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News

c-Abl, an additional tyrosine kinase required for T cell development and function

T cell receptor (TCR) signaling involves a cascade of tyrosine kinase activation. Members of three well-characterized kinase families are required for this pathway, including a Src family kinase (Lck and/or Fyn), a Syk family kinase (Zap70), and a Tec family kinase (Itk). Upon antigen recognition, these kinases are recruited into TCR signaling complexes in a sequential manner, leading to the tyrosine phosphorylation of downstream signaling molecules, and thereby promoting T cell activation. Accordingly, deficiencies in each of these kinases cause disrupted thymocyte development and defective activation of mature T cells.^{1,2} In this issue of *Cell Cycle*, Silberman et al. show that c-Abl, a tyrosine kinase well known for its association with cancer, becomes the fourth tyrosine kinase to contribute to T cell development and function.

Previous reports have shown that c-Abl-deficient mice have impaired lymphocyte development, resulting in splenic and thymic atrophy, lymphopenia, and increased susceptibility to infection.^{3,4} However, mice carrying a germline deficiency in c-Abl have a broad range of abnormalities, including increased neonatal lethality; hence, a detailed investigation of the T cells in these mice was not feasible. To avoid this complication, Silberman et al. used a conditional knockout strategy, where c-Abl could be selectively deleted in T cells. With this approach, they showed that a T cell-specific c-Abl deficiency leads to thymic atrophy and defective peripheral T cell activation, confirming the long held speculation that c-Abl plays an autonomous role in T cell development and activation. Silberman et al. carefully studied the thymic atrophy resulting from the absence of c-Abl, and analyzed both proliferation and apoptosis of the c-Abl^{-/-} thymocytes. Interestingly, they found that the proliferation of c-Abl^{-/-} thymocytes was not altered relative to wild-type thymocytes; instead increased numbers of c-Abl^{-/-} thymocytes, particularly CD4-8+ and CD4+8+ cells, showed evidence of undergoing apoptosis. Biochemical studies revealed that phosphorylation of the p38 MAP-kinase on Thr180/Tyr182 was consistently higher in c-Abl^{-/-} thymocytes than control cells, likely contributing to the enhanced susceptibility of these cells to spontaneous apoptosis.

Silberman et al. also showed that mature peripheral T cells lacking c-Abl had a phenotype distinct from thymocytes. Specifically, peripheral

c-Abl^{-/-} T cells were impaired in their ability to proliferate in response to mitogenic stimulation. In addition, cell surface receptors that are normally upregulated following T cell activation were not appropriately induced in the c-Abl^{-/-} T cells. Addition of exogenous IL-2 only partially compensated for the impaired expansion of the c-Abl^{-/-} T cells following in vitro activation, indicating that the defect in these cells was not simply a result of insufficient secretion of IL-2. This study also showed that c-Abl^{-/-} peripheral T cells, like the thymocytes from these mice, had defects in survival, resulting in enhanced apoptosis of proliferating c-Abl^{-/-} T cells compared to those from wild-type mice.

Finally, Silberman et al. examined whether the impaired development and in vitro function of c-Abl^{-/-} T cells led to defective T cell responses in intact animals. Using a transplantable tumor model, these studies revealed that, contrary to control mice, mice with c-Abl^{-/-} T cells fail to control tumor cell growth. Detailed analysis showed that c-Abl^{-/-} T cells were less efficient at killing the tumor cells, and further, that the levels of tumor-specific antibodies in the sera of conditional c-Abl^{-/-} mice were also reduced relative to controls. Together these data support the conclusion that c-Abl is important for the optimal function of both CD8+ (tumor cell killing) and CD4+ (B cell help) T cells, providing a compelling explanation for the inability of these mice to reject the transplanted tumor.

When the bcr gene rearranges adjacent to the abl gene due to chromosomal translocation, the fusion protein Bcr-Abl is generated.⁵ This fusion protein has constitutive Abl tyrosine kinase activity and is responsible for 95% of patients with CML and 25% of adult patients with ALL.⁶⁻⁸ However, recent studies have shown that c-Abl is not only oncogenic when fused to BCR, but also when its expression level or activity is upregulated. For example, increased c-Abl expression was detected in some T cell lymphomas due to decreased levels of microRNA-203; this microRNA normally targets c-Abl mRNA, thereby down-regulating c-Abl protein levels.⁹ The work of Silberman et al. provides a better understanding of the function of c-Abl in T cells, and thus provides insight into the potential mechanisms by which dysregulated c-Abl activity can contribute to T lymphoma formation.

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