IN THE SPOTLIGHT

PD-1 Shapes B Cells as Evildoers in the Tumor Microenvironment

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Summary: Protumorigenic PD-1^{hi} B cells, induced in hepatocellular carcinoma, suppress tumor-specific T-cell response via IL10-dependent pathways upon PD-1/PD-L1 interaction. Anti–PD-1 or anti–PD-L1 antibodies may function not only through blocking the PD-1 coinhibitory pathway in T cells but also via abolishing the suppressive function of regulatory B cells. *Cancer Discov; 6(5); 477–8. ©2016 AACR.*

See related article by Xiao et al., p. 546 (7).

Tumor cells often induce an immunosuppressive microenvironment against antitumor immune responses. Besides regulatory T cells, myeloid-derived suppressor cells, and tumor-associated macrophages, regulatory B cells (Breg) have recently been reported to be key immune suppressors that silence antitumor responses and promote tumor progression in some types of tumors. Bregs were first discovered as inhibitors in autoimmune diseases, because B-cell–deficient mice (μMT) failed to control experimental autoimmune encephalomyelitis (EAE) and could not undergo spontaneous remission (1). The exacerbated EAE in μMT mice was later attributed to a deficiency in IL10-producing B cells (2), or so-called B10 cells. Emerging data indicate that tumor-infiltrating B cells are not irrelevant bystanders in tumor progression, but rather actively regulate antitumor immune responses (3–6). Tumor-infiltrating B cells with distinct phenotypes and functions may play specific roles in antitumor responses (5). Despite recent advances in understanding the role of tumor-infiltrating B cells, direct evidence supporting an immunosuppressive role for B cells in human cancers, such as specific knowledge of the subset compositions, regulation, and functional relevance of B cells in cancer environments, is still lacking.

In this issue of *Cancer Discovery*, Xiao and colleagues (7) present a comprehensive study of a novel PD-1^{hi} regulatory B-cell subset in human hepatocellular carcinoma (HCC). This newly identified subset of PD-1^{hi} regulatory B cells is correlated with tumor stage and early recurrence in patients. PD-1^{hi} Bregs exhibit a unique CD5^{hi}CD24$^{-/+}$CD27^{hi}CD38^{dim} phenotype that differs from conventional regulatory B cells. PD-1^{hi} B cells can be specifically induced by the culture supernatant of primary HCC cells *in vitro*. Environmental hyaluronan (HA) fragments from hepatoma cells induce PD-1^{hi} Bregs via TLR4 activation, and TLR4-mediated BCL6 upregulation is critical for induction of PD-1^{hi} Bregs. Triggering PD-1 through PD-L1 induces production of IL10 by PD-1^{hi} Bregs, which suppress tumor-specific immunity and promote tumor progression.

Immunosurveillance, as a primary defense against cancer, is a process for the immune system to recognize and destroy tumor cells. However, some tumor cells can escape elimination by the immune system via activation of immunosuppressive feedback loops, which result in the induction of T-cell tolerance and the failure of tumor rejection. PD-1 signaling is one such inhibitory pathway, and its activation has been investigated in several cancer types (8). Binding of PD-1 on T cells with PD-L1 on antigen-presenting cells (APC) and other cells is a major mechanism triggering T-cell exhaustion during tumor progression. Costimulatory receptors primarily function to modify T-cell receptor signaling, but PD-1 exhibits a more dominant function in inhibiting IFNγ, TNFα, and IL2 production than in promoting cellular proliferation (9). PD-1 can be expressed on T cells, B cells, natural killer T cells, activated monocytes, and dendritic cells (9). The role of PD-1 on T cells has been well studied, but this role has not been so well studied in regard to B cells. Xiao and colleagues demonstrate that PD-1 expression on B cells endows them with suppressive function. Upon interaction with PD-L1, PD-1^{hi} B cells start to produce IL10, which serves as an immunosuppressive cytokine that regulates cytotoxic T-cell activation. Prolonged exposure of immune cells to inhibitory cytokines, such as IL10, during tumor progression causes T-cell dysfunction. These results identify a new mechanism for how PD-1–PD-L1 interactions between regulatory B cells and other cells induce the immune tolerance of T cells in the tumor. Anti–PD-1 and anti–PD-L1 antibodies have been broadly tested in several types of cancers in clinical trials (8). The main mechanism of tumor control by these antibodies is believed to be through blocking inhibitory signaling pathways in T cells. But anti–PD-1 and anti–PD-L1 antibodies can also work by removing the suppressive function of Bregs. As shown in Fig. 1A, PD-1–PD-L1 interactions could induce T-cell dysfunction through two different pathways in the tumor: (i) PD-L1 on monocytes or macrophages directly inducing effector T-cell dysfunction by triggering PD-1 on T cells; or (ii) PD-L1 triggering PD-1 on regulatory B cells for producing IL10, inducing effector T-cell dysfunction. Thus, anti–PD-1 or anti–PD-L1 antibodies may also function in two different ways: (i) directly interrupting the interaction of T-cell PD-1 with PD-L1 on monocytes or

