





## CD28 Signal

The sole interaction of the T cell receptor complex with peptide-MHC molecules does not induce T cell activation but long-term hypo-responsiveness, anergy or, alternatively, cell death (6 for review, 7). Much of this data has been obtained from *in vitro* studies. In addition, animal models and particularly the analysis of the CD28<sup>-/-</sup> mouse provide another clue regarding the importance of co-stimulatory molecules, since these animals fail to form germinal centers in response to immunization and can initiate, but not sustain antigen dependent proliferative responses (8). These data suggest that one of the key functions of co-stimulatory molecules such as CD28 is to sustain T cell response through a mechanism that is not well understood. However, it is known that CD28 interacts with at least two counter-receptors CD80/B7.1 and CD86/B7.2 present on APC. CD28-ligand interaction together with TCR ligation will induce T cell proliferation, upregulation of cytokine production as well as cytokine receptor expression, and up-regulation of factors involved in T cell survival such as *bcl-xL* (11 for review).

## Secondary Stages: Up-regulation Loops

After TCR ligation, certain molecules will be upregulated (e.g. adhesion molecules) that will participate in a second stage of CD4 T cell activation : the amplification of the T cell response. In addition, TCR ligation will increase T cell adhesion to APC by increasing the avidity of the adhesion molecules for their ligands, a mechanism which is particularly important for molecules of the integrin family (LFA-I) (9).

The up-regulation of CD40-ligand (CD154) upon TCR ligation is a critical event in T cell activation. CD154 will then interact with CD40 present on APC such as dendritic cells and induce all the critical pathways necessary for co-stimulation (10 for review). Hence, CD40 ligation will result on one hand in the induction of cytokine production such as the IL-12 in APC, which will favor differentiation as well as pro-inflammatory cytokine production. On the other hand, CD40 ligation will up-regulate the expression of co-stimulatory molecules on the APC such as B7.1/CD80 and B7.2/CD86, CD54, CD58, CD44 and 4-1BB-ligand. As a consequence of these first events induced in the APC, the T cell activation sequence will proceed: APC co-stimulatory molecules will interact with ligands present on T cells. Optimally, the following will be a few of the receptor-ligand pairs to form: CD28-CD80/CD86, CD2-CD58, and CD137/CD137L.

Thus, various T cell surface molecules have been identified and described here which regulate T cell activation. Many other molecules provide co-stimulatory signals such as 4-1BB/CDw137, CD47, CD27 or SLAMF7/CDw150 (12-16). However, it is still to be determined whether they display redundant or specialized functions.

## Cytokine Receptors

Cytokine receptors also play a major role in the regulation of T cell activation. The common IL-2 receptor  $\gamma$  chain is involved in the prevention of T cell anergy (17). Various cytokines sharing this common  $\gamma$  chain are all involved in T cell activation, namely IL-2, IL-4, IL-7 and IL-15. Regulatory regions present in the 5' region of multiple genes including the IL-2 receptor  $\gamma$  chain are thus upregulated by enhanced transcription, suggesting the use of the Jak-STAT pathway (see cytokine insight). This mechanism is of the utmost importance since it will further amplify the immune response both in an autocrine manner for CD4 cells, and in a predominantly paracrine manner for CD8 cells.

## Negative Regulation

Negative regulation of T cell activation has also been identified involving molecules that will interfere with TCR signals. Three subgroups of negative receptors are currently being analyzed extensively:

- Molecules binding CD80 and CD86 such as CTLA-4/CD152
- Molecules interacting with class I MHC such as the Killer Inhibitory Receptors/Natural Killer Receptors
- CD95 ligand/Fas ligand.

CTLA-4/CD152 is closely related to CD28, as it binds to CD80 and CD86, but is only expressed on activated T and B cells (18). Its expression is induced by TCR ligation along with CD28 co-stimulation and by IL-2. CD152 expression is puzzling since most of the molecule is localized inside the cell where it interacts with the AP-2 complex (19, 20). Its role was emphasized by CTLA-4<sup>-/-</sup> mouse studies which demonstrated that T cells (21, 22) displayed extensive spontaneous proliferation. This leads to uncontrolled T cell expansion and the massive involvement of lymphoid organs. It also regulates T cell activation, mainly by providing negative signaling that inhibits IL-2 production, CD69 and CD25 expression (23).



Other negative regulators of T cell activation include the tyrosine phosphatase-containing domains of CD45, and, the Killer Inhibitory Receptors (KIRs). KIRs were first discovered in NK cells but are also present on T cells (24, 25) (see Natural Killers insight). KIRs are potent negative regulators of TCR signaling, down-regulating T cell activation upon their ligation by MHC class I molecules. They inhibit cytotoxicity and cytokine production, and thereby regulate various T cell functions. Interestingly, activating members of this family have also been described.

CD95L/Fas ligand expression is upregulated by TCR ligation (26). This molecule is expressed on the cell surface and is also cleaved and released into the supernatant. Both forms interact with CD95/Fas and induce T cell death. This mechanism eliminates Fas-expressing activated T cells as well as naive T cells. The result is regulation of the immune response by elimination of subsets of T cells at specific stages of activation. This will occur in cells which are not protected by regulators of Fas-mediated apoptosis (for example, by the FLIP molecule) (27-29).

## Conclusion

Altogether various families of T cell surface receptors regulate T cell activation. These surface receptors permit the fine tuning of the many steps of the activation of naive T cells. These molecules also participate in the final differentiation of auxiliary and cytotoxic T cells into effector cells such as Th1, Th2 and Th3 which produce IFN and Lymphotoxin (Th1), IL-4 (Th2) and TGF (Th3). These subsets (in mice and perhaps in humans) are known to be critically involved in activation and in differentiation of memory T cells, finally leading to the development of an efficient long lasting immune response.

Daniel OLIVE, M.D., Ph.D.

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