microenvironment that facilitate immune escape and may contribute to treatment resistance. CTLA-4 is a major inhibitory immune checkpoint regulating T-cell activation through interaction with CD80 and CD86. However, its significance in AML appears to extend beyond expression level alone and may depend on cellular context, regulatory T-cell activity, ligand availability, and integrated immune phenotypes. This mini review discusses the biological and clinical relevance of the CTLA-4/CD80/CD86 axis in AML and highlights emerging evidence supporting a context-dependent role of CTLA-4 in disease immunobiology and outcome.

Keywords: Acute myeloid leukemia, CTLA-4, CD80, CD86, Regulatory T cells, Immune checkpoints

Abbreviations: AML-Acute myeloid leukemia; CTLA-4-Cytotoxic T-lymphocyte-associated protein 4; Tregs- Regulatory T cells; OS-Overall survival

Introduction

Acute Myeloid Leukemia (AML) is characterized by extensive molecular and cellular heterogeneity. Beyond leukemia-intrinsic genetic alterations, increasing evidence indicates that remodeling of the bone marrow immune microenvironment contributes to immune escape and disease progression. Multiple mechanisms have been implicated, including impaired antigen presentation, dysfunctional effector T cells, expansion of regulatory T cells (Tregs), and altered expression of co-stimulatory and inhibitory immune checkpoint molecules [1,2]. Among these pathways, CTLA-4 is particularly intriguing. Although traditionally regarded as an inhibitory T-cell receptor, its biological relevance depends on the cellular context in which it is expressed and on interactions with its ligands CD80 and CD86. Consequently, assessment of CTLA-4 expression alone may provide an incomplete representation of this regulatory pathway in AML.

CTLA-4/CD80/CD86 Axis in AML

CTLA-4 (CD152) is a key negative regulator of T-cell activation. It shares the ligands CD80 (B7-1) and CD86 (B7-2) with the co-stimulatory receptor CD28 but binds them with greater affinity, thereby limiting CD28-mediated T-cell activation [3]. Its biological relevance therefore depends on ligand availability and the cellular populations involved. In AML, leukemic cells can express CD80/CD86 and directly interact with T cells. Persistent interactions between myeloid leukemia cells and T lymphocytes may promote dysfunctional immune states characterized by altered checkpoint expression and impaired cytokine production [4]. Thus, the CTLA-4/CD80/CD86 axis is best viewed as a dynamic interface between leukemic blasts and the immune compartment (Figure 1).

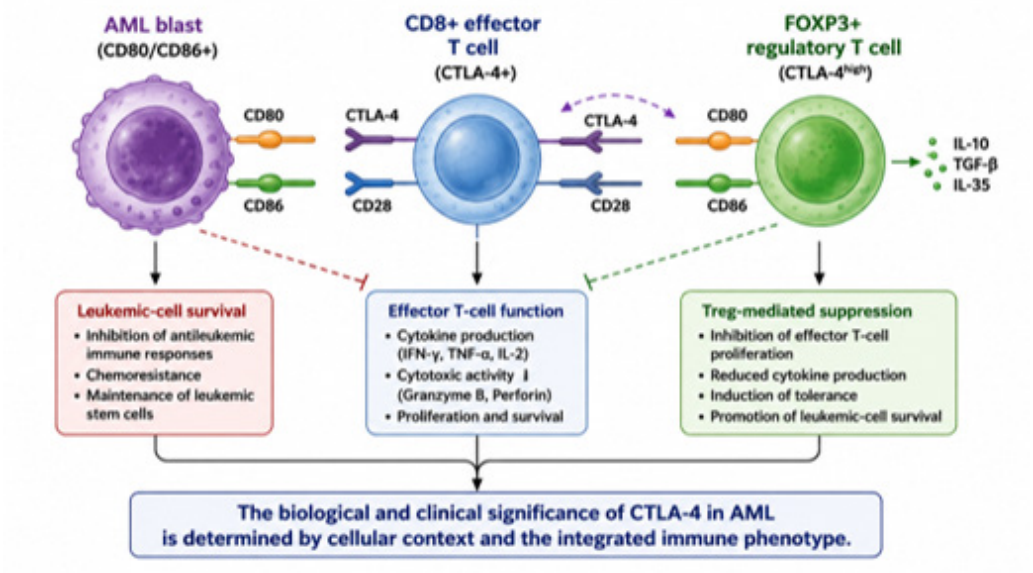

Figure 1: Context-dependent role of the CTLA-4/CD80/CD86 immune checkpoint axis in AML. Interactions between CD80/CD86-expressing leukemic blasts, CTLA-4-expressing effector T cells, and FOXP3+ regulatory T cells may shape the functional immune state of the AML microenvironment. The resulting balance between immune activation and suppression may influence T-cell cytotoxicity, cytokine responses, leukemic-cell survival, and ultimately clinical outcome.

Regulatory T Cells and Immune Suppression

Tregs represent an important component of this network. FOXP3+ Tregs constitutively express high levels of CTLA-4 and can suppress effector T-cell activation through competition with CD28 for CD80/CD86 and additional regulatory mechanisms [3]. Increased frequencies and enhanced suppressive activity of Tregs have been reported in AML, including preferential accumulation within the bone marrow [5,6].