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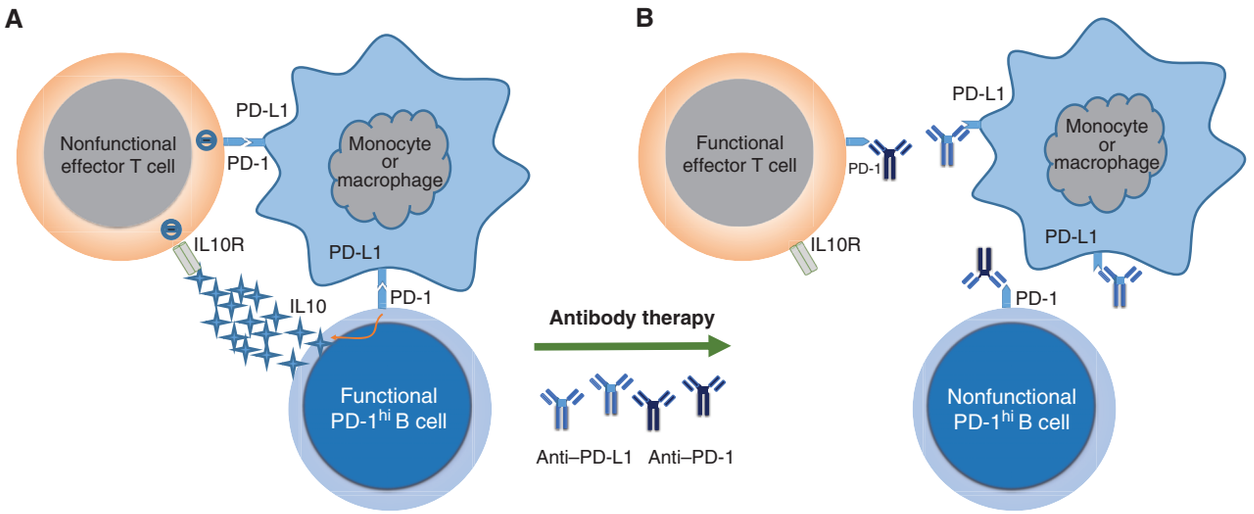

Figure 1. The role of the PD-1–PD-L1 interaction in suppressing tumor-specific T-cells and the potential mechanism of how anti–PD-1/anti–PD-L1 works in tumor treatment. **A,** by interacting directly with PD-L1^{+} monocytes or macrophages, the PD-1^{hi} B cells induce T-cell dysfunction via IL10-dependent pathways, and PD-L1^{+} monocytes or macrophages can also directly induce T-cell dysfunction by a PD-L1–PD-1 interaction. **B,** anti–PD-1 or anti–PD-L1 antibody can block the PD-1–PD-L1 interactions of T cells or PD-1^{hi} B cells with monocytes or macrophages, which rescues the function of effector T cells.

macrophages; or (ii) interrupting interaction of PD-1 on regulatory B cells with PD-L1 on monocytes or macrophages, removing the suppressive effect of regulatory B cells on effector T cells (Fig. 1B). These two different pathways can exist separately or coexist in the tumor microenvironment. This mechanism may explain why anti–PD-1 or anti–PD-L1 can also control some tumors with PD-1–negative tumor-infiltrating T lymphocytes (8).

