Published in final edited form as:

Cancer J. 2014 ; 20(4): 254–255. doi:10.1097/PPO.0000000000000062.

From the Guest Editor Tumor Site Immune Modulation Therapy

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T lymphocytes are the principal effectors of the antitumor immune response. While engagement of antigen-specific T cell receptors is a prerequisite for T cell activation, additional signals stem from costimulatory and coinhibitory molecules that fine-tune and/or dictate T cell function. While costimulatory molecules facilitate T cell immune responses, coinhibitory molecules physiologically limit the magnitude and duration of T-cell activation, thereby preventing the excessive immune responses that cause tissue damage.

The programmed cell death 1 (PD-1) gene was initially identified in association with programmed cell death in murine hybridomas and hematopoietic cell lines by Ishida and colleagues.¹ Genetic ablation studies of PD-1 on 2C T cell receptor transgenic T cells showed augmented responses to allogeneic antigens,² indicating that PD-1 on T cells can play an inhibitory role in response to antigen.² Concurrently, a B7 family homolog, B7-H1, was molecularly cloned and found to suppress human T cell responses.³ One year later, it was discovered that B7-H1 binds PD-1 and acts as a major ligand that suppresses T cell responses.⁴ To date, 5 molecules have been identified in the B7-H1/PD-1 pathway (Fig. 1).

Dong and colleagues⁵ first exploited the role of the B7-H1/PD-1 pathway in tumor escape of immune response and the use of antibody blockade of this pathway for cancer therapy. Their experiments demonstrated that (i) many human cancers overexpress B7-H1; (ii) tumor-associated B7-H1 is inhibitory for antitumor T cell function; (iii) expression of B7-H1 on tumor cells is induced by interferon γ ; and (iv) antibodies against B7-H1 augment antitumor T cell activities.⁵ These findings, along with subsequent studies, laid the foundation for the first-in-man clinical trial using anti-PD-1 monoclonal antibodies to treat advanced solid tumors.⁶

A successful immunotherapy of established tumor requires not only the generation of systemic immunity but also overcoming of immune suppression in tumor site. In contrast to other immune therapeutic agents that aim to systemically boost tumor immunity, blockade of the B7-H1/PD-1 pathway by monoclonal antibodies selectively and effectively modulates immune responses at the tumor site. This specificity is largely due to the selective induction and expression of B7-H1 in the tumor microenvironment. This selectivity not only allows a more “targeted” augmentation of the immune response but also avoids the consequences of a broad, systemic autoimmune toxicity.

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The author declares no conflict of interest.

Armed with our understanding of immune responses, how they are generated, sustained, and immortalized, and the molecular pathways underlying their immunobiology, one could generate a road map that outlines the actions that are necessary to induce potent, targeted tumor immunity for cancer therapy (Fig. 2). The importance of the tumor microenvironment and tumor site immune modulation cannot be understated; a deeper understanding of the interactions in this environment is necessary for further modulation of immune evasive mechanisms and the design of future therapeutic options. Cancer treatment has entered a golden era where immunotherapy and therapeutic agents that deliberately and specifically modulate the immune response take center stage.

Acknowledgments

The author thanks Beth Cadugan for editing the manuscript.

The work was partially supported by National Institutes of Health grants CA121974, CA142779, and CA16359 and the United Technologies Corporation endowed professorship.

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Figure 1.

The B7-H1/PD-1 immune modulatory pathway. Five molecules are found in this pathway. B7-H1 (PD-L1) binds PD-1 as a major ligand to transmit a T cell-suppressive signal. In addition, B7-H1 could also interact with CD80 to inhibit T cell responses. Note here that B7-H1 could also act as a receptor to deliver an antiapoptotic signal to tumor cells or antigen-presenting cells. B7-DC (PD-L2) also interacts with PD-1 with affinity that is similar to B7-H1, while the function of this interaction in the regulation of immunity in vivo is less clear. B7-DC binds RGMb to participate in respiratory tolerance.

Figure 2.

Induction of immune responses to cancer. During the growth of cancer, tumor antigens are released and presented by professional antigen-presenting cells (APCs). After migration to lymphoid organs, the APCs stimulate activation of naive T cells, and this process is regulated by costimulation and coinhibition. Successful antigen presentation and costimulation lead to generation of effector T cells (T_e), which, after they exit lymphoid organs, reach tumor sites to execute effector functions, and a small fraction of T_e become long-term memory T cells (T_m). The strategies to stimulate tumor immunity include (1) cancer vaccines that enhance antigen presentation; (2) checkpoint blockades (anti-CTLA-4) and/or enhanced costimulation to systemically amplify T cell activation; (3) adoptive transfer of activated or genetically engineered T cells to provide more T_e; and (4) tumor site immune modulation to prevent B7-H1/PD-1 pathway-mediated suppression.