AML-associated Tregs may inhibit conventional T-cell proliferation and cytokine production, thereby contributing to an immunosuppressive environment permissive for leukemic-cell survival [5,6]. Thus, the interplay between CTLA-4-expressing effector T cells, CTLA-4+FOXP3+ Tregs, and CD80/CD86-expressing AML blasts may be more biologically informative than measurement of CTLA-4 expression alone.

Clinical Relevance: Beyond CTLA-4 Expression

The prognostic significance of CTLA-4 in AML remains controversial. Expression-based studies have associated increased CTLA-4 and coordinated expression of multiple immune checkpoints with adverse outcome [7]. However, cellular-level analyses suggest a more complex relationship.

In our previous integrative analysis, unsupervised hierarchical clustering of immune checkpoint expression on blast cells and T-cell and NK-cell subsets identified two distinct AML immune phenotypes with significantly different overall survival (OS) [8]. Among 52 patients with complete data, Cluster 2 showed markedly higher CTLA-4 expression across several immune populations, particularly cytotoxic CD8+ T cells (95.8% vs 7.5%, $p<0.001$), yet demonstrated significantly superior OS (median not reached vs 5.4 months, $p=0.029$). CTLA-4 elevation was the most distinctive feature of this favorable immune phenotype [8,9].

These observations challenge the simplistic concept that increased CTLA-4 expression necessarily reflects greater immune suppression and poorer prognosis. Instead, its clinical significance may depend on T-cell subset, activation state, CD80/CD86 availability, regulatory T-cell activity, and co-expression of other immune checkpoints. Integrated immune phenotyping may therefore provide greater biological and prognostic information than assessment of individual checkpoint molecules [10,11].

Future Perspectives and Conclusion

Future studies should move beyond descriptive CTLA-4 assessment toward integrated characterization of the entire CTLA-4/CD80/CD86 axis. Combining receptor–ligand profiling with Treg characterization and functional measures of cytokine production, CD8+ T-cell cytotoxicity, and leukemic blast apoptosis could clarify how distinct checkpoint phenotypes translate into functional immune suppression.

Ultimately, the CTLA-4/CD80/CD86 axis represents a complex regulatory network connecting AML blasts, effector T cells, and Tregs. Defining its cellular and functional context may facilitate the identification of immune-based biomarkers for treatment response

and prognosis and provide a rationale for more precisely targeted immunotherapeutic strategies in AML.

Acknowledgements

None.

Conflict of Interest

MJ declares no conflict of interest. MG declares participation in advisory boards and speaker's bureau of Swixx Biopharma, Recordati, and SOBI.

References

1. Vago L, Gojo I (2020) Immune escape and immunotherapy of acute myeloid leukemia. J Clin Invest 130(4): 1552-1564.
2. Isidori A, Salvestrini V, Ciciarello M, Loscocco F, Visani G, et al. (2014) The role of the immunosuppressive microenvironment in acute myeloid leukemia development and treatment. Expert Rev Hematol 7(6): 807-818.
3. Wei SC, Duffy CR, Allison JP (2018) Fundamental mechanisms of immune checkpoint blockade therapy. Cancer Discov 8(9): 1069-1086.
4. Ozkazanc D, Yoyen-Ermis D, Tavukcuoglu E, Buyukasik Y, Esendagli G (2016) Functional exhaustion of CD4+ T cells induced by co-stimulatory signals from myeloid leukaemia cells. Immunology 149(4): 460-471.
5. Szczepanski MJ, Szajnik M, Czystowska M, Mandapathil M, Strauss L, et al. (2009) Increased frequency and suppression by regulatory T cells in patients with acute myelogenous leukemia. Clin Cancer Res 15(10): 3325-3332.
6. Wan Y, Zhang C, Xu Y, Wang M, Rao Q, et al. (2020) Hyperfunction of CD4+CD25+ regulatory T cells in de novo acute myeloid leukemia. BMC Cancer 20(1): 472.
7. Chen C, Liang C, Wang S, Chio CL, Zhang Y, et al. (2020) Expression patterns of immune checkpoints in acute myeloid leukemia. J Hematol Oncol 13(1): 28.
8. Jagurinoski M, Vasilev G, Vladimirova R, Muhtarova M, Guenova M (2024) Integrative analysis of immune checkpoint molecules expression defines distinct prognostic clusters in AML patients. 29th Congress of the European Hematology Association, Madrid, Spain. HemaSphere 8(S1): P1812.
9. Jagurinoski M (2025) Comparative study of secondary and myelodysplasia-related acute myeloid leukemias [PhD thesis]. SHATHD-Sofia.
10. Williams P, Basu S, Garcia Manero G, Hourigan CS, Oetjen KA, et al. (2019) The distribution of T-cell subsets and the expression of immune checkpoint receptors and ligands in patients with newly diagnosed and relapsed acute myeloid leukemia. Cancer 125(9): 1470-1481.
11. Boddu P, Kantarjian H, Garcia Manero G, Allison J, Sharma P, et al. (2018) The emerging role of immune checkpoint based approaches in AML and MDS. Leuk Lymphoma 59(4): 790-802.