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Reversing fibrosis to treat cirrhosis

New research may offer a way to reverse liver cirrhosis, the chronic scarring that impairs liver function and causes up to 800,000 deaths annually worldwide. Studies in mice focused on blocking a protein called ribosomal S-6 kinase (RSK), which is involved in scar formation as part of the body's natural healing response.

Martina Buck and Mario Chojkier of the University of California at San Diego carried out the studies using mice with severe liver fibrosis induced by the liver toxin carbon tetrachloride. Mice that were treated with a RSK inhibitor, while still being exposed to the toxin, did not develop further liver fibrosis and in fact experienced some regression of the damage that had already been done (*PLoS One* **2**, e1372; 2007). "Our latest finding proves that we can actually reverse the damage," stated Buck. In contrast, other mice that were given the toxin but not the inhibitor showed signs of continuing damage.

These results may hold promise in the future for treating liver cirrhosis as well as other conditions that feature excessive scarring, such as viral hepatitis, pulmonary fibrosis and even scarring related to burn injuries. The ability to reduce fibrosis would also decrease the incidence of primary liver cancers, since most of these are secondary to cirrhosis.

Reprogrammed skin cells treat sickle cell anemia

Recent studies have shown that mouse and human fibroblasts can be reprogrammed into a pluripotent state. A group of scientists used these induced pluripotent stem (iPS) cells to treat mice that were engineered to carry the defective human gene that causes sickle cell anemia. The study, led by Rudolf Jaenisch of the Whitehead Institute for Biomedical Research (Cambridge, MA), is the first to prove the therapeutic applicability of iPS cells.

The researchers generated iPS cells by infecting skin cells of a mutant mouse with retroviruses that activated pluripotency genes (*Science* **318**, 1920–1923; 2007). They then corrected the defective gene in the iPS cells and differentiated them into healthy hematopoietic progenitor cells, which they transplanted into diseased mice. This treatment corrected the disease and reversed the symptoms of the sickle cell defect.

Although many obstacles must still be overcome before iPS cells can be used in humans, the team's results help to reinforce the idea that these cells may one day be able to replace embryonic stem cells as therapeutic agents. Embryonic stem cells are problematic not only because of ethical controversy, but because of the risk that recipient and donor cells will be immunologically incompatible.

Overcoming fragile X

A team of researchers has successfully corrected symptoms of fragile X syndrome in mice. Fragile X, which is caused by a mutation of the gene *FMR1* on the X chromosome, is the most common form of heritable mental retardation and is the leading identified cause of autism.

The research, led by Mark F. Bear of the Picower Institute for Learning and Memory at the Massachusetts Institute of Technology (Cambridge), tested a theory that Bear proposed in a previous study: that many symptoms of fragile X result from unchecked activation of metabotropic glutamate receptors, including the receptor mGluR5.

The team generated a line of mice lacking the functional homolog of the human gene *FMR1*. These mice, which serve as a useful model for fragile X syndrome, were crossed with a line of transgenic mice with reduced mGluR5 expression (*Neuron* **56**, 955–962; 2007).

The researchers then examined several mouse phenotypes associated with common symptoms of the human disorder, including abnormalities in the dendritic spines, seizures and selective impaired cognitive function. Many of the symptoms present in the mouse model for fragile X were corrected in the double mutant mice.

These results may have profound implications for treatment of fragile X syndrome and autism in humans.