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A set point in the selection of the αβTCR T cell repertoire imposed by pre-TCR signaling strength

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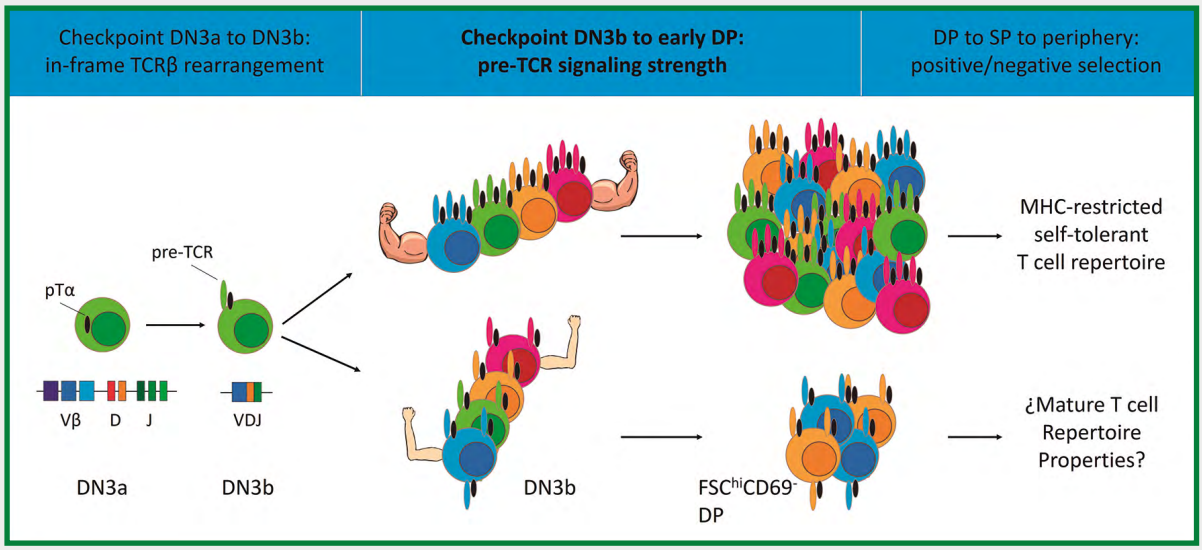
The ability of the T cell receptor (TCR) to generate signals of different intensity allows for the generation of a diverse, protecting, and self-tolerant T cell repertoire. Signaling via the TCR is induced upon its interaction with cognate peptide–major histocompatibility complex (pMHC) ligands. The TCR has low affinity for pMHC, but is able to cause activation and response upon specific recognition of a small number of these pMHC ligands on professional antigen-presenting cells (APCs) or target cells. The molecular mechanisms underlying this high sensitivity and graded signaling capacity are of interest because of the crucial role of TCR-mediated signaling in protective immunity and homeostasis. Previously, we found that TCRs organize in nanoclusters at the cell surface of mature T cells already before antigenic stimulation and that this organization provides T cells with enhanced sensitivity for its pMHC ligands. We generated mice expressing TCR-associated CD3ζ chains with a single amino acid mutation in their trans-membrane



domain that impairs the formation of TCR nanoclusters and affects the TCR sensitivity of T cells. Analysis of the successive T cell developmental stages in such mice shows that the mutation impairs the maturation of T cell progenitors with in-frame rearranged TCRβ genes already at the earliest T cell developmental checkpoint, which is dependent on signaling through the pre-TCR. The mutation reduces the signaling capacity of the pre-TCR, indicating an important role for pre-TCR nanoclustering in its quantitative signaling capacity. Sequencing of rearranged TCRβ genes in the precursor populations directly preceding and following pre-TCR-driven differentiation provided evidence that pre-TCR signaling intensity shapes the diversity of the TCRβ repertoire available for positive and negative selection, and hence of the final αβTCR repertoire. We uncovered a pre-TCR signaling–dependent and repertoire–shaping role for β-selection beyond selection of in-frame rearranged TCRβ chains.

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