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INTRODUCTION

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Introduction to checkpoint inhibitors and cancer immunotherapy

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Immune responses are regulated by an exquisite system of checks and balances that enable effective protective immunity and tolerance. A number of immunological checkpoints control cells of the innate and adaptive immune system that determine their function. Stimulatory checkpoint pathways promote activation of naive T cells, as well as effector, memory and regulatory T cell responses. Inhibitory checkpoint pathways limit the threshold for T cell activation and duration of immune responses, and have diverse effects that regulate resolution of inflammation, tolerance and homeostasis. Tumors have hijacked inhibitory checkpoints to evade immune eradication. Blockade of the T cell checkpoint inhibitors CTLA-4 and PD-1 has shown remarkably durable clinical responses, but is effective in only a subset of patients.[1–5] Combination therapy approaches are further improving response rates.[6] These successes have stimulated great interest in determining the roles of innate and adaptive checkpoints in controlling the immunosuppressive tumor microenvironment, and developing strategies to target these checkpoints for cancer immunotherapy.

Reviews in this issue of Immunological Reviews discuss innate and adaptive immunological checkpoints and their immunoregulatory roles in the pathogenesis of cancer, autoimmune diseases, and graft rejection. In this introduction, I will provide an overview of the checkpoint pathways in this issue.

Insights into mechanisms regulating T cell activation led to the development of CTLA-4 and PD-1 blockade as strategies for cancer therapy. Our knowledge of T cell activation has progressed significantly from the two-signal concept for T cell activation, proposed by Lafferty and Cunningham to explain activation of naive T cells.[7–9] According to this model, T cell activation requires a first signal provided by provided by interaction of antigenic peptide/MHC complex with the T cell receptor (TCR), which confers specificity to the response, and a second antigen-independent costimulatory signal. The interaction between the CD28 costimulatory receptor and its ligands CD80 (B7-1) and CD86 (B7-2) fulfilled many requirements for the costimulatory signal envisioned by Lafferty and Cunningham (see [10] this issue). However, the discovery of CTLA-4 as a CD28 homolog that possessed potent inhibitory functions, dramatically changed our perception of the two signal model.[10–13] We now appreciate that there are a number of inhibitory (coinhibitory) as well as stimulatory (costimulatory) second signals that can modulate T cell receptor (TCR)—mediated T signals. Inhibitory checkpoints tune and shape activating signals to safeguard tolerance and immune homeostasis and protect against immune-mediated tissue damage. In addition, these inhibitory checkpoints are key mediators of T cell dysfunction (exhaustion) that develops during cancer and thereby prevents effective anti-tumor immunity.

The critical role of these inhibitory checkpoints in cancer is illustrated by the remarkable effects of blockade of the CTLA-4 and PD-1 checkpoints for cancer.[1,5,14] Seminal studies showing that anti-CTLA-4 blocking antibodies could promote anti-tumor immune responses in mouse tumor models[15] led to the clinical development of the anti-CTLA-4 antibody ipilimumab for cancer therapy and its FDA approval for melanoma. The most striking effect of CTLA-4 blockade is the ability to induce long-lasting tumor regression.[4] PD-1 pathway blockade has impressive clinical trial results with 30%-50% response rates in a broad range of tumors, and is FDA approved for melanoma, non-small cell lung cancer, kidney cancer, Hodgkin Disease, head and neck, and bladder cancer.[2,3,5,14,16,17] There is great interest in identifying approaches to extend this benefit to more patients. The success of anti-CTLA-4 and anti-PD-1 cancer immunotherapy has stimulated the search for other inhibitory checkpoints to target for cancer therapy. The innate and adaptive inhibitory checkpoint molecules reviewed in this issue (Figure 1) are therapeutic targets for cancer immunotherapy.

T cell costimulatory and coinhibitory pathways provide critical checkpoints that regulate adaptive immunity. T cell costimulatory pathways fall into two major families, the Ig superfamily which includes CD28, ICOS,[10] TMIGD2 (IGPR-1/CD28H)[18] (which are CD28 family

This article introduces a series of reviews covering Checkpoint Inhibitors and Cancer Immunotherapy appearing in Volume 276 of *Immunological Reviews*.

