

GENETIC PROFILE OF POSITIVE SELECTION AND LINEAGE COMMITMENT  
IN DEVELOPING T LYMPHOCYTES

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Identifying genetic events that underlie T lymphocyte development at the CD4<sup>+</sup>CD8<sup>+</sup> (double positive, DP) thymocyte stage, and more specifically, discriminating between positive selection and lineage commitment processes will help answer outstanding questions concerning how these mechanisms work together to produce self-tolerant effector T cells. Genetic profiles of DP thymocytes from TCR transgenic mouse models have been generated through differential gene microarray analysis. By using OT-I/TAP<sup>o</sup> mice (MHC class I-restricted mice with a defect in MHC class I antigen presentation and, thus, a defect in thymocyte positive selection), DP thymocytes were isolated at the stage before they undergo positive selection. By comparing the genetic profile of these thymocytes with the profiles of CD8-destined DPs from MHC class I-restricted OT-I mice which are not TAP-deficient and do undergo selection, a list of 60 genes that may be important in positive selection and/or lineage commitment was compiled. Next, gene expression data was generated using CD4-destined DPs isolated from MHC class II-restricted OT-II mice and OT-I/dLGF mice whose cells mature into the CD4 lineage instead of the CD8 lineage due to a constitutively active Lck. Comparing gene expression data from CD4-destined DPs with data from CD8-destined DPs and pre-selection DP thymocytes revealed distinctions between genes involved in positive selection and those involved in lineage commitment to the CD4<sup>+</sup> or CD8<sup>+</sup> T cell lineage. Candidate genes identified by gene microarray analysis are being classified into functional categories within positive selection (TCR selection and tuning and thymocyte survival and migration) and CD4<sup>+</sup> or CD8<sup>+</sup> lineage commitment (co-receptor expression, chromosomal remodeling of cytokine genes, and effector function preparation).