The Immune System and the Risk of Lymphoma

Grace Teng, PhD and David Schatz, PhD

Not every lab discovery leads directly to a clinical application, but progress in cancer care depends on insights from basic science into the fundamental mechanisms of biology.

A recent paper in the journal *Cell* offers a good example. Scientists from Yale Cancer Center and elsewhere have been studying links between lymphoma and a biological mechanism called V(D)J recombination. This mechanism recombines broken pieces of DNA, and is essential for the development of T cells and B cells, lymphocytes that form the adaptive immune system. Yet this process of genetic recombination is also risky. The paper's lead author, Grace Teng, PhD, a postdoctoral fellow and Associate Research Scientist in Immunobiology, wrote that these developing T and B cells "perch on the edge of genomic instability."

"When broken DNA ends are flopping around in the cell, they can become joined in a haphazard fashion," explained Dr. Teng. "A lot of cancers are associated with these erroneous repair processes. The fact that lymphocytes have to go through programmed DNA damage during development makes them particularly susceptible to errors. That's why lots of lymphomas stem from B and T cells."

In short, the mechanism that creates our adaptive immune system also exposes us to the risk of lymphoma. "New lymphocytes are being generated in our bodies at a tremendous rate every day," said another of the paper's authors, David Schatz, PhD, Professor of Immunobiology and of Molecular Biophysics and Biochemistry, "and the V(D)J recombination process happens hundreds of millions, if not billions of times per day. So the risk is ongoing and chronic, and even an extremely low error rate gives you a significant risk."

Dr. Teng's research also uncovered an unexpected wrinkle in V(D)J recombination: breaks of DNA in the "wrong" places. In V(D)J recombination, DNA is cut by two proteins called recombination activating genes 1 and 2 (RAG1 and RAG2), which Dr. Schatz discovered 25 years ago. They were thought to cut DNA in a small, limited part of the genome, as a way of protecting the rest of the genome from flawed cuts. But Dr. Teng and her colleagues found RAG1 and RAG2 in thousands of off-target sites. "That seemed to constitute a much broader, more significant threat than previously suspected," said Dr. Schatz.

Dr. Teng and colleagues knew that the RAG complex prefers to sever DNA at specific spots called Recombination Signal Sequences (RSSs), which are abundant in the normal cutting sites. Researchers found that in the off-target sites, RSSs are significantly depleted. That means fewer places for RAG to cut, which lessens the risk of incorrectly refitted strands of DNA.

"You end up with two different compartments of the genome," said Dr. Teng, "one enriched with RSSs, and another where there's not much of the DNA sequence for RAG to cut." This compartmentalization seems to protect the genome from inappropriate cuts in the off-target sites.

That begs another question: why didn't evolution remove this bug from the system? Dr. Schatz points out that RAG1 and RAG2, with the threat of lymphoma they carry, have been present during vertebrate evolution for hundreds of millions of years. The depletion of RSSs at off-target sites might be evolution's way of putting the threat on the back-burner.

"Cancer is generally a disease of old age," said Dr. Schatz, "and hence lymphomas that would kill people at 50 or 60 would have been a very weak evolutionary force for most of human evolution. I suspect that's why this hasn't been completely selected against."

These discoveries might someday help physicians predict which parts of the genome are at greatest risk of lymphoma. "As basic scientists," said Dr. Schatz, "we're not looking at how the immune system is interacting with tumors, but at what gave rise to the tumors in the first place."