New reagents for genomic engineering of mouse models to understand human disease

August 19 2009

A new study published in *Disease Models and Mechanisms*, reports new tools for generating specifically targeted genetic mutations in bacteria, mammalian cells and mice. The new recombinase, Dre, is similar to its predecessor, Cre, but targets unique sites within DNA for recombination. It may be used in combination with currently available methods to produce more complex mouse models to understand disease.

The ability to specifically target and modify genes in the mouse allows researchers to use this small rodent to study how certain genes contribute to human disease. A common method used to make genetic changes in mice and cells is called site-specific recombination, where two DNA strands are exchanged. The two strands may contain very different sequences, but are designated at their ends by specific target sequences that are not commonly found elsewhere in the genome. A protein, called a recombinase, cuts the DNA at its target sites and rearranges it. Scientists use this technique to exchange a naturally occurring DNA sequence for an altered or deleted gene to gain insight into the gene's normal function or how it contributes to disease.

Currently there are a few systems available to create genetic mutations in mice, including the recombinases FLP and Cre. These proteins are very efficient genetic modifiers and specifically target their appropriate sequences. They can also be turned on or off at precise times, or within specific tissues, to make carefully reegulated genetic changes. However, the small number of available methods that can be used together to mutate genes limits the complexity of the modifications that can be

produced. For example, it would be informative to independently regulate the temporal and tissue-specific expression of genes with overlapping functions to understand their individual and combined effects.

Scientists now report that a new recombinase, Dre, induces controlled genetic changes in mice. Dre works similarly to the currently popular recombinase Cre, with an important exception: Dre recognizes a distinct target sequence and only recombines DNA around its target sequence, even if the target sequence for Cre is present. The ability of the related proteins, Cre and Dre to distinguish their own target sequences indicates that Dre can be used in combination with Cre, and other recombinases, to produce more sophisticated mouse models. This should facilitate the analysis of complex gene interactions and how they function in disease.

This technological advance also highlights the progress that might be made through open reagent sharing within the scientific community. The discovery of Dre recombinase was originally reported by Sauer and McDermott at the Stowers Institute for Medical Research. The Institute holds an intellectual patent for the system that allows it to be shared openly for non-commercial purposes and evaluates requests on a case-by-case basis for its use by for-profit institutions. Thus, the authors of the new DMM report do not have any proprietary claims to the system that they used to create this valuable mouse model. This is the first of a series of Resource Articles that will appear in *Disease Models and Mechanisms* intended to promote collaboration, and the development and sharing of new tools to understand or treat human disease. These DMM articles specifically state how other researchers can access the reagents presented. More discussion about the sharing of scientific resources and collaboration is published in an editorial by the Editor-in-Chief, Vivian Siegel, in Volume 2 Issue 9/10 of DMM.

More information: The study is published in the September/October

2009 issue of the new research journal, *Disease Models & Mechanisms* (DMM), dmm.biologists.org/

Source: The Company of Biologists (news : web)