Expression and Function of B7 Family Molecules on Blasts of Patients with Myelodysplastic Syndromes

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Optimal activation of T cells requires second, costimulatory signals together with the first signal delivered by engagement of the T-cell receptor with the peptide-MHC complex on antigen presenting cells (APCs), such as macrophages, B cells, and dendritic cells. The interaction between B7 molecules, i.e., B7-1 (CD80)/B7-2 (CD86), on APCs and CD28/CTLA-4 molecules on T cells is the most well-characterized costimulatory signal pathway and is thought to be crucial in eliciting an antitumor immune response. Recently, several new members of the B7 family, B7-H1, B7-H2, B7-H3, and B7-H4, have been identified. B7-H1 inhibits the proliferation of T cells through a counterreceptor, programmed death 1 (PD-1), and delivers a stimulatory signal to T cells through an as yet unidentified counterreceptor other than PD-1[1,2]. We detected the expression of B7-H1 on activated T cells and some tumor cells, such as those from melanoma, lung, ovarian, and colon cancers, and showed that B7-H1 on tumor cells suppresses antitumor immunity by inhibiting the proliferation of tumor-specific cytotoxic T lymphocytes (CTLs)[3]. Consistent with these results, patients with renal cell carcinoma and breast cancer expressing B7-H1 have been reported to have a poor prognosis. B7-H2 is expressed on professional APCs and tumor cells, such as those from glioma and gastric carcinoma. The counterreceptor of B7-H2, inducible costimulator (ICOS), is expressed on activated T cells. The B7-H2-ICOS signal induces T cells to proliferate and to secrete both Th1 and Th2 cytokines, such as interleukin (IL)-4 and interferon-γ, but not the potent Th1 cytokine IL-2. Furthermore, the B7-H2-ICOS signal induces IL-10 production.

When we investigated the expression of B7 family molecules in hematological malignancies, B7-H1 or B7-H2 or both were detected in leukemia, myeloma, and lymphoma cells. We have recently reported that cells from many patients with acute myeloid leukemia (AML) express B7-2 and B7-H2 molecules and that B7-1 and B7-H1 expression is rare[4]. Patients with B7-H2-positive AML had significantly shorter survival times. Furthermore, B7-2 expression was associated with hyperleukocytosis. Consistent with these findings, AML cells expressing B7-2 and B7-H2 induced allogeneic $CD4^+$ T cells to proliferate and secrete IL-4 and IL-10 *in vitro*, effects that were partially blocked by antibodies against B7-2 and B7-H2[4]. These cytokines induced by AML cells expressing B7-2 or B7-H2 may inhibit tumor-specific Th1 cell differentiation and CTL activity, resulting in the creation of a favorable environment for the growth of leukemic cells. In addition, other groups have shown that patients with AML or myeloma expressing B7-2 have significantly shorter survival times. These data suggest that the expression of B7 family molecules contributes to the proliferation of malignant cells by helping them evade antitumor immune responses in hematological malignancies.

Myelodysplastic syndromes (MDS) are malignant disorders of hematopoietic cells with poor prognosis that typically occur in elderly people and often progress to AML. The dysfunction of T cells has been reported in MDS. We have previously reported on the pathobiology, methods of diagnosis, and possibility of immunotherapy in MDS[5]. In this study, we used 3-color flow cytometry analysis[5] to investigate the expression of B7 family molecules on blasts obtained from patients with MDS or with acute leukemia transformed from MDS (MDS-AL).

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We also compared the levels of B7 expression on blasts in MDS with those in patients with *de novo* AML. Our results obtained so far show that the expression pattern of B7 family molecules on blasts differs between MDS and *de novo* AML. Unlike in *de novo* AML, in MDS and MDS-AL, B7-H2 expression was rare, but blasts from many patients expressed B7-H1 as well as B7-2. Surprisingly, B7-1 expression, which was negative in almost all patients with *de novo* AML, was detected in some patients with MDS or MDS-AL. These results suggest that the properties of blasts differ between MDS and *de novo* AML. Moreover, the detection with flow cytometry of B7-1 expression on blasts may be useful in differential diagnosis. To clarify the significance and functions of B7 molecules on MDS blasts, we investigated the ability of B7-positive blasts to proliferate and survive, the relationship between B7 expression and disease progression (e.g., International Prognostic Scoring System, chromosome abnormality, and survival), and the effect of B7 expression on host immune defense against tumors, e.g., inhibition of CTL proliferation. The results of our study may lead to a better understanding of pathobiology and immunological status and to the development of effective immunotherapy based on the manipulation of B7 molecules in MDS.

References

1. Tamura H, Dong H, Chen L, et al.: B7-H1 costimulation preferentially enhances CD28-independent T-helper cell function. Blood 2001; 97: 1809–1816.
2. Tamura H, Ogata K, Dong H, Chen L: Immunology of B7-H1 and its roles in human diseases. Int J Hematol 2003; 78: 321–328.
3. Dong H, Strome SE, Tamura H, et al.: Tumor-associated B7-H1 promotes T-cell apoptosis: A potential mechanism of immune evasion. Nat Med 2002; 8: 793–800.
4. Tamura H, Dan K, Ogata K, et al.: Expression of functional B7-H2 and B7.2 costimulatory molecules and their prognostic implications in *de novo* acute myeloid leukemia. Clin Cancer Res 2005; 11: 5708–5717.
5. Ogata K, Nakamura K, Tamura H, et al.: Clinical significance of phenotypic features of blasts in patients with myelodsplastic syndromes. Blood 2002; 100: 3887–3896.