**Letter to the Editor**

**Potential mechanisms of spontaneous regression in patients with B-cell lymphoma; the significance of co-stimulatory molecules in lymphoma cells**

**Keywords:** spontaneous regression, remission, lymphoma

**TO THE EDITOR**

Spontaneous regression (SR) of malignant tumors has been observed in several types of tumors including lymphoma, kidney cancer, melanoma, and neuroblastoma.\(^1\) SR is currently of interest for many clinicians because of an increased number of methotrexate-related lymphoproliferative disorders, and because SR is observed in many patients after withdrawal of methotrexate.\(^2\) In terms of a mechanism, anti-tumor immune responses by host T lymphocytes reacting against tumor cells are believed to be involved in SR,\(^3\) and several cases have recently been reported. In a recent issue of Journal of clinical and experimental hematopathology (JCEH), Tanaka et al. described a case of diffuse large B-cell lymphoma (DLBCL) with SR.\(^4\) A 35-year-old man had multiple mesenteric lymphadenopathy and a thickened small intestine wall, and was diagnosed with DLBCL (germinal center origin) without infection with Epstein-Barr virus (EBV) following laparoscopic lymph node biopsy. However, symptoms were improved and abnormal accumulation of fluorodeoxyglucose was disappeared 3 months after the biopsy. In addition, Abe et al. previously reported in JCEH a case of DLBCL harboring EBV infection with SR and reviewed some published SR cases of aggressive non-Hodgkin’s lymphoma.\(^5\) SR has also been seen in low-grade lymphoma. Matsuo et al. described a case of bilateral conjunctival extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue with SR.\(^6\) Ye et al. just recently published four cases of SR in patients with mantle cell lymphoma.\(^7\) SR is preferentially seen in extranodal lymphoma including in the intestinal tract.

SR (also referred as “healing”) is also observed in patients with non-hematological malignant tumors such as lung cancer, kidney cancer, breast cancer, and melanoma.\(^8\)-\(^11\) These solid cancers are known as immunogenic tumors because of increased expression of neoantigens, and anti-tumor therapy using immune checkpoint blockade antibodies and cytokines such as interferons have been used for these cancers.\(^12\),\(^13\) However, mutation burdens of high-grade lymphomas are less than those of melanoma and lung cancers, indicating that unknown mechanisms are involved in SR in lymphoma cases.\(^14\)

CD80 and CD86 are well-known co-stimulatory molecules expressed on antigen-presenting cells including B cells. CD80 is expressed on lymphoma cells in 90% of DLBCL cases,\(^15\) and the expression of both CD80 and CD86 is widely seen in leukemia or lymphoma cell lines in the NCi-60 cancer panel database [GEO data set, GDS4296]. As shown in figure 1, CD80 expression was observed in B-cell lymphoma and B-cell lymphoma cell lines. In addition, human leukocyte antigen (HLA)-DR, one of major histocompatibility complex (MHC) class II molecules, is also expressed in 65% of DLBCL cases, and HLA-DR-positive cases show a significantly better clinical course.\(^16\) Given that lymphoma cells in DLBCL expressing co-stimulatory molecules such as CD80/CD86 and MHC class II molecules, lymphoma cells may have the higher immunogenic potential than other solid tumors. In support of this, Allison (received the Nobel Prize in 2018) et al. previously found that ectopic expression of CD80 on tumor cells induces T cell-mediated rejection in murine models by not CD4-positive T cells but CD8-positive T cells.\(^17\) In addition, clinical trials with tumor cell vaccines using CD80-transfected autologous or allogenic tumor cells were performed for kidney cancer, lung cancer, and acute myeloid leukemia.\(^18\) As a result, some patients who enrolled in these trials showed significant tumor reduction.\(^19\),\(^20\) Although the overall response rate was limited, these findings indicate that CD80-expressing tumor cells could enhance anti-tumor immune responses. The interaction between CD80/CD86 and CD28 activates tumor-specific T cells to produce interleukin (IL)-2, which in turn triggers T cell proliferation in autocrine and paracrine manners in tumor microenvironment (Figure 2). Given that the interaction between CD80/86 and CTLA-4 results in T cell inactivation, therapies to block CTLA-4-mediated immunosuppression may improve this immune response.

