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Clinical Cancer Research

Letter to the Editor

PD-L1 Expression in B-cell Lymphomas and Virus-Associated Malignancies—Letter

Mads Hald Andersen

In a very important recent study, Chen and colleagues describe that PD-L1 (B7-H1, CD274) is expressed on both malignant cells and infiltrating macrophages in a subset of aggressive B-cell lymphomas (1). The article highlights the possibilities of targeting the PD-1/PD-L1 pathway in these malignancies. Interactions between PD-1 on T cells and the ligand PD-L1 (B7-H1) control the induction and maintenance of peripheral T-cell tolerance during normal immune responses. Accordingly, tumor-infiltrating lymphocytes are inhibited by PD-L1 at the tumor site because of elevated levels of PD-1 on the surface of such T cells. Indeed, blockade of either PD-1 or PD-L1 resulted in objective clinical responses (2). Remarkably, an association between objective clinical response and PD-L1 expression on tumor cells was described (2). Taube and colleagues furthermore recently described that T cells may actually trigger their own inhibition by secreting cytokines that drive tumor PD-L1 expression (3). However, the immune system itself seems also to have established a respective counteractive mechanism, that is, PD-L1–specific, $CD8^+$, cytotoxic T cells. Thus, PD-L1–reactive T cells can readily be isolated from peripheral blood of patients with cancer (melanoma) and to a lesser extent from blood of healthy donors (4). These PD-L1–specific T cells not only recognized and killed melanoma cells as well as cutaneous T-cell lymphoma cells, but also additionally PD-L1–expressing antigen-presenting cell (APC) in a PD-L1–dependent manner (4, 5). PD-L1 can furthermore be internalized, processed, and cross-presented on the cell surface by APC. This is notable, because soluble PD-L1 has been detected in the sera from patients with cancer. Thus, induction of PD-L1–specific T cells should boost immunity by killing of immune suppressive tumor cells as well as PD-L1–expressing stroma cells contributing to the permissive microenvironment. There is a major difference between blocking PD-L1 (or PD-1) function by antibody therapy, and generating a human leukocyte antigen-restricted T-cell response against processed and thus derived PD-L1 epitopes. PD-L1 antibodies target surface protein, whereas PD-L1–specific T cells recognize and kill cells, which are expressing PD-L1 epitopes on the surface derived from intracellular PD-L1.

It is important to note that PD-L1 additionally is expressed on normal immune cells, and is further upregulated upon activation in response to, for example, IFNγ. Nevertheless, PD-L1–specific T cells may be immensely useful to exploit for immunotherapy against certain cancers. Although not directly related, the publication by Chen and colleagues identifies a group of cancers with vigorous PD-L1 expression that may be suitable targets for such specific immunotherapy.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

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