

A co-stimulatory trap set by myeloid leukemia cells

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The straightforward notion that tumor cells always exert immunosuppressive functions has been contradicted by the finding that myeloid leukemia cells can express potent co-stimulatory molecules. Indeed, the co-stimulatory support offered by leukemia cells can provoke helper T-cell responses. Unfavorably, this interaction allows leukemia cells to acquire immunosuppressive capacities.

Robust immune responses are required for the eradication of malignant cells.^{1,2} Circulating cancer cells are considered to be more susceptible to immune attacks as their likelihood to encounter immune cells is enhanced, and they are devoid of a protective (immunosuppressive) microenvironment.¹ On the other hand, antitumor immune response not always correlate with reduced tumor growth and increased patient survival.^{1,2} Moreover, immunostimulatory interventions have been shown to enhance the ability of immune effectors to eradicate some, but not all, cancer cells.² Essentially, a reduction in the immunogenic signals originating from tumors can limit the effector phase of immune responses. The current dogma in tumor immunology is that cancer cells express inhibitory molecules and anti-inflammatory cytokines to escape antitumor responses.¹ However, this scenario is becoming ever more intriguing as co-stimulatory molecules can also be found on neoplastic cells. Acute myeloid leukemia (AML) perfectly exemplifies this paradoxical situation. The potent co-stimulatory molecules of B7 superfamily B7-2 (CD86) and B7-H2 (inducible costimulator ligand, ICOSL) have indeed been detected on surface of AML cell subpopulations.³⁻⁵ These molecules are critical for T-cell activation and hence for successful antitumor immune responses. CD28 is the T-cell receptor for B7-1

(CD80) and B7-2, which are critical co-stimulatory molecules for the priming of naïve helper T cells.⁶ On the other hand, B7-H2 serves as a ligand for CD28 and ICOS, providing signals for the persistence of T-cell activation.⁶ Intriguingly, in several independent studies, the presence of B7-2⁺ and/or B7-H2⁺ AML cell subpopulations has been attributed a strong negative prognostic value, being associated with poor clinical outcomes such as hyperleukocytosis and limited disease-free or relapse-free survival.³⁻⁵

In our study, we conditioned a well-characterized AML cell line, namely, HL-60 cells, and were able to model the interaction between B7-2- and/or B7-H2-expressing leukemia cells and helper T cells.⁷ We obtained similar results with other myeloid leukemia cell lines. Under conditions of suboptimal stimulation of the T-cell receptor (TCR) complex, AML cells generated potent co-stimulatory signals that were required for helper T-cell responses.⁷ The upregulation of T-cell activation markers (e.g., CD154, CD25 and CD69), T-cell expansion, as well as the secretion of T_H1 and T_H17 cytokines including interferon γ (IFN γ), tumor necrosis factor α (TNF α) and interleukin (IL)-17A were the result of the interaction between helper T and AML cells, and co-stimulation was largely mediated by the B7-2⁺ AML cell subpopulation (Fig. 1).⁷

T-cell responses provoked by leukemia cells resulted in a rapid alternation of the expression of B7 ligands on AML cells. In particular, AML cells upregulated the ligands for programmed cell death 1 (PD1), namely, B7-H1 (PD-L1) and B7-DC (PD-L2).⁷ The inhibitory receptor PD1 is expressed by activated T cells and mediates the resolution of immune responses mainly by interfering with CD28-derived co-stimulatory signals.⁸ Vice versa, when co-stimulatory signals are simultaneously delivered, the inhibitory effects of PD1 can be weakened.^{8,9} In addition, the expression of co-stimulatory AML cells downregulated B7-H2 molecules.⁷ Thus, upon an initial engagement with helper T cells, leukemia cells acquired an inhibitory phenotype. We confirmed that these AML cells in turn are able to inhibit T-cell responses and direct the differentiation of helper T cells toward a regulatory (Treg) phenotype (Fig. 1).

Tumor cells hide from immune recognition and/or cope with immune attacks.¹ In other words, tumor cells that can successfully evade antitumor immunity may emerge as a consequence of adaptation to the selective pressure imposed by the immune system.¹ Our results demonstrate the capacity of the leukemia cells to rapidly adapt to antitumor immune responses.^{7,10} In our experience, only a small sub-population of leukemia cells

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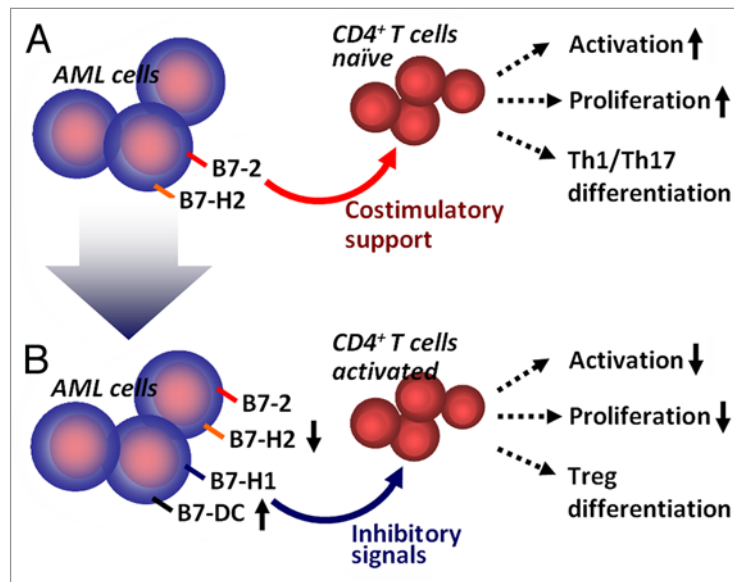


Figure 1. Co-stimulatory interactions between helper T cells and acute myeloid leukemia cells. **(A)** The initial engagement between acute myeloid leukemia (AML) cells that harbor B7-2 (CD86) and/or B7-H2 (ICOSL) provokes T-cell responses and T_H1/T_H17 differentiation. **(B)** In turn, helper T-cell responses modulate the expression of B7 family molecules on AML cells. In particular, B7-H2 levels are decreased while B7-H1 (PD-L1) and B7-DC (PD-L2) are upregulated. The AML cells gain immunosuppressive functions, hampering helper T-cell responses and favoring the differentiation of regulatory T cells, especially through the PD1 pathway.

originally expressed B7-2 and/or B7-H2, whereas most of them adopted these immunosuppressive characters de novo in response to an antitumor immune response.⁷ Thus, during immune evasion, cancers may benefit from being composed of heterogeneous cell sub-populations.

In conclusion, AML cells can elicit helper T-cell responses but quickly alter their immune phenotype and resist immune attacks. Our findings may have important implications for the development of novel immunotherapeutic approaches against AML.^{7,10}

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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