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# $CD4^+CD25^+$ Regulatory T Cell Selection

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We have been examining the processes that give rise to CD4+ CD25+ regulatory T cells (Treg) during immune repertoire formation *in vivo* using transgenic mice that co-express the influenza virus hemagglutinin (HA) as a neo-self antigen and T cell receptors (TCRs) with varying affinities for the major I-Ed-restricted determinant from HA (S1). We have previously shown that thymocytes expressing a TCR with a high intrinsic affinity for the S1 peptide (termed the TS1 TCR) undergo selection to become CD4+ CD25+ Treg in a lineage of mice (HA28) that express the HA under the control of the SV40 early region promoter/enhancer[1]. S1-specific CD4+ T cells are as abundant in TS1xHA28 mice as in TS1 mice that lack the HA transgene; however, roughly half of the S1-specific CD4+ T cells in TS1xHA28 mice are CD25+ CD45Rbint, and can suppress the S1-specific proliferative responses of S1-specific CD25- CD45RBhigh T cells with which they co-exist[2]. By mating a TCR transgenic mouse (termed TS1(SW)) expressing a TCR with a low intrinsic affinity for the S1 peptide with HA28 mice and with additional lineages of HA Tg mice that and with additional , we obtained evidence that a low affinity for a self-peptide precludes CD4+ CD25+ Treg formation[1]. Together, these studies indicated that CD4+ CD25+ Treg formation can occur via a thymic selection event that is distinct from positive selection and deletion, and is dependent on a high affinity interaction between thymocytes and the S1 self-peptide.

To further understand processes leading to CD4+ CD25+ Treg formation, we have been examining S1-specific CD4+ T cell development in additional lineages of HA Tg mice that exhibit distinct patterns of expression of the neo-self HA. PEV-HA express the HA under the control of the β-globin locus control region, and TS1xPEV-HA mice contain similar numbers and proportions of CD4+ CD25+ Treg as are present in TS1xHA28 mice. Significantly, this indicates that the generation of CD4+ CD25+ Treg that occurs in the absence of significant deletion of S1-specific thymocytes in TS1xHA28 mice is not due to some idiosyncratic expression of HA that is particular to the HA28 lineage. We have also examined previously described lineages of HA Tg mice that express HA under control of the SV40 promoter/enhancer (termed HA12 and HA104 mice)[3]. Unlike TS1xHA28 mice, S1-specific thymocytes are substantially deleted in TS1xHA12 and TS1xHA104 mice, reflecting differences in HA expression induced by transgene integration events. Despite thymic deletion, peripheral CD4+ T cells are present in TS1xHA12 and TS1xHA104 mice that evade deletion through use of endogenous TCR β-chains, and significant fractions of these cells are also CD4+ CD25+ Treg. These studies provide evidence that CD4+ CD25+ Treg formation can occur in the context of significant deletion of autoreactive thymocytes. Ongoing studies in this system should increase our understanding of processes leading to CD4+ CD25+ Treg formation.

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3. Riley, M.et. al 2000. Graded deletion and virus-induced activation of autoreactive CD4+ T cells. J. Immunol, 165: 4870-4876.