Evolving Understanding of T-cell Cosignaling Pathways

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We read with great interest the previously published article "Costimulation Blockade in Kidney Transplantation: An Update" written by Malvezzi et al.[1] In the setting of solid-organ transplantation, it represents a great progress to explore the blockade of some costimulation pathways as an efficient immunosuppressive tool instead of using calcineurin inhibitors. In the section of targeting costimulation pathways, Malvezzi et al[1] summarized main T-cell surface signaling molecules, including costimulation and coinhibition. Cosignaling molecules are controllers of T-cell responses to antigens. By selectively turning on and/or off costimulatory and coinhibitory pathways, the T-cell receptor (TCR) signal could be transiently regulated in positive and negative directions. cluster of differentiation (CD), CD28/CD154(CD40L)/inducible costimulator had a positive regulatory effect on T-cell activation, whereas cytotoxic T-lymphocyte-associated antigen-4/programmed death ligand-1 was negative. Based on this article, we will provide some progress in costimulation pathways over the past few years, as shown in Figure 1.

First, as we all know, programmed death 1 (PD-1) and its ligands, mainly PD-L1 and PD-L2, deliver inhibitory signals that regulate the balance among T-cell activation, tolerance, and exhaustion. PD-1 is a CD28 family member. PD-L1 (B7-H1) and PD-L2 (B7-DC) are B7 family members. Several previous findings pointed out a significant bidirectional inhibitory interaction between B7-1 (CD80) and PD-L1, which added an additional dimension to immunoregulatory functions of the B7:CD28 family.[2-5] The competition assays in vitro showed that PD-1 and B7-1 competed for binding to PD-L1 and block each other's binding.[6,7] Extremely low levels of PD-1 are sufficient for potent inhibition in the earliest stages of T-cell activation.[8] However, this potent inhibition effect of PD-1 depends on the colocalization of TCR and CD28, which initiate the T-cell activation. Therefore, PD-1 plays an extremely important role in the negative regulation of T cells.[9,10]

Second, the expression of PD-1 and its ligands is widespread. PD-1 can be expressed on T cells, B cells, natural killer T cells, activated monocytes, and dendritic cells (DCs). PD-1 is not expressed on resting T cells. It is induced to express after activation.[3-5,11] The expression of PD-L1 and PD-L2 differ in patterns and vary across species. Research data on PD-L2 exhibited a smaller interspecies gap, whereas PD-L1 had a larger expression gap between mice and humans. PD-L1 is constitutively expressed on mouse T and B cells, DCs, macrophages, mesenchymal stem cells, and bone marrow–derived mast cells. However, it is minimally expressed on resting naive human CD4 and CD8 T cells.[12] It is upregulated on several cell types after activation.[2,7] Compared with PD-L1, the expression of PD-L2 is increasingly restricted. It is induced to express on DCs, macrophages, and bone marrow–derived mast cells.[2,5,9,11] Although PD-1 and PD-L1 are simultaneously expressed on T cells and PD-L1 has a high expression on activated T cells in mouse, and studies revealed that PD-L1 could attenuate TCR-mediated T-cell stimulation, PD-1 is the principal inhibitory molecule after T-cell activation, just like CTLA-4. Binding of PD-1 to its ligand PD-L1 or PD-L2 delivers a negative signal by the recruitment of Src homology 2-domain–containing tyrosine phosphatase 2 to the phosphorylated tyrosine residue in the cytoplasmic region.[4] Moreover, the result that PD-L1 fails to inhibit PD-1 deficient T cells indicates that PD-L1 conveys suppression signal via its interaction with PD-1.[3] Consequently, PD-1 plays a major role in activated T-cell inhibition.

Third, the interaction on T-cell responses is comprehensive complex. It is also related to binding affinity, the expression position, spatial conformation, etc. As far as PD-1 and its ligands are concerned, although PD-1 seems to be an exclusive coinhibitor, PD-L1 and PD-L2 have dual functions of coinhibitors and costimulators. A series of in vivo studies indicate that endogenous PD-L1 could act as coinhibitor[2,3,13] or costimulatory,[6,14-17] whereas PD-L2 mainly acts as costimulatory.[18,19] Some observations strongly suggested that PD-L1 and PD-L2 costimulated T-cell growth through a non–PD-1 receptor.[20,21] From an affinity point of view, molecular pairs were ranked according to their binding affinity as B7-1: CTLA-4 > PD-1: PD-L1/PD-L2 > PD-L1: B7-1 > B7-1: CD28,[2,7] which implies that interactions between cosignaling pathway participants on T cells are sequential. Between T cells and antigen-presenting

Received 21 March 2022. Revision received 6 April 2022.

Accepted 7 April 2022.

