ASM MEETING

ANTIBODIES FIND A NEW ROLE—AS ENZYMES

SAN DIEGO—Immunologists and molecular biologists have exploited antibodies' highly specific and selective binding affinities to perform functions as diverse as purifying proteins and delivering cytotoxic molecules to tumor cells. Now the chemists are defining a new function for antibodies—as enzymes. The technology of creating catalytic antibody molecules, though still very much in its infancy, is touted by many as a major scientific breakthrough, exposing yet another frontier to explore.

To effectively design enzyme-like catalysts, it is essential to understand the precise nature of an enzyme-catalyzed reaction. Peter Schultz (University of California, Berkeley), speaking at the Second Annual American Society for Microbiology Conference on Biotechnology here in late June, pointed out that these reactions are characterized by the formation of a Michaelis complex, in which substrate is first bound in the enzyme active site, held in close proximity to the catalytic groups. The reactants must be activated to form a transition state (active complex) before they can be chemically transformed into products. The enzyme must bind the transition state better than it does the substrate to get a reduction in the free energy of activation.

Schultz outlined three current strategies for creating catalytic antibodies. The first, and most familiar, is to generate a combining site that is complimentary—both in electronic and steric structure—to the transition state of the enzymatic reaction. Ideally, this antibody would preferentially bind and stabilize the transition state relative to the ground state of either the substrates or products. Because transition states are ephemeral, however, one must instead make antibodies to close analogs. As Schultz puts it, "You can't put a transition state into a bottle, much less a mouse."

In fact, this analog approach seems to work. Schultz and his colleagues have generated and characterized monoclonal antibodies that are capable of selectively hydrolyzing aryl carbonates and esters. Schultz has also found that MOPC167, an antibody (from Jack Richards at Cal Tech) that binds nitrophenylphosphoryl choline, is, in fact, catalytic. Nitrophenylphosphoryl choline happens to be a transition state analog. And Richard A. Lerner's group (The Research Institute of Scripps Clinic, La Jolla, CA) has raised monoclonal antibodies to haptens that exhibit the properties of an esterolytic transition state for carboxylic esters. They have demonstrated that these antibodies behave as catalysts with the appropriate ester substrates. Likewise, Alfonso Tramontano (also at Scripps) reported at the meeting that his group has obtained monoclonal antibodies to analogs for the transition state for esterolysis reactions. Many of these antibodies are catalytic.

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COURTESY A. TRAMONTANO, SCRIPPS; REDRAWN BY JIM STONE

The ester hydrolysis reaction, exhibiting the transition state and a stable analog.

Although creating antibodies that are able to hydrolyze carbonates and esters is an important first step, catalytic reactions of more general interest remain the goal. Schultz feels that the next step is to create catalytic antibodies that hydrolyze amides. "There are no restriction-like enzymes for proteins, no class of sequence-specific proteases that we can cut proteins apart with," explains Schultz. "These could be extremely useful. You can imagine, for instance, cleaving viral coat proteins with catalytic antibodies that are sequence-specific peptidases." Other reactions that might be catalyzed by transition state stabilization include cleaving sugars and nucleic acids, and paracyclic reactions.

The second strategy for creating catalytic antibodies involves orientational catalysis. It should be possible to use an antibody's specificity and affinity to bind and orient two substrates in a reactive conformation. As one lowers a molecule's degree of freedom, Schultz says, there is a large rate acceleration. Schultz has tested this hypothesis, again in a simple system—the catalysis of an acyl transfer reaction. So far he has found several antibodies that act in a manner consistent with this concept.

The third approach to designing catalytic antibodies is to chemically modify an antibody to include a catalytic group. This would involve inserting synthetic groups such as cofactors, nucleophiles, or redox-active metals into the binding site.

—Jennifer Van Brunt

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