Regarding EBV-infected lymphoma or lymphoproliferation, anti-EBV immune responses are believed to induce anti-lymphoma immune responses and SR.\(^22\) However, EBV-transformed B lymphocytes and EBV-infected lymphoma cells produce IL-12, which is a cytokine to promote cellular immunity and is produced after CD40 ligation.\(^23\) IL-12 production from lymphoma cells may be involved in SR in EBV-infected lymphoma or lymphoproliferative disorders.

Traumatic stress or injury including biopsy is considered to be a trigger for SR, and occasionally, administration of corticosteroids, anti-lymphoma drugs, or infection may cause the initiation of SR.\(^1\),\(^3\) We propose a possibility that, after
Fig. 1. CD80 expression in lymphoma tissues and cell lines. (A) The immunostaining using anti-CD80 monoclonal antibody (clone EPR1157, Abcam) was performed as described previous methods. Lymphoma cells were weakly positive for CD80 in diffuse large B-cell lymphoma (A), and strongly positive in two B-cell lymphoma cell lines (SLVL and BALL1) (B). Scale bar; 20μm.

Fig. 2. Scheme of the suggested mechanisms of spontaneous regression (SR). (A) In the growing phase of lymphoma, lymphoma cells are protected from microenvironment that includes cytotoxic T lymphocytes. Stress or injury disrupts the microenvironment, and immune reactions between T lymphocytes and lymphoma cells can be initiated. (B) Co-stimulatory molecules such as CD80/CD86 stimulate lymphoma-specific T cell response. Activated T lymphocytes proliferate and attack lymphoma cells, which present neoantigens or viral antigens with HLA class I or class II molecules.
lymphoma cells are exposed to anti-lymphoma T lymphocytes by physical disruption of the microenvironment, immune reaction between lymphoma cells and lymphoma-specific T lymphocytes may be initiated. Damage-associated molecular patterns are also considered to be involved in this immune reaction by activating the STING pathway in antigen-presenting cells.24

Recent advances of immunotherapy indicated the significance of programmed death-1 (PD-1) and its ligands such as PD-L1 and PD-L2. PD-L1-expression in lymphoma cells was seen in 11% of cases and reportedly associated to poor clinical course in DLBCL.25 PD-L1 expression in lymphoma cells were potentially mediated by Stat3 activation which were suggested to be induced by macrophage-derived molecules are also expressed on myeloid cells such as tumor associated macrophages.26 Down-regulation of these factors might be linked to SR in lymphoma cases.

In conclusion, the expression of CD80/CD86 on lymphoma cells is potentially associated with activation of anti-lymphoma T cell responses and clinical SR. HLA-DR expression on lymphoma cells may also influence activation of lymphoma-specific CD4-positive helper T cells in the microenvironment. CD86, in contrast to CD80, is constitutively expressed on both malignant B cells and nonmalignant stromal cells. CD80 (B7.1) is expressed on both malignant B cells and nonmalignant stromal cells in non-Hodgkin lymphoma.4 As a therapeutic strategy, anti-CTLA-4 antibody rather than anti-PD-1/PD-L1 antibody may be helpful to enhance anti-lymphoma T cell response in cases of CD80/CD86-positive lymphoma.

CONFLICT OF INTEREST

All authors have no financial competing interests to declare.

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Yoshihiro Komohara,1,3) Mamoru Harada2)

1) Department of Cell Pathology, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan,
2) Department of Immunology, Faculty of Medicine, Shimane University, Shimane, Japan,
3) Center for Metabolic Regulation of Healthy Aging, Kumamoto University, Kumamoto, Japan

Corresponding author: Yoshihiro Komohara, Department of Cell Pathology, Graduate School of Medical Sciences, Kumamoto University, Honjo 1-1-1, Kumamoto, 860-8556, Japan.

E-mail: ycomo@kumamoto-u.ac.jp

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