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Y.-l.Y. completed writing of the article. Y.-y.L. participated in the writing and revision of the article. F.-h.X. designed the article and guided writing.

This work is supported by the National Natural Science Foundations of China [82171814]. The funders have no roles in study design, data collection and analysis, decision to publish, or preparation of the article.

The authors declare no conflicts of interest.

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ISSN: 0041-1337/20/1068-e388

DOI: 10.1097/TP.0000000000004181

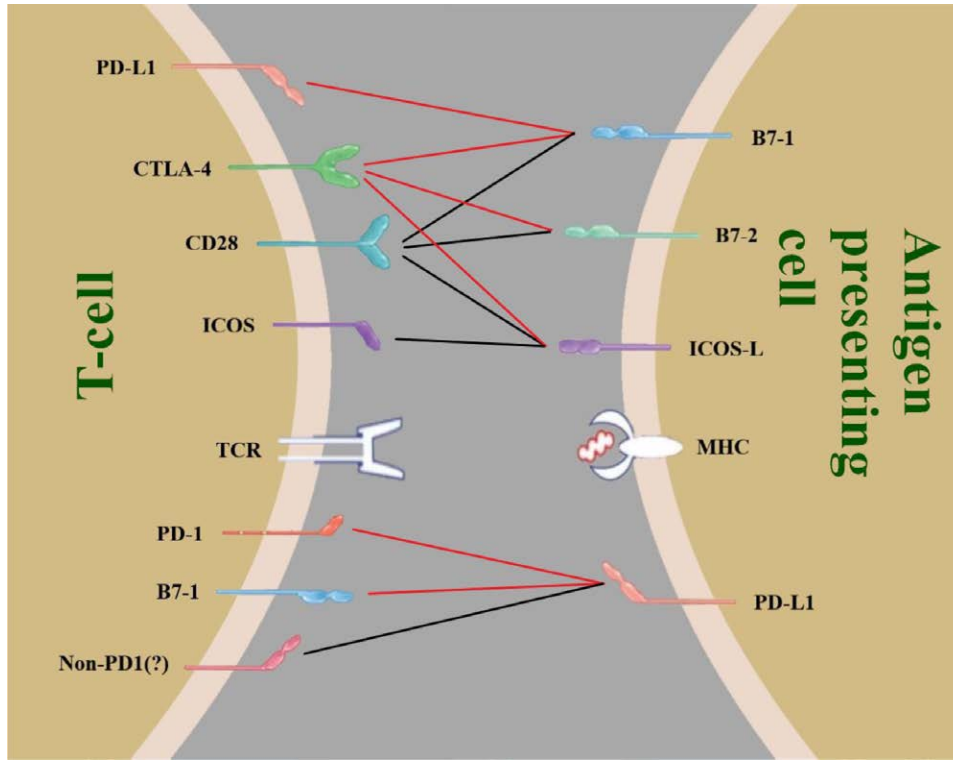

FIGURE 1. Major T-cell cosignaling pathways. Black lines indicate stimulating signals on T cells, whereas red lines indicate inhibitory signals. CD, cluster of differentiation; CTLA-4, cytotoxic t-lymphocyte-associated antigen-4; ICOS, inducible costimulator; ICOS-L, ICOS ligand; MHC, major histocompatibility complex; PD-1, programmed death 1; PD-L1, programmed death ligand-1; TCR, T-cell receptor.

cells (APCs), it is possible that PD-L1 mainly on APC cell preferentially binds PD-1 on T cell, whereas B7-1 (mainly on APC cell) preferentially binds CTLA-4 on T cell. When PD-L1 and B7-1 are simultaneously expressed on the same cell or expressed on 2 different cells, their interactions are different in the aspect of spatial conformation. The interaction between PD-L1 and B7-1 occurs in cis when they are located in the same cell.[7,22,23] However, binding between PD-L1 and B7-1 on different cells still remains controversial.[24] Some reports suggested that PD-L1 and B7-1 on different cells bound in trans,[2,23,25] whereas others indicated that the interaction occurred not in trans.[7,23]

Apart from cosignaling pathway participants (CD28, CD80/86, CTLA-4, PD-1, PD-1L, and inducible costimulator ligand) mentioned above, several novel negative immune regulation molecules have been introduced over the past few years, such as lymphocyte activation gene-3 (LAG-3 or CD223), T-cell immunoglobulin and mucin-domain–containing-3, T-cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domain, V-type immunoglobulin domain-containing suppressor of T-cell activation, and so on.[26] These negative regulatory molecules provide new targets for inhibiting T-cell activation and are worth our concern.

In summary, there is a dynamic and complex interaction network among PD-1, PD-L1/PD-L2/, B7-1 and CTLA-4. PD-L1 has dual functions as coinhibitor and costimulator.

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