Unlocking secrets of antibody binding

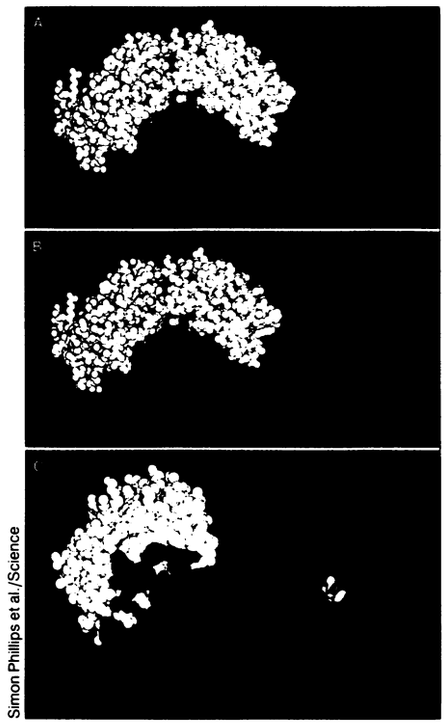
Researchers are jimmying open the tight fit of antibody and antigen, taking their first detailed three-dimensional look at the way the two bind. So far, the picture indicates that the traditional "lock and key" metaphor still fits. At the same time, other scientists are attempting to use the amino acid sequence of an antibody to predict the structure of the antibody's binding sites. Taken together, the two pieces of research have implications for attempts to understand how an essential bit of the immune system works – how antibodies recognize and bind to foreign bodies like viruses. Ultimately, the work may help researchers learn how to modify antibodies for more effective disease control, or even to design antibodies from scratch.

Until now, ideas about the way antibodies bind to foreign bodies have been largely based on studies done with haptens. These are small molecules that, unlike true antigens, cannot stimulate an immune response on their own, though they will bind with antibodies that are already circulating. Researchers haven't known how well such studies reflect natural antibody-antigen binding.

Now, using monoclonal antibody technology, scientists at the Institut Pasteur in Paris and the University of Leeds in England have been able to produce enough antibody to do an X-ray crystallographic analysis of an antibody-antigen complex. (The scientists used only the antigen-binding fragment of the antibody.) The newly characterized complex, described in the Aug. 15 SCIENCE, differs in crucial ways from antibody-hapten binding, says Peter Shenkin of Columbia University in New York City, who also studies antibody structure.

In antibody-hapten binding, the hapten buries itself deep in a cleft-like pocket of the antibody, making contact with relatively few of the antibody's amino acids. In contrast, the antigen makes extensive contact with a "large . . . and rather flat surface" of the antibody, the researchers write. Binding occurred at 17 of the antibody's amino acid residues. The residues are distant from each other in the amino acid sequence, but because of the folding of the polypeptide chain, they are adjacent on the antibody's surface. "It's not just one little piece of the molecule that's important for binding," Shenkin says, "but the whole thing."

The analysis also indicates that binding does not change the structure of either interacting unit. The evidence regarding the antibody is not conclusive; even if correct, the stability in this particular antibody-antigen complex may be an idiosyncratic characteristic rather than a general one. But if borne out by further research, it would have great practical significance to scientists who hope someday to modify antibodies or even to design them from scratch – against pathogens like the AIDS virus, for instance, for which the body apparently has no effective defense. According to Arthur Lesk, part of an associated research team attempting to predict antibody structure, it would mean that "if you asked me to design an antibody in the lab, I could deal with rigid models. I wouldn't have to . . . deal with designing something that could undergo some kind of conformational change."



Simon Phillips et al./Science

Three-dimensional views of antibody and antigen. (A) Antigen-antibody-complex structure as determined by the crystallography group. Two chains of the antibody are shown in blue and yellow; the antigen is green, with a deeply mating amino acid unit shown in red. (B) The models have been pulled apart to show matching protuberances and depressions. (C) End-on view shows binding at many sites. Contacting residues are shown in red and purple.

According to Lesk and the modeling group's leader, Cyrus Chothia – both at the MRC Laboratory of Molecular Biology in Cambridge, England – work on antibodies may add to the understanding of protein design. "What we want," Chothia says, "are rules which say how a change in sequence produces changes in structure."

Antibodies make an ideal model system for that investigation because the problem is confined: Much of the amino acid sequence remains the same from antibody to antibody. The near-infinite range of antigen specificity is determined by changes in short, looping sequences called hypervariable regions, so researchers can concentrate on these smaller bits of the amino acid sequence.

Using known structures of antibodies as a data base, the researchers developed a tentative set of predictive rules. For instance, each hypervariable region seems to be limited in its "choice" of structural conformation, according to Lesk. "So although we don't know what [the structure] is, in an unknown case, it can't be just anything – it's one of several in a discrete, well-defined class." According to Lesk, relatively few amino acid residues determine the choice of conformations and ultimately the specificity of the antibody. "This allows us to look at a new sequence and pay particular attention to those crucial residues" when predicting the structure, Lesk says.

These proposed rules were supported by a largely successful effort at predicting the structure of the antibody, the researchers write. They correctly predicted the framework, the relative positions and the folds of four of the six hypervariable loops. According to Lesk, as more crystallographic analyses are done, "that will give us a much wider data base on which to base the predictions. . . . The predictions will only get better."

– L. Davis

Silkwood case laid to rest

The Karen Silkwood radioactive-contamination case ended out of court last week with a settlement of $1.38 million awarded to Silkwood's heirs.

Silkwood died in a 1974 car crash on her way to a meeting with a New York Times reporter and a union representative, to whom she planned to give evidence of safety violations at the Kerr-McGee plutonium-processing plant where she worked. Silkwood's children and father sued the Oklahoma City-based corporation in 1976, charging that the owners of the Crescent, Okla., plant were responsible for exposing Silkwood to dangerous levels of radiation. Despite a 1979 appeal by Kerr-McGee, the Supreme Court in 1984 upheld the Silkwoods' right to use state law to seek $10 million in punitive damages from a federally regulated industry (SN:2/4/84,p.74), and sent the case back to the lower court for review.

Donald Winston of the Atomic Industrial Forum in Bethesda, Md., says that despite the Silkwood case, the states' role in regulating nuclear safety is "not really clear." Sara Nelson of the Silkwoods' legal team, the Christic Institute of Washington, D.C., counters, "If people are injured by this industry's recklessness and maliciousness, and if they want to move against it through state law, they can do so." □