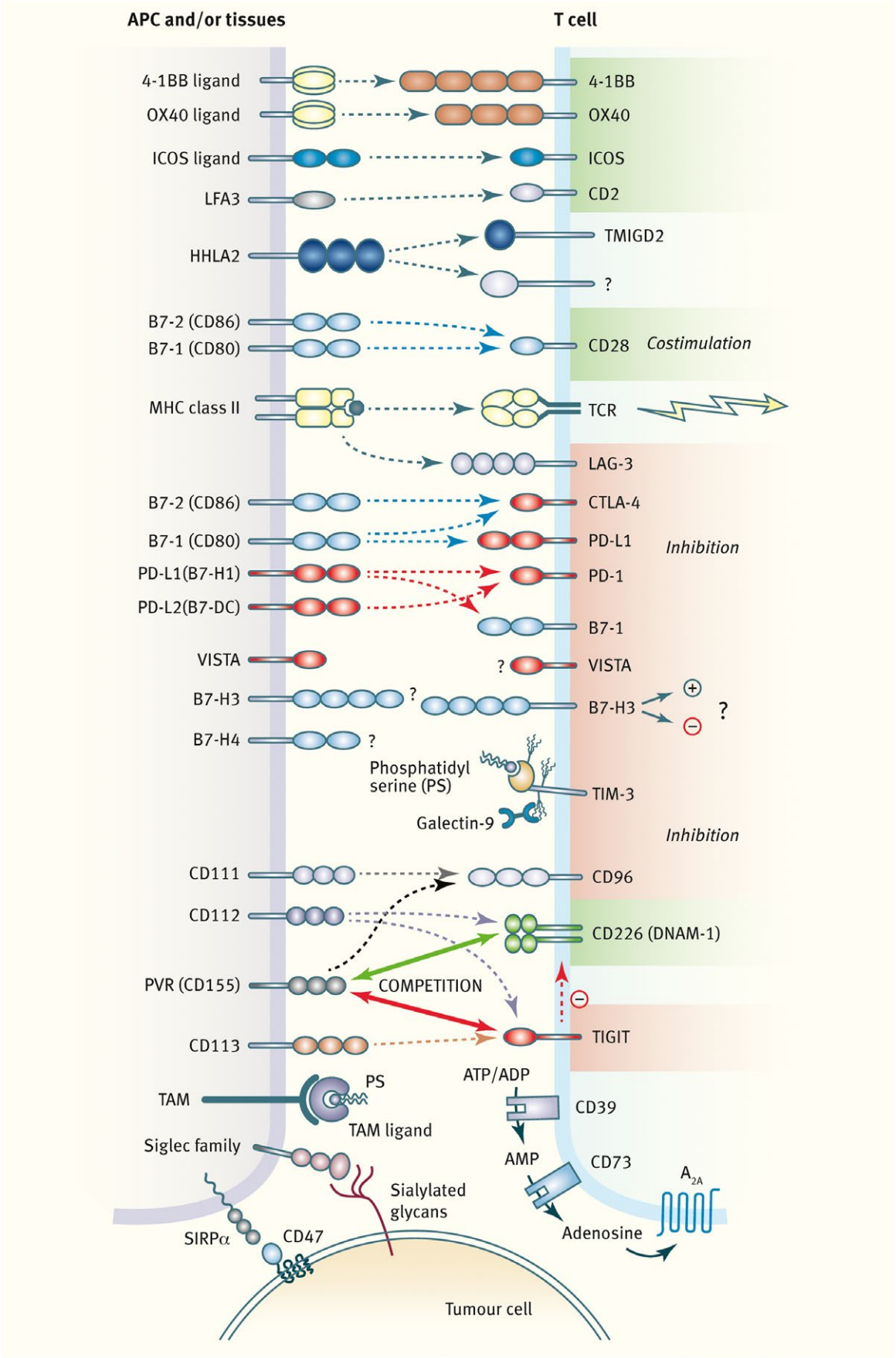
APC and/or tissues
T cell
4-1BB ligand
4-1BB
OX40 ligand
OX40
ICOS ligand
ICOS
LFA3
CD2
HHLA2
TMIGD2
?
B7-2 (CD86)
B7-1 (CD80)
CD28
Costimulation
MHC class II
TCR
LAG-3
B7-2 (CD86)
CTLA-4
B7-1 (CD80)
PD-L1
Inhibition
PD-L1(B7-H1)
PD-1
PD-L2(B7-DC)
B7-1
VISTA
?
VISTA
B7-H3
?
B7-H3
?
B7-H4
?
Phosphatidyl serine (PS)
TIM-3
Galectin-9
Inhibition
CD111
CD96
CD112
CD226 (DNAM-1)
PVR (CD155)
COMPETITION
CD113
TIGIT
ATP/ADP
TAM
PS
CD39
TAM ligand
Siglec family
AMP
CD73
A2A
Sialylated glycans
SIRPα
CD47
Adenosine
Tumour cell

