Boom Time for Monkey Research

Macaque researchers have blazed a trail of biomedical firsts. Now, with macaque genomic tools at last in hand, this research is rushing ahead in new directions.

THE RHESUS MACAQUE IS THE UNSUNG hero of the maternity ward. In 1940, Nobel laureate Karl Landsteiner and his student Alexander Weiner discovered in this monkey a blood protein they called the Rh (for Rhesus) factor. Researchers soon found the Rh factor in some but not all humans and realized that a mother could react immunologically against the factor in her fetus. Now a simple test and a vaccine prevent that reaction—and resulting mental retardation or even death in about 20,000 U.S. newborns a year.

Thanks to Landsteiner, the Rh factor was among the early contributions that this 60-centimeter-tall monkey made to human health. More recently, the macaque has revealed new insights into disorders as diverse as AIDS and depression. But researchers seeking to understand the genetic underpinnings of macaque diseases and behavior have been thwarted. Unlike mice and humans, macaque genetics was virtually unexplored territory until recently, with relatively few genes identified.

And so about 5 years ago, Jeffrey Rogers and Michael Katze decided it was high time to push macaque biology into the 21st century. Infected by the excitement over the human genome, they decided to go after the macaque genome and to develop the tools to pin down the genes underlying the disorders and behaviors they studied.

They have succeeded in spades. On page 222, they and their colleagues at Baylor College of Medicine in Houston, Texas, describe the high-quality draft sequence of the rhesus macaque (Macaca mulatta) genome. Katze, a virologist at the University of Washington, Seattle, used this sequence to develop a macaque-specific microarray that reveals the expression of thousands of genes at once. Rogers, a geneticist at the Southwest National Primate Research Center in San Antonio, Texas, has drawn up genetic linkage maps for both baboons and rhesus macaques and is genotyping thousands of macaques in pursuit of specific genes—genes that the sequence will make easier to find. “You now will have the tools and reagents to do in macaque what you can do in humans and in mice,” says Katze. “It will completely transform the rhesus as an animal model in human disease in every way.”

Already, these efforts are leading to a better understanding of how genes are regulated in diseases such as influenza, and what variants of genes are important for certain behaviors. Researchers are also figuring out how macaques differ genetically from humans—a key step in understanding both the value and limitations of these monkeys as surrogates for humans in experimental work. In AIDS research, for example, it’s important to find out where gene expression in humans and macaques diverges. Otherwise, “we are never going to get the right cure or the right [drug] target,” says geneticist Timothy Ravasi of the University of California, San Diego.

Building genomic tools

The list of “first discovered in” macaques is impressive. For example, using macaques, researchers demonstrated both that a virus caused polio and, ultimately, the efficacy of the polio vaccine. Since 1985, these animals have been sine qua non for HIV studies and vaccine trials because they can be infected by a simian cousin of the HIV virus that causes a progression of disease similar to that in humans. Then too, monkeys behave much more like people than, say, mice or rats, and they have proven to be good stand-ins for humans in neuroscience and behavioral studies. For example, long-term observations of monkeys raised with their parents or just peers led to key insights into the role of mothering in shaping personalities. Back in the 1990s, the first primate embryonic stem cell came from a macaque. All told, researchers publish about 2000 papers a year on macaques.
macaques, with publicly funded researchers conducting studies on about 40,000 animals and drug companies, many more.

But without good genetic tools, macaque research could only go so far. Researchers could document an immune response, for example, but not the changes in gene expression associated with that response. They could identify genetically based behaviors—headbanging similar to that in humans occurs naturally in some macaques—but had no way to track down the genes involved, much less knock out a gene. That’s a big contrast with mice, in which researchers have characterized genes involved in dozens of human diseases, thanks to mutagenesis and gene-knockout technologies. Researchers have also developed mouse- and human-specific microarrays—chips or glass slides in which probes of short DNA sequences measure the activity of thousands of genes at once and reveal complex gene circuits. “I envy people who work in human and mouse,” says Shoukhrat Mitalipov, a developmental biologist at the Oregon National Primate Research Center in Beaverton.

Dozens of macaque researchers have made do with microarrays equipped with human DNA probes, but they have never been sure how well the results represented the monkey’s gene activity. The average 3% difference between macaque and human genes means that for some genes the macaque sequence may be invisible to a human-based microarray. “If you want to know exactly what’s expressed in monkeys, you have to use monkey sequence,” says Shrikant Mane, a neuroscientist at Yale University.

Those frustrations drove Katze, Rogers, and their Baylor colleagues to pull together a proposal in 2002 to the National Human Genome Research Institute to sequence the macaque genome. They got the go-ahead in 2005 for the $20 million project, with Baylor’s Richard Gibbs leading the sequencing effort and coordinating more than 100 researchers from around the world. As soon as the data started trickling in, Katze teamed up with Agilent Technologies in Santa Clara, California, to put together a macaque microarray based on the new sequences. Several prototypes later, they came up with one with all the macaque’s 20,000 genes represented on it.

At the same time, a group led by Robert Norgren, a neuroscientist at the University of Nebraska Medical Center in Omaha, had started on its own gene-chip design. The researchers first used the human DNA sequence to track down the equivalent sequence in macaque, working with Affymetrix Inc. in Santa Clara, California. Initially, the macaques’ lungs severely overreacted to the 1918 flu virus, the researchers reported in the 18 January issue of *Nature*. With both viruses, the macaques’ first line of defense, the innate immune system, kicked in, with genes for inflammatory molecules revving up. In the macaques battling the modern virus, that reaction was temporary, but in those with the 1918 flu, the genes were not only more active but also active much longer, causing extensive tissue damage.

