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Turning the Tide of Lymphocyte Costimulation

Yuwen Zhu and Lieping Chen¹

The interaction between the T cell and the APC is the pivotal step that controls a series of events, including T cell activation, cell division, and effector differentiation. During the 1980s, with cloning and crystallization of MHC and the TCR locus, the specificity of T cell activation was understood to be dictated through the TCR, which recognizes Ag in the form of peptide fragments presented by MHC molecules on APC (1, 2). However, at the same time, it was also recognized that it was not only the Ag but also other stimulus signals provided by APCs that determined the consequence of T cell recognition. The early work of Lafferty and coworkers on the generation of CTLs found that only cells of hematopoietic origin within transplanted tissues were capable of initiating an immune response (3). They interpreted this observation by extending the two-signal model originally proposed by Bretscher and Cohn for B cell activation to T cell activation (4). According to this model, the APC provides, in addition to the Ag, a secondary signal to the T cell that regulates the outcome of T cell activation. Without the secondary signal, T cell activation by the Ag alone could lead to anergy. This model gained extensive support in numerous experimental systems, especially in in vitro cell culture systems (5, 6). However, the exact molecule responsible for this postulated “cosignal” was still unidentified.

Several adhesion molecules expressed on APCs or T cells, including CD28, have been shown to affect T cell activation (7). CD28 was originally identified through Abs against human T lymphocytes as an Ag specifically expressed on CD4⁺ T cells and the majority of CD8⁺ cells (8, 9). Early studies suggested that CD28 bore most of the features characterizing a costimulatory signal (10, 11). For example, CD28 engagement by itself did not activate T cells but could do so in conjunction with TCR signaling to promote T cell division and cytokine production. The synergistic effect was evident when the Ag dose was suboptimal. In addition, the CD28 receptor on the T cell initiated a signaling pathway that could be distinguished from the signal through the TCR. Interestingly, signaling through CD28, but not through other known T cell adhesion molecules, provided a helper signal to purified T cells upon activation that bypassed the requirement of accessory cells (12). Furthermore, Fabs of the CD28 mAb served as a blocking agent to inhibit the T cell response, suggesting a natural costimulatory counterreceptor for CD28 on APCs (13). Many other molecules also appeared to have “costimulatory” function for T cells; however, subsequent experiments demonstrated that they were largely adhesion molecules (7). This mystery was unlocked

upon the identification of B7/BB-1 (also known as B7-1 or CD80) as the counterreceptor for CD28 by P. Linsley and his colleagues at the Bristol-Myers Squibb Pharmaceutical Research Institute (formerly Oncogen) in Seattle, WA. Only since then has CD28 been recognized as the key costimulatory signal receptor for T cells (14). This study, which has been selected as this month's *Pillars of Immunology* selection, opened a new era in the field of lymphocyte costimulation.

To identify the potential ligand for CD28, Linsley and his colleagues developed a cell-based adhesion screening assay specifically mediated through the CD28 Ag (14). Chinese hamster ovary (CHO)² cells expressing CD28 Ag were plated as base. The tumor cell lines tested were radiolabeled and added to the CHO cell monolayer. The monolayer was thoroughly washed prior to the measurement of cell adhesion by radioactivity. This simple assay was capable of identifying tumor cells that adhered to the monolayer through interactions with CD28. The authors found that several lymphoblastoid and leukemic B cell lines, as well as activated primary B cells, interacted specifically with the CHO monolayer expressing CD28, suggesting that the natural ligand for CD28 was a B cell surface Ag. Based on this, mAbs known to recognize B cell surface molecules were added to test their ability to block CD28-mediated adhesion. Among them, the Ab for B7/BB-1 specifically interfered with the CD28-mediated adhesion, suggesting that B7/BB-1 interacted with CD28 to mediate the tumor cell adhesion. Furthermore, COS cells transfected with B7/BB-1 adhered specifically to CD28, confirming that B7/BB-1, a member of the Ig superfamily that was independently molecularly cloned (15), was the natural ligand for CD28. The follow-up studies by Linsley and colleagues indicated that, similar to CD28 Abs, B7/BB-1 was also capable of costimulating T cell proliferation and promoting cytokine production through CD28 (16). Therefore, B7/BB-1 represents the first identified functional counterpart for CD28.

The finding by Linsley has had a great impact on today's understanding of the regulation of the T cell response. It endowed the two-signal model with its first solid molecular evidence since it was proposed. Since then, this model has been refined and is well accepted today. Directly inspired by Linsley's study, the other molecules in this pathway, CD86 (B7-2 or B70) and its homologous partner, CTLA-4, were quickly identified and their critical roles in the immune response were revealed (17, 18). As a result, T cell costimulation became one of the most exciting fields in immunology during the following decade. To date, the CD28/B7 molecules, together with their homologous

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² Abbreviation used in this paper: CHO, Chinese hamster ovary.

family members, are still the major known cosignals that control T cell responses (19, 20). Furthermore, a better understanding of the CD28/B7 costimulatory pathways has offered fresh insights into methods of controlling the immune response and novel immunotherapies for cancer, transplantation, and autoimmune disease.

Disclosures

The authors have no financial conflict of interest.

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