What Mice Can Do for Us: Extending the Field of Neuroscience

By Jack M. Gorman, MD

Many people believe the recently announced sequencing of the human genome is very important. What they do not realize is that it is not nearly as important as the sequencing of the mouse genome, at least as far as the central nervous system is concerned. Over the course for the next few years, we are going to learn a lot more once the mouse genome is completely sequenced than we will from the human genome.

The reason for this bold assertion is easy to see in this month's issue of *CNS Spectrums*. A group of world-famous neuroscientists takes us through the insights gained from studying the behavior of genetically altered mice. We have little access to genes that are specifically expressed in the brain, and our illnesses are complex and heterogeneous. This has made finding disease or even vulnerability genes for most neurologic and psychiatric illnesses difficult and, at times, frustrating. We now have a long list of linkages to regions on chromosomes for some of these illnesses, like schizophrenia and bipolar disorder, but actual genes are still elusive.

But mice may help us find some of these genes. By knocking-out or over-expressing specific genes and then studying the results, scientists are rapidly gaining important information about the precise functions of many central nervous system genes. The exponential growth in this type of research may make it seem as if developing genetically altered mice is an easy task, but in fact it is technically challenging and ripe for disappointment for the dedicated laboratory scientists who attempt. Nevertheless, great progress has been made. Not only can genes be deleted or over-expressed in the developing embryonic brain of mice, but also newer techniques allow inducible knockouts and knockins and also regional specificity. This means, for example, that a specific gene can be knocked-out at a specific time in the mouse's life in a specific brain region. By studying the resulting change in the animal's ability to learn, remember, or behave, it is possible to link specific genes to specific functions. The next task then, is to query whether an abnormality in that gene might affect similar function in a human and, therefore, be responsible, at least in part, for disease.

There are, of course, problems with this strategy. First, even compared with rats, mice have a relatively limited repertory of behaviors and cognitive functions that are relevant to humans. There is no mouse model of schizophrenia or depression and only partial ones for multiple sclerosis or epilepsy. To solve this problem, researchers have focused on specific aspects of these complex illnesses. Some of the cognitive deficits, for example, typically manifested by patients with schizophrenia can be mimicked in mouse models and made tractable to genetic investigation. Many behavioral tests were originally developed for use in rats, and they now need to be reformatted for mice. What behavioral scientists would really like to have are genetically altered rats. Someday, this may possible.

Secondly, it is now apparent that when genes are knocked-out in developing brain, compensatory factors may take place that obscure the effect of the genetic deletion. It is puzzling, for example, how a mouse without the gene encoding the transcription factor cyclic adenosine monophosphate response element binding protein (CREB) could possibly survive, given the critical important that CREB seems to have in neuronal function. It must be that the brain adjusts during development, so that whatever the loss of CREB does, we cannot see it entirely in the CREB knockout. The inducible knockouts, previously mentioned, may help with this problem.

Finally, the genetically altered mouse strategy depends on there being an overlap between human and murine genes. Indeed, it may be disconcerting to know that most of our genes are also found in mice. Mice and humans are not all that different from a genetic point of view. What may be different, however, is the expression of genes. Neuropsychiatric diseases may not involve the actual loss of gene function because of mutation but rather a change in the expression of the gene in question, such that it either leads to the translation of too much or too little protein. A relatively new technology involving the quantification of gene expression using microarrays is beginning to help with this problem. This method requires access to mRNA in the specific tissue under investigation because different organs in the body, like the brain, have completely different expression patterns. We can get mRNA for mouse brains and from postmortem human brains, but have no access to it from living humans.

Despite these limitations, the trajectory of research in genetically altered mice is impressive. When the mouse genome is fully sequenced, it should move even faster. This will be good news for those of us interested in brain function. CNS

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