To make matters worse, the subsequent ability of the cell to attack the virus was dampened in the monkeys with the more deadly flu. Type 1 interferon proteins typically activate genes for other proteins that inhibit viral replication. But with the 1918 virus, this genetic pathway seemed disturbingly quiet.

Katze is now one of dozens of infectious-disease researchers using monkey-specific microarrays, including in AIDS research. The microarrays are proving their worth in other disciplines too. To take just one example, neuroendocrinologist Cynthia Bethea of the Oregon National Primate Research Center is using the arrays to delve deeper into the effects of estrogen and progesterone on serotonin, a brain chemical important in mood, appetite, and sex drive.

She and her colleagues have compared gene expression in serotonin-producing nerve cells in menopausal monkeys with and without hormone treatments. Her unpublished results show that with hormone exposure, “there’s a dramatic shift” in a biochemical pathway that leads to enhanced production of serotonin, she says. That pathway involves tryptophan, which these nerve cells can use to make either serotonin or a toxin that destroys the nerve cell. In macaque hormone recipients, Bethea’s team finds increases in the gene activity of five enzymes used to convert tryptophan to sero-
The Rhesus Macaque Genome

To explore this idea further, Bethea wants to coax embryonic stem cells to become specialized serotonin-producing nerve cells in a lab dish. Here too, the microarrays come in handy, as a tool to examine the nerve cells’ gene expression. So far, the chips show that Bethea has some work to do: The lab dish neurons still express many genes typically active only in developing neurons.

Better gene hunts

At the same time that dozens of researchers are building up a picture of overall gene activity in macaques, Rogers has been working toward tracking down specific genes, taking data from many macaque individuals. Last year, he and his colleagues published a genetic linkage map of the rhesus macaque containing known landmarks or bits of identifiable DNA, places where the sequence varies from one individual to the next. These maps help researchers home in on specific genes when used with family studies. (The sequence itself, in contrast, comes from a single macaque and provides few clues about what varies between individuals.) And thanks to long-term breeding programs for the rhesus macaque, Rogers and his colleagues can work with large families whose genealogies are known or can be determined. The stage is set to do genetic epidemiology, says Rogers.

For example, researchers have long studied various behaviors in macaques, including indicators of anxiety or shyness, such as how long it takes an infant to walk away from its mother and explore new surroundings. Judy Cameron of the Oregon primate center has recorded how infants react to such novel situations and found that the exploratory behavior “is strongly heritable,” says Rogers.

But until recently, Cameron and others had no way to narrow down where along the macaque’s 21 pairs of chromosomes the gene or genes responsible for this behavior are located. Now Rogers and Cameron are using the genetic map to note which landmarks are frequent in infants who are timid or in those who are adventurous, for example. The landmarks will help researchers identify the general vicinity of the genes. Then the team will search the genome sequence at that location for possibly relevant genes and test them. “We’re very excited,” says Rogers. “This will provide important new information about the genetics of susceptibility to psychiatric disorders among humans.”

Other groups are taking a similar tack to uncover genes for vulnerability to stress or risks for neurological and eventually heart and other diseases. Their analyses are just the beginning of a revolution in macaque research. “As we know much more about the genome, we are in a position to do much more sophisticated work in this species,” says immunologist Norman Letvin of Harvard Medical School in Boston. “There will be a great deal of work going forward now that these tools are available.” Landsteiner would be proud.

—ELIZABETH PENNISI

Genomicists Tackle The Primate Tree

The deciphering of the human genome was a humbling experience. The promise of the project, in the words of James Watson, was “to find out what being human is.” But even when most of the 3 billion bases of the human genome had been properly placed, much about the sequence defied understanding. Where in the 20,000 human genes uncovered are the ones that set Homo sapiens apart from other mammals, or other primates? To find out, genomicists have been scrambling for more data ever since, most recently from primates. “The goal is to reconstruct the history of every gene in the human genome,” says Evan Eichler, a geneticist at the University of Washington, Seattle. And that requires data from our relatives.

DNA from different branches of the primate tree will allow us “to trace back the evolutionary changes that occurred at various time points, leading from the common ancestors of the primate clade to Homo sapiens,” says Bruce Lahn, a human geneticist at the University of Chicago in Illinois.

In 2005, the unraveling of the chimp genome provided tantalizing hints about differences between us and our closest relative (Science, 2 September 2005, p. 1468). Now on page 222, the third primate genome, that of the rhesus macaque, begins to put the chimp and human genomes into perspective. Macaques are Old World monkeys, which split perhaps 25 million years ago from the ape lineage that led to both chimpanzees and humans (see diagram, p. 219). So when compared to apes, monkeys can help identify the more primitive genetic variants, allowing researchers to tease out the changes that evolved only in apes. Researchers want to take such analyses back to even more ancient evolutionary divergences, and so seven more primate genome sequences are under way, as is the sequencing of the DNA of two close nonprimate relatives. Together, these genomes “should teach us general principles of primate evolution,” says Lahn.

A consortium of more than 100 researchers who have been unraveling the macaque genome are detecting genes that have changed...
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