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## Distinct phases in the positive selection of CD8<sup>+</sup> T cells distinguished by intrathymic migration and T-cell receptor signaling patterns.

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**Authors:** Jenny O Ross, Heather J Melichar, Byron B Au-Yeung, Paul Herzmark, Arthur Weiss, Ellen A Robey

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### Public Summary:

Positive selection of CD8 T cells in the thymus is thought to be a multistep process lasting 3-4 days, during which immature thymocytes that are only weakly reactive with self peptides receive signals from the thymus to survive and become mature T cells. The discrete steps involved in this process are poorly understood. Here, we examine phenotypic changes, calcium signaling, and intrathymic migration in a synchronized cohort of thymocytes undergoing positive selection in situ. Our results identify distinct phases in the positive selection of thymocytes that are distinguished by their T cell receptor-signaling pattern and intrathymic location and provide a framework for understanding the multistep process of positive selection in the thymus.

### Scientific Abstract:

Positive selection of CD8 T cells in the thymus is thought to be a multistep process lasting 3-4 d; however, the discrete steps involved are poorly understood. Here, we examine phenotypic changes, calcium signaling, and intrathymic migration in a synchronized cohort of MHC class I-specific thymocytes undergoing positive selection in situ. Transient elevations in intracellular calcium concentration ( $[Ca^{2+}]_i$ ) and migratory pauses occurred throughout the first 24 h of positive selection, becoming progressively briefer and accompanied by a gradual shift in basal  $[Ca^{2+}]_i$  over time. Changes in chemokine-receptor expression and relocalization from the cortex to medulla occurred between 12 and 24 h after the initial encounter with positive-selecting ligands, a time frame at which the majority of thymocytes retain CD4 and CD8 expression and still require T-cell receptor (TCR) signaling to efficiently complete positive selection. Our results identify distinct phases in the positive selection of MHC class I-specific thymocytes that are distinguished by their TCR-signaling pattern and intrathymic location and provide a framework for understanding the multistep process of positive selection in the thymus.

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