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Researchers solve another mystery in B lymphocyte development

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A new study published online in *Nature Immunology* ahead of the June 2009 print issue has found that homologous immunoglobulin (lg) alleles pair up in the nucleus at stages that coincide with V(D)J recombination of the heavy and light chain (Igh and Igk) loci. Researchers led by Jane A. Skok Ph.D., assistant professor in the Department of Pathology at NYU School of Medicine and a member of the NYU Cancer Institute, showed that the V(D)J recombinase, which consists of the RAG1 and RAG2 proteins, mediates this pairing and helps ensure that only one allele undergoes recombination at a time (a process known as allelic exclusion).

In "RAG-1 and ATM Coordinate Monoallelic Recombination and Nuclear Positioning of Immunoglobulin Loci," researchers found that RAG-mediated cleavage occurs on one allele at a time at every stage of Igh and Igk recombination; introduction of a double-strand break on one lg allele induces repositioning of its homologous partner to pericentromeric heterochromatin (a repressive compartment of the nucleus). This repositioning, surprisingly enough, depends on the DNA damage sensing factor ATM. It appears that cleavage activates ATM to act in trans on the uncleaved allele to reposition it in a repressive compartment of the nucleus, thereby preventing simultaneous recombination on both alleles and thus reducing the chance of translocations.

"This work deepens our understanding of the mechanisms that are in place for preventing translocations during V(D)J recombination that

might ultimately lead to leukemias and lymphomas," says Skok. "It also helps us understand why individuals with a genetic deficiency in ATM suffer more cancers arising from such translocations."

Leukemias and lymphomas are very common cancers, especially in children. Chromosomal translocations involving the antigen receptor loci are a common underlying mechanism.

"V(D)J recombination plays a crucial role in the development of the immune system," says Skok. "But because it entails the repeated cutting and joining of DNA gene segments, it carries a risk of translocation."

Skok says that given the deleterious consequences, it is essential that B and T cells tightly regulate the recombinase, the accessibility of substrates for RAG cleavage, and the activities of the DNA damage response and repair machineries. Skok and researchers propose that homologous pairing of alleles undergoing recombination has a number of functions: (i) To protect genomic stability by ensuring that broken ends are aligned with homologous alleles rather than in contact with other loci. (ii) To provide a means for repair proteins recruited to sites of DSBs to act in trans on the uncleaved allele to prevent simultaneous cleavage on the latter. (iii) To ensure sequential recombination of individual alleles to help maintain allelic exclusion. In this sense homologous pairing of Ig alleles is analogous to pairing of X chromosomes which has an important role in X inactivation in developing female cells. The data suggest that in parallel with X inactivation, homologous pairing of Ig loci contributes to allelic exclusion by ensuring that only one allele is targeted for recombination at any time.

Source: New York University School of Medicine (news : web)