The genius of a disorderly enzyme

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(PhysOrg.com) -- USC Dornsife researchers uncover how the inefficiency of activation-induced deoxycytidine deaminase is good for your immune system.

Why is antibody diversity important? Think about it like this, said Myron Goodman: “Why don’t you die when I sneeze? It’s because you have a powerful immune system. And the way to get a decent immune system is for your body to have a way to respond to insults it has never seen before.”

Random patterns of deamination by the enzyme activation-induced deoxycytidine deaminase (AID) are the key to generating antibody diversity, a crucial component to a healthy immune system, according to a new study by USC Dornsife researchers published in The Journal of Biological Chemistry.

Having variation in the types of antibodies produced by your body gives it a fighting chance to respond to those “insults.” Antibodies protect against invasion by antigens such as bacteria or viruses by locating them in the body and neutralizing them. To do that, antibodies must bind to antigens. The more variation in the types of antibodies produced by the body, the more likely they will be able to bind to and fight off antigens, which come in many forms.

To create antibody diversity, mutations must occur in the variable region of immunoglobulin genes, the region where antibodies bind to invaders. Generating those mutations has to be a really random process according to Goodman, professor of biological sciences and chemistry in USC Dornsife. This is where AID steps in.

Goodman and his colleagues monitored the actions of AID as it scanned single-stranded DNA or transcribed double-stranded DNA. The enzyme essentially moves back and forth along the DNA strand and sporadically deaminates, or converts, cytosine to uracil triggering a mutation in tri-nucleotide motifs – sequences comprising three bases – found along the DNA.

Unlike most enzymes that are exquisitely efficient in targeting favored motifs, they found that AID was extremely inefficient. AID initiated chemical reactions in favored motifs only about 3 percent of the time. By mutating the motifs so haphazardly, the researchers suggest that AID produces antibody diversity.

The study also sheds light on a little-studied group of enzymes. Enzymes like AID that scan single-stranded DNA have been studied far less extensively than enzymes that scan double-stranded DNA.

“This is the first really clear picture of what AID is doing during the scanning process,” Goodman said.

To identify and describe AID's complex process during scanning, the team used a genetic assay to measure the distribution of AID-induced mutations on individual DNA molecules and then analyzed the mutational data computationally using a random walk model, developed for the study by USC Dornsife researcher Peter Calabrese. By combining the genetic and computational analyses, they were able to calculate the distribution of mutations that occurred with a remarkable fit to their experimental data. The fit entailed matching theory to experiment for the patterns of closely spaced mutations and separately for the distances between mutated and non-mutated target motifs.

Their paper, "An Analysis of a Single-stranded DNA Scanning Process in which AID Deaminates C to U Haphazardly and Inefficiently to Ensure Mutational Diversity" published online May 12, was selected by *The Journal of Biological Chemistry* as a "Paper of the Week" to appear in the July 15 print issue.

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