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Emerging Concepts Targeting Immune Checkpoints in Cancer and Autoimmunity

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Preface

The homeostasis of the immune system is maintained by positive and negative factors including effector/regulatory cells as well as positive intracellular signals/negative regulators. Autoimmune diseases and allergic diseases are states in which this balance inclines to the excessive “positive.” In contrast, tumor microenvironment provides negative signals for immune systems, which suppress anti-tumor immunity. Those include regulatory T cells (Tregs) and myeloid-derived suppressor cell (MDSC) as well as immune regulatory molecules such as PD-L1, indoleamine 2,3-dioxygenase (IDO), TGF- β . Autoimmunity and anti-tumor immunity are two sides of the same coin. Indeed, knockout mice of various molecules so-called “immune checkpoints” often develop autoimmune diseases. Thus, the understanding of the mechanism of immunological balance is important for the treatment of both autoimmune diseases and cancer.

Typical positive and negative T cells of immune balance are effector T cells and regulatory T cells (Tregs), respectively. Major Treg cells developed in the thymus are called thymus-derived Treg (tTreg) cells. Treg cells are specified by an expression of the transcription factor Forkhead box P3 (Foxp3), which plays crucial roles in the differentiation, maintenance, and function of tTreg cells. Treg cells are believed to be involved in autoimmune diseases and allergy because Treg cells suppress excess immunity against a diverse range of antigens, including self-antigens, commensal bacteria-derived antigens, and environmental allergens. Tregs have been shown to be abundant in tumor tissues and suppress anti-tumor immunity.

In recent years, anti-tumor immunity has attracted attention not only by immunologists but also by cancer researchers. T-cell activation is initiated through antigen recognition by the T-cell receptor (TCR) and co-stimulatory signals such as CD28. On the other hand, the inhibitory signals for T-cell activation (i.e., immune checkpoints) are crucial for the maintenance of self-tolerance and prevention of autoimmunity as well as excess immune responses. The two immune checkpoint receptors, cytotoxic T-lymphocyte-associated antigen 4 (CTLA4, also known as CD152) and programmed cell death protein 1 (PD1, also known as CD279), have been most actively studied in the context of clinical cancer immunotherapy. It has

been shown that PD1 recruits the tyrosine phosphatase, which inhibits TCR signaling, while CTLA4 inhibits CD28-mediated co-stimulatory signals. Antibodies against CTLA-4 and PD-1 have been shown to significantly improve survival in patients with metastatic cutaneous melanoma and other cancers. The action of PD-1 and CTLA-4 is now called “immune checkpoints,” since these molecules are involved in T-cell exhaustion and anergy. Clinical efficacies of these antibodies proved that anti-tumor immunity can be enhanced by inhibiting immune checkpoints. However, PD-1 and CTLA4 are not the only molecules that negatively regulate T-cell activation. There are a number of cells and signals that suppress effector T-cell activation.

In addition to TCR and co-stimulatory signals, T-cell activation requires the third signal: signals from the cytokine receptors. For example, IL-2 is necessary for the proliferation of T cells, and IL-12 and IFN γ are important for Th1 differentiation and CTL activation. Various roles of IFN γ in anti-tumor immunity have been established. IL-15 has been shown to be necessary for memory T-cell survival. Thus, negative regulators of the cytokine signaling must be important immune checkpoint molecules that regulate anti-tumor immunity. The suppressors of cytokine signaling (SOCS) family proteins have been shown to negatively regulate cytokine signaling by binding to the receptors and/or JAK tyrosine kinases. Suppression of SOCS1 has been shown to cause autoimmunity and enhance anti-tumor immunity. Therefore, such negative regulators of cytokine signaling can be considered as the third immune checkpoint molecules.

Now we can extend the concept of immune checkpoints to “molecules and cells which negatively regulate T-cell activation.” These molecules and cells must be involved in immune homeostasis and could be new targets of autoimmune diseases and cancer immunotherapy. This book is focusing on molecular and cellular biology of “extracellular” and “intracellular” immune checkpoint regulators. Such factors are regulatory T cells and tolerogenic dendritic cells, as well as signal inhibitors such as SOCS, tyrosine phosphatases, ubiquitin ligases, and miRNAs. I hope this CTMI volume promotes the understanding and application of “extended” immune checkpoint regulators.

Tokyo, Japan

Akihiko Yoshimura

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