

## 'Constitutive signaling in the basal state controls gene expression profiles in T lymphocytes '

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Engagement of the T cell receptor (TCR) by antigen-presenting cells leads to robust activation of many signaling molecules, among which the small GTPase Ras. Active GTP-bound Ras functions as a branch-point and initiates various MAP Kinase signaling cascades leading to downstream events like upregulation of the activation marker CD69. Constitutive levels of Ras-GTP and other activated signaling molecules can be detected in resting T lymphocytes but the biological implications are largely unknown.

We have recently published that a TCR-independent constitutive signal controls gene expression profiles in the Jurkat T cell line and mouse thymocytes. We demonstrated in resting cells that expression of a cluster of genes, including *RAG-1* and *RAG-2*, is repressed by constitutive signals requiring the adapter molecules LAT and SLP-76. This TCR-like pathway results in constitutive low-level activity of Erk and Abl kinases. Inhibition of Abl by the drug STI-571 or events upstream of Erk increases *RAG-1* expression.

To study Ras activity in the basal state, we have isolated a panel of somatic mutant Jurkat clones by screening for lines that failed to upregulate CD69 in response to the phorbol ester PMA. Utilizing one of these clones, we established a pathway that involves a Ras GTPase, RasGRP1, and PKC kinases. In this RasGRP1 deficient clone, with decreased basal Ras-MAP kinase signaling, gene expression patterns are also altered in the basal state compared to wildtype Jurkat cells.

Our data suggest that physiologic gene expression programs depend upon tonic activity of signaling proteins independent of receptor ligation. Through *in vitro* assays we are identifying key molecules for this instructive signal and focus on the type of transcriptional control. In addition, we are in the process of generating *in vivo* mouse models to inducibly turn-off tonic signaling.