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● ● ● NEOPLASIA

Comment on Bassing et al, page 2163

RAGs found “not guilty”: cleared by DNA evidence

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A recent paper from the Alt laboratory shows that recombination activating genes (RAGs) are not responsible for double-strand DNA breaks associated with some chromosomal translocations in pre-T-cell lymphomas.

B- and T-cell lymphomas and leukemias are frequent hosts to chromosomal translocations, duplications, and deletions, the best studied of which are known to result in the hyperactivation of oncogenes or the fusion of 2 genes into a chimeric oncogene. How do these DNA-rearranging events occur? For the most part, there are 2 basic requirements: 2 distant double-strand DNA breakages, and joining of the wrong ends together. A fair amount of circumstantial evidence implicates the recombination activating gene (RAG) proteins, RAG-1 and RAG-2, as key suspects in the DNA breakage step for some of these translocations. This is because at the pre-T and pre-B stages of development, RAGs naturally cut the DNA at the T-cell receptor (TCR) and B-cell receptor (BCR or immunoglobulin) loci as part of V(D)J recombination. In this physiologic process, RAGs cleave the DNA adjacent to segments encoding the various parts of the receptor, and the segments are stitched together into a functional receptor gene. The inherent imprecision in this process, in addition to the combinatorial possibilities of the segments that can be used, is the basis for much of the diversity seen in the adaptive immune system. However, pathologic consequences occur when RAGs cut other loci and join them aberrantly. Biochemical studies using purified recombinant RAG protein complexes have shown that their minimal target is the DNA sequence CACA, which occurs millions of times in the typical 6-billion base pair human nucleus. Thus, it has long been suspected that RAGs may be respon-

sible for many of the chromosomal abnormalities in lymphocytes.

H2ax^{-/-} p53^{-/-} mice, which typically die from pre-T-cell lymphomas with clonal chromosomal defects, offer an opportunity to test that hypothesis. A significant proportion of the T-cells of H2ax^{-/-} mice contain translocations, but for the most part they do not develop lymphomas. On the other hand, p53^{-/-}

and p53^{-/-} RAG2^{-/-} mice die from pre-T-cell lymphomas, but mostly without clonal translocations, deletions, or duplications. Could the chromosomal abnormalities seen in the lymphomas of H2ax^{-/-} p53^{-/-} mice be due to RAGs? In this issue of *Blood*, Bassing and colleagues find that H2ax^{-/-} p53^{-/-} RAG2^{-/-} mice still die from pre-T lymphomas and that these lymphomas still have clonal chromosomal defects. Thus, the RAGs are probably not responsible for these translocations. It would appear that loss of p53 is responsible for the lymphoma and loss of H2ax is responsible for the translocations. So, going back to the translocation paradigm, what is causing the double-strand breaks if not RAGs? And how might H2ax prevent these translocations? These are questions for another study. It is worth noting, however, that in actual patients, a significant proportion of translocations may still be mediated by the RAGs, while in this system loss of H2ax might drastically increase the proportion of translocations by other mechanisms. Still, this study does open the door to the possibility that these other mechanisms may operate to the extent that H2ax—as well as the other components along the same or similar pathways—might fail.

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● ● ● IMMUNOBIOLOGY

Comment on Crompton et al, page 2053

Attack of the CD4 clones

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Latent human cytomegalovirus (CMV) infection is associated with vast clonal expansions of cytotoxic CD8⁺ and CD4⁺ T cells.

The human persistent herpes virus CMV has evolved in close relationship with its host, during which it has developed a wide variety of strategies to escape the immune system, which in its turn has responded with a refined series of defense lines. Latent CMV infection is accompanied by an increase in the number of circulating resting, effector-type CD4⁺ and CD8⁺ T cells with constitutive cytolytic activity. Although it is yet unsettled whether these cells are all CMV specific, it has become clear that T-cell responses to CMV are among the

broadest and strongest analyzed so far, occupying a considerable fraction of the T-cell compartment.¹

Cytotoxic CD28⁻CD4⁺ T cells emerge during primary CMV infection just following the decrease in viral load (see figure). Importantly, a considerable fraction of these cells can lyse CMV-antigen-expressing target cells, restricted by HLA class II. The CMV-specific cytotoxic CD28⁻CD4⁺ T cells present during latency were shown to have developed, through very strong selection, from the virus-specific cells early in primary infection.²