Editorial

Catalytic Antibodies and Antibody Engineering

Sequence hypervariability in antibodies makes possible the evolution of new functions in these molecules, including catalysis. The quest to discover and invent catalytic antibodies and understand their mechanism of catalysis derives from the simple expectation that these reagents will combine the exquisite specificity of antibodies with the ability of enzymes to catalyze chemical transformation of defined target molecules. Antibodies can recognize small arrays of atoms as well as large epitopes composed of as many as 15–25 amino acid residues. The target molecule for an antibody might be either a small hapten or a macromolecule, such as a protein or nucleic acid. Thus it does not stretch the imagination to visualize uses for catalytic antibodies in organic chemistry, industry, and medicine.

The analogy between enzyme- and antibody-active sites has long been discussed *(1)*. However, antibodies are not conventional enzymes. Antibodies use a common molecular scaffold onto which individual specificities evolve over the course of the maturation of the immune response. Identification of common structural motifs between enzymes displaying different specificities, on the other hand, remains elusive. The active site of many enzymes may be smaller than that of antibodies. In comparison with enzymes, antibodies may more efficiently recognize substrate regions distant from the chemical center of the reaction. Enzymes have evolved naturally to catalyze biochemical reactions. Although the traditional function of antibodies is to bind ligands, there are now several instances of catalysis or stoichiometric chemical activity by naturally occurring autoantibodies and antibodies raised against unactivated ligands *(2–5)*. Antibodies raised against substrate analogs (e.g., transition state analogs, *see below*) display chemical reactivities not predicted by the design of the immunogen *(6)*. Is it likely, then, that chemical reactivity is an intrinsic property of antibody molecules? The selection of antibodies from large libraries and the manipulation of their binding function can now be achieved using recombinant DNA and phage display methods *(7)*. Unless there is selection *against* catalysis by antibodies in vivo, systematic

screening of the immune repertoire against ordinary unactivated ligands might well turn up many new catalytic antibodies.

Research in catalytic antibodies was boosted considerably by the germinal studies of Tramontano and coworkers *(8)* showing enzymatic activity of antibodies raised against molecules that looked like the transition state. Provided that shape complementarity with the transition state obtained by this approach is combined with active participation of antibody functional groups in the chemistry of the reaction, efficient catalysis could be achieved. Initial attempts to place charged residues capable of this type of chemistry in the antibody active site have been reported *(9)*.

Expectations associated with further research on catalytic antibodies include: (i) identification of the physiological and pathophysiological roles for catalytic antibodies formed in response to natural antigens, and (ii) isolation of antibodies capable of the facile and specific chemical transformation of compounds important in medicine and industry. The stage is set for attempts to achieve directed evolution of catalytic antibodies in vitro using principles derived from the examination of both "natural" and "designer" catalysis by antibodies. From the technical viewpoint, the development of methods permitting the direct selection of catalytic antibodies, independent of their ability to bind presumed transition state analogs or substrate ground states, is likely to be fruitful.

The research on catalytic antibodies has operated at the interface of several scientific disciplines. Immunology, chemistry, enzymology, and more recently, molecular biology, are increasingly playing a significant role in the development of this field. In keeping with the breadth of the discipline, the participants at this conference had interests ranging from autoimmunity, enzymes, synthetic peptide catalysts, and idiotypic networks, to directed evolution. One consequence of having to work at interfaces is that collaborations become vital. Though establishing collaborations is time-consuming, they provide for a dynamic process and yield fresh insights and perspectives. The conference was held on the Volga river amid reminders of Russia's historic past and achievements and its currently changing values. With this backdrop, it was inevitable that cultural, governmental and scientific boundaries would appear inconsequential, fostering interactions of the type summarized in the General Discussion section of this volume.

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