Liver regeneration may be simpler than previously thought

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The way the liver renews itself may be simpler than is commonly assumed for other organs. New what scientists had been assuming. A new study, appearing in the April 13 issue of *The Journal of Biological Chemistry*, provides new information on the inner workings of cells from regenerating livers that could significantly affect the way physicians make livers regrow in patients with liver diseases such as cirrhosis, hepatitis, or cancer.

"The human liver is one of the few organs in the body that can regenerate from as little as 25 percent of its tissue," says Seth Karp, assistant professor of surgery at Harvard Medical School, Boston, and main author of the study. "It is not known how the liver does it, but our results provide some details of what makes the liver so unique."

Although organ regeneration has been observed in many animals, the details of how it happens at the cellular level are still not completely understood. So far, scientists have shown that cells that participate in tissue regeneration behave as if they were part of a growing organ in an embryo. In other words, the cells act as if the liver is growing, as do other organs in a developing embryo.

Many of the proteins that induce organ regeneration have been identified and scientists are now trying to make organs regrow by stimulating these proteins. Regrowing livers this way would be especially useful for patients whose livers are so damaged – say, by a tumor that has spread to most of the liver – that a large part would be removed. Unless such patients receive the right amount of liver transplant from an organ donor, they do not always survive. Quickly stimulating the growth of the remaining portion of their liver could be their only chance of survival.

To investigate how the liver regenerates, Karp and his colleagues set out to determine which proteins are involved in the regenerating cells. The scientists were also interested in testing whether regenerating cells behave like embryonic ones, as processes may explain why the liver is so uniquely capable of renewal and repair after injury, the scientists thought.

Karp's team considered two samples of mice. The first consisted of embryonic mice at various stages of development while the second was composed of adult mice to which two-thirds of their liver were removed. Using techniques such as DNA microarrays – which determine which genes are active in a cells – and software programs that analyze the collected information, the scientists listed all the proteins that help the cells grow and proliferate in both samples.

The results were unexpected. The researchers noticed that only a few proteins were common to both processes. Proteins called transcription factors, which affect DNA in the cell's nucleus, were highly involved in the development of embryos' livers but not in adult liver regeneration. Instead, proteins that help cells proliferate were active