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Scientists identify DNA that regulates antibody production

November 20 2009

(PhysOrg.com) -- When foreign invaders trip the immune system's alarm, antibodies need to be specially sculpted to attack them head on. New research now shows that gene segments called enhancers control the reshuffling of antibody genes that makes such a precise and coordinated attack possible.

Performance enhancers are the currency of a competitive society. But there's one that we have always had: For millions of years, segments of our DNA have improved the performance of our genome, revving up protein production at those times we need it most. New research from Rockefeller University and the University of Michigan Medical School now show that these genome enhancers regulate how our bodies make germ-fighting antibodies, molecules that keep savvy viruses and bacteria at bay.

The research, which appears this month in the Journal of Experimental Medicine, represents a major technological advance that will allow scientists to understand the role of enhancers in the immune system — work that has stymied researchers for decades. "Many people left the field because working with antibody enhancers was so difficult," says F. Nina Papavasiliou, head of the Laboratory of Lymphocyte Biology at Rockefeller. "It seemed like there was no way around the problem."

Enhancers are short swaths of DNA that regulate genes from a distance, often megabases away. Generally, this distance from the genes they regulate makes enhancers hard to study. But immunoglobulin enhancers

have been particularly problematic because of an additional twist: they are close to chromosome ends, which makes altering their local sequence especially difficult.

Instead of tampering with enhancers in place, Wesley Dunnick, a professor at the University of Michigan Medical School, devised a way to move the entire locus — the enhancers along with adjacent antibody genes that contain information about foreign invaders — onto an artificial bacterial chromosome. Placement on the artificial chromosome allows for the modification of the excised locus with relative ease: using tools pioneered at Rockefeller by Peter Model and Nathaniel Heintz, Dunnick could delete or mutate enhancer sequences at will. He then re-inserted these modified chromosomes into the mouse. Like a bubble floating in the genome, these artificial chromosomes would land randomly onto the mouse genome and get incorporated into it, now allowing him to study the effect of these modified enhancers on the generation of antibodies.

In response to the unlimited number of foreign antigens (bits of microbes, chemicals and other substances) that can invade our bodies, the immune system must be able to tailor-make an unlimited number of antibodies. However, the amount of DNA in a cell is limited, so antibody-producing B cells must mutate and re-arrange their antibody genes to step up to the challenge (using processes called somatic hypermutation and class switch recombination, respectively).

In collaboration with the Papavasiliou lab, Dunnick discovered that mice carrying the artificial chromosomes with the antibody genes behave in ways that are indistinguishable from unmanipulated mice: they recombine and mutate their antibody genes to generate highly specific attacks on foreign invader. But for that, they absolutely need their enhancers: without them, the cell's machinery can transcribe and translate the antibody genes, but can't rearrange or mutate them,

suggesting that the enhancers function as a loading dock for a common initiator molecule, which is then hauled to the antibody genes.

The experiments show that the enhancers of antibody genes are vital in springing the immune system to action, and suggest that mutations in the enhancers may make an individual more susceptible to infections, even infections for which he should have been vaccinated. “The main goal of vaccination is to produce, in a short amount of time, antibodies that are diversified to be most effective against a particular virus or bacterium,” says Dunnick. “We were fortunate to identify the control elements that are critical for this antibody diversification.”

More information: *The Journal of Experimental Medicine* online: November 11, 2009. Switch recombination and somatic hypermutation are controlled by the heavy chain 3' enhancer region, Wesley A. Dunnick, John T. Collins, Jian Shi, Gerwin Westfield, Clinton Fontaine, Paul Hakimpour and F. Nina Papavasiliou

Provided by Rockefeller University (news : web)