CANCER DISCOVERY

Published OnlineFirst February 13, 2014; doi: 10.1158/2159-8290.CD-RW2014-035

T Cells Prevent the Development of Spontaneous B-cell Lymphomas

- **Major finding:** T-cell immune surveillance blocks lymphoma formation in mice lacking *Blimp1* or overexpressing *Bcl6*.
- **Mechanism:** Polyclonal $CD8^+$ T cells eradicate transformed B cells in a Fas ligand-dependent manner.
- **Impact:** B-cell lymphoma development may require escape from T-cell mediated immune surveillance.

Inactivating mutations in the plasma cell differentiation gene *BLIMP1* (also known as *PRDM1*) and activating mutations in the transcriptional regulator *BCL6* are frequent in diffuse large B-cell lymphoma (DLBCL), the most common type of non-Hodgkin lymphoma, but healthy individuals can harbor such mutations without signs of disease. In addition to pointing to a requirement for additional mutations, this observation is consistent with the possibility that the immune system can remove transformed B cells and prevent cancer growth. Afshar-Sterle and colleagues established that T cells have a critical role in this immune surveillance mechanism because T cell–sufficient mice with B cell–specific deletion of *Blimp1* failed to develop lymphoma, whereas T cell–deficient mice succumbed to DLBCL-like disease. Similarly, T cell–deficient *Bcl6*-transgenic mice, but not their T cell–sufficient counterparts, rapidly developed lymphoma with complete penetrance. Restoration of the polyclonal $CD8^+$ T-cell population specifically restricted lymphoma formation in immunodeficient mice injected with DLBCL-specific lymphoma cells, identifying $CD8^+$ cells as the cell population most likely responsible for T-cell mediated lymphoma surveillance. The control of B-cell lymphomas by $CD8^+$ T cells depended on costimulation and specific antigen recognition, and yet, several mechanisms common to $CD8^+$ T-cell function were dispensable, such as perforin and granzymes. Interestingly, $CD8^+$ T cells lost their ability to control B-cell lymphoma cell growth in the absence of Fas ligand signaling, suggesting one mechanism that $CD8^+$ T cells use to impede spontaneous B-cell lymphoma development and raising the possibility that suppression of Fas ligand expression could represent a way for B-cell lymphomas to escape immune surveillance. Although it remains unclear how $CD8^+$ T cells recognize transformed B cells, these data provide direct evidence of a T-cell mediated immune surveillance mechanism that prevents lymphoma development.

Afshar-Sterle S, Zotos D, Bernard NJ, Scherger AK, Rödling L, Alsop AE, et al. Fas ligand-mediated immune surveillance by T cells is essential for the control of spontaneous B cell lymphomas. Nat Med 2014 Feb 2 [Epub ahead of print].