FIGURE 1 Overview of innate and adaptive checkpoint pathways. Innate immune cells express checkpoint molecules that regulate their functions. Inhibitory checkpoint molecules (e.g. TAM receptors, Siglecs, CD47) expressed by innate immune cells inhibit their activity and limit adaptive immunity. Adaptive checkpoint molecules regulate T cell responses. Activation of naive T cells is mediated by TCR recognition of antigen presented on APCs and costimulatory signals provided by CD28 interactions with CD80 and CD86. Upon T cell activation, a second tier of costimulatory pathways is upregulated. There also are many inhibitory checkpoint receptors that are upregulated on T cells and inhibit T cell responses. Their ligands can be expressed by APCs, non-hematopoietic cells, and tumors. Binding partners for B7-H3, B7-H4, VISTA are not yet known. Several receptors have multiple binding partners as indicated in this Figure

members) and CD226,[19] and TNF:TNR receptor family, which includes Ox40 and 4-1BB.[10] There is an abundance of inhibitory checkpoints which can influence T cell responses. These include the B7: CD28 family members CTLA-4, PD-1/PD-L, B7-H3 (CD276),[18,20] B7-H4 (B7x/B7S1/VTCN1),[18,20,21] HHLA2 (B7H7/B7-H5)[18] and VISTA (PD-1H, DD1alpha, c10orf54, Gi24, Dies1, SISP1),[20,22] the Ig superfamily members LAG-3,[23] TIGIT and CD96,[19] the ectonucleotidases CD39 and CD73[24] and TIM-3 (T cell–immunoglobulin–mucin domain 3)[25] which has Ig and mucin domains. Reviews in this issue focus on the inhibitory adaptive checkpoints and discuss their immunoregulatory functions and their translation to therapy.

Similar to T cells, innate immune cells express checkpoint molecules that regulate their ability to initiate and shape adaptive immune responses.[26–28] APCs of the innate immune system mediate the activation and recruitment of T cells through antigen recognition, acquisition, processing and presentation to T cells, expression of costimulatory ligands, and production of a variety of effector molecules. Inhibitory checkpoint molecules expressed by innate immune cells inhibit their activity and limit adaptive immunity. Given that innate immune cells can stimulate or dampen anti-tumor immunity, there is growing interest in blocking inhibitory innate immune checkpoints to enhance anti-tumor immunity. Reviews on CD47,[27] the TAM receptor family of tyrosine kinases (Tyro, Axl and MerTK)[26] and Siglecs[28] discuss the functions of these innate inhibitory checkpoints and potential as targets for cancer immunotherapy.

These reviews demonstrate the significant recent advances in our understanding of innate and adaptive checkpoints. This progress provides a foundation with tremendous potential for discovering and developing effective immunotherapies for cancer and other immune-mediated diseases, as these checkpoints are key regulators of the immunosuppressive tumor microenvironment. However, many important questions remain to be resolved to address the challenges of translating these checkpoints to therapy. First, further work is needed to understand the extent to which inhibitory checkpoints provide redundant or unique functions, and whether there is a hierarchy in the orchestration of their signals. For example, coinhibitory receptors can be coexpressed on T cells, and coblockade of the inhibitory receptors PD-1 and CTLA-4,[13] or PD-1 and Tim-3,[25 23] or PD-1 and TIGIT,[19] or PD-1 and Vista[20,22] can lead to better tumor clearance than blockade of each alone. It is not yet clear whether synergy results from coblockade on the same cell or different cells. A better understanding of the molecular pathways triggered by the inhibitory checkpoint molecules is needed to determine shared and unique signaling nodes, as well as mechanisms of synergy between inhibitory checkpoint pathways. Second, the cell-type specific functions of checkpoint molecules are only beginning to be understood. There is an increasing appreciation of the opposing effects of checkpoint pathway modulators on effector and regulatory T cells.[10] This poses challenges for clinical translation of immune tolerance strategies, and the need to induce tolerance in all T cell subpopulations, both effector and regulatory.[10] Some checkpoint receptors such as Tim-3 are expressed on myeloid cells as well as T cells,[25] suggesting roles on innate and adaptive immunity. Finally, inhibitory checkpoint blockade carries the risk of autoimmune adverse events, given the roles of inhibitory checkpoint molecules in T cell tolerance.[10,13,18,19,21,23,24,26,28] A better understanding of how to uncouple anti-tumor activity from loss of self tolerance is necessary to increase therapeutic efficacy of checkpoint blockade. With the FDA approval of anti-CTLA-4 (Ipilimumab) and anti-PD-1 (Nivolumab and Pembrolizumab) for cancer immunotherapy, and a number of other checkpoints currently in clinical trials, our understanding on the therapeutic potential of targeting checkpoint pathways will continue to grow in the imminent future.

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CONFLICTS OF INTEREST

A. H. S. holds patents and receives patent royalties related to the PD-1 pathway.

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