To overcome tumor immune tolerance, identification of the dominant immunosuppressive cells and pathways in the tumor will be an alternative way to redesign future treatment. Each individual tumor microenvironment is possibly controlled by a distinct profile of suppressive molecules or cellular populations. This study has demonstrated that the PD-1^{hi} B cell is one sort of immunosuppressive cell that is specifically induced in the hepatocellular carcinoma microenvironment. If PD-1^{hi} B cells are the dominant immunosuppressive cells in HCC, or even in other types of cancer, an anti-CD20 antibody can potentially be used to transiently deplete these cells and remove the suppression (10). The authors propose that soluble factors derived from cancer cells promote PD-1 expression. Determining the nature of such factors will bring great benefit to clinical treatment. In addition to the proposed monocytes, other sources of PD-L1 interaction with PD-1 on B cells cannot yet be ruled out. It would be interesting to know whether B-cell and/or T-cell dysfunction can be corrected by PD-1 blockade on B cells, and whether IL10 production from those Bregs can be suppressed after anti–PD-1 or anti–PD-L1 treatment in the clinic. The requirement of PD-1 or PD-L1 signaling for the generation of those Bregs should be investigated in a follow-up study. Overall, this study has opened a new avenue for the study of B cell–mediated suppression and provided new insights into possible manipulation by B cell–mediated suppression through PD-1 overexpression.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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REFERENCES

1. Wolf SD, Dittel BN, Hardardottir F, Janeway CA Jr. Experimental autoimmune encephalomyelitis induction in genetically B cell-deficient mice. J Exp Med 1996;184:2271–8.
2. Fillatreau S, Sweenie CH, McGeachy MJ, Gray D, Anderton SM. B cells regulate autoimmunity by provision of IL-10. Nat Immunol 2002;3:944–50.
3. Qin Z, Richter G, Schuler T, Ibe S, Cao X, Blankenstein T. B cells inhibit induction of T cell-dependent tumor immunity. Nat Med 1998;4:627–30.
4. Olkhanud PB, Damdinsuren B, Bodogai M, Gress RE, Sen R, Wejksza K, et al. Tumor-evoked regulatory B cells promote breast cancer metastasis by converting resting CD4(+) T cells to T-regulatory cells. Cancer Res 2011;71:3505–15.
5. Zhang Y, Gallastegui N, Rosenblatt JD. Regulatory B cells in anti-tumor immunity. Int Immunol 2015;27:521–30.
6. Roghanian A, Fraser C, Kleyman M, Chen J. B cells promote pancreatic tumorigenesis. Cancer Discov 2016;6:230–2.
7. Xiao X, Lao X-M, Chen M-M, Liu R-X, Wei Y, Ouyang F-Z, et al. PD-1^{hi} identifies a novel regulatory B-cell population in human hepatoma that promotes disease progression. Cancer Discov 2016;6:546–59.
8. Zou W, Wolchok JD, Chen L. PD-L1 (B7-H1) and PD-1 pathway blockade for cancer therapy: mechanisms, response biomarkers, and combinations. Sci Transl Med 2016;8:328rv4.
9. Keir ME, Butte MJ, Freeman GJ, Sharpe AH. PD-1 and its ligands in tolerance and immunity. Annu Rev Immunol 2008;26:677–704.
10. Affara NI, Ruffell B, Medler TR, Gunderson AJ, Johansson M, Bornstein S, et al. B cells regulate macrophage phenotype and response to chemotherapy in squamous carcinomas. Cancer Cell 2014;25:809–21.

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