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POSTER ABSTRACT

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Abstract

Lck Regulates Cell Cycle Progression and Survival in CD8⁺ T Lymphocytes, by ^{1,2}Steven D. Levin, ¹Bryan Bell, ¹Judy Y. Chen, ¹K. Lee Hendrix, ¹Michael Lee, and ¹Patty A. Trobridge, ¹Department of Immunology, University of Washington, Seattle, Washington 98195 and ²ZymoGenetics, Inc. 1209 Eastlake Avenue E., Seattle, Washington 98102.

T cells from mice in which the activity of the Src-family kinase Lck has been perturbed exhibit diminished proliferation after stimulation through the TCR and CD28 as judged by incorporation of tritiated thymidine (³H-dT). At least part of this defect can be explained by the fact that these Lck-mutant T cells produce less IL-2 than control cells. However, closer analysis of the basis for this has revealed some striking differences in the regulation of proliferation and cell survival in CD4⁺ and CD8⁺ T cells. Specifically, we have noted that proliferation of CD4⁺ cells in vitro can be restored to normal levels by addition of exogenous IL-2, whereas the proliferation of CD8⁺ cells can not be normalized in this way. Careful examination of CD8⁺ T cells stimulated in vitro reveals that the proliferation defect in these cells is due to a combination of diminished cell survival after stimulation as well as slower progression through the cell cycle. The reduced survival correlates with poor induction of the anti-apoptotic protein Bcl-X_L in the Lck mutant T cells. The retarded cell cycle progression is most obvious during the first cell division following stimulation. Moreover, the delay in DNA synthesis correlates closely with diminished and delayed induction of Cyclin D3, while other aspects of cell cycle regulation appear normal including the induction of cyclin D2 and the degradation of p27^{Kip1}. Our evidence suggests that the first round of proliferation of CD8⁺ cells induced by antigen receptor engagement is facilitated by rapid TCR/CD28-mediated induction of Cyclin D3, whereas subsequent rounds of DNA synthesis are dependent upon IL-2-mediated Cyclin D2 induction and p27^{Kip1} degradation. A similar analysis of CD4⁺ cells reveals that they only minimally upregulate expression of Cyclin D3, but do upregulate Cyclin D2 in response to IL-2. This probably explains the restoration of normal proliferation of CD4⁺ T cells in Lck mutant mice by addition of exogenous IL-2. Moreover, these observations indicate fundamental differences in the wiring of signaling pathways between CD4⁺ and CD8⁺ T cells, and their regulation of cell cycle progression, and may explain why CD8⁺ cells respond to stimulation much more rapidly than CD4⁺ cells.