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## **Dendritic cells cooperation for CD4+ T cell activation**

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Immature thymocytes that are positively selected based upon their response to self-peptide-MHC complexes develop into mature T cells that are not overtly reactive to those same complexes. Developmental tuning is the active process through which TCR-associated signaling pathways of single-positive thymocytes are attenuated to respond appropriately to the peptide-MHC molecules that will be encountered in the periphery (1, 2). We previously reported that tuning of CD4+ T cells is an active process requiring expression of MHC class II molecules in the thymic medulla (3). We now explore the cellular and molecular mechanisms that mediate tuning. Changes in T cell responsiveness to weak ligands are fixed by the late stages of thymic medullary residency. Analysis of bone marrow chimeras and transgenic mice with limited expression of MHCII showed that both thymic medullary epithelium and thymic DCs can mediate tuning. MHCII interactions with the polymorphic TCR but not with the CD4 co-receptor decrease T cell responsiveness. TCR-MHCII interactions in the medulla alter the function of key TCR signaling molecules. Developmental tuning is associated with altered localization of Lck, increased expression of SHP-1, and decreased activation of ERK by weak peptide ligands. Thus, post selection interactions between maturing SP thymocytes and MHC class II-positive thymic stroma reorganize the signaling machinery to prevent overt self-reactivity and autoimmunity in mature peripheral T cells (4).

### **References**

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