

B7-1 and B7-2 Selectively Recruit CTLA-4 and CD28 to the Immunological Synapse

Tsvetelina Pentcheva-Hoang, Jackson G. Egen, Kathleen Wojnoonski and James P. Allison

T cell activation requires engagement of unique T cell receptors (TCR), as well as signals from the costimulatory molecule CD28. Upon binding to its ligands, B7-1 (CD80) and B7-2 (CD86), CD28 enhances T cell proliferation and survival. A close homologue, cytotoxic T lymphocyte antigen 4 (CTLA-4), also binds B7-1 and B7-2, but it inhibits T cell activation. B7-1 and/or B7-2 expression on the antigen presenting cell (APC) is insufficient to recruit CD28 or CTLA-4 to the T cell/APC interface (immunological synapse) – TCR signaling is required. A question that arises is whether ligand binding is then necessary for concentrating CD28 and CTLA-4 at the synapse, especially in light of the recent discovery of CD28 and CTLA-4 isoforms that lack extracellular domains and thus function in a ligand-independent manner.

Our studies demonstrate that ligand binding is important for the localization of both CD28 and CTLA-4 to the immunological synapse. While CD28 is recruited to the synapse in the absence of B7-1 and B7-2 binding, it is not effectively stabilized there, as its localization can be disrupted by CTLA-4. In the case of CTLA-4, ligand binding is critical for its concentration at the synapse.

The reported affinity differences between CD28 and CTLA-4 binding to B7-1 and B7-2 may serve to selectively regulate CD28 and CTLA-4 function by differentially recruiting and/or stabilizing these molecules at the immunological synapse. Using APC expressing only single ligands, we found that B7-2 is the primary ligand responsible for CD28 concentration at the synapse, while B7-1 is the principal ligand mediating CTLA-4 localization to the synapse. These results are consistent with physicochemical studies that found large avidity differences among the various receptor/ligand combinations and predicted that the ratio of engaged CD28 to engaged CTLA-4 in the synapse will be higher when B7-2 is expressed on the APC relative to when B7-1 is expressed. Our experiments verify this hypothesis and show for the first time that the reported affinity differences in ligand binding translate into selective recruitment of CD28 or CTLA-4 to the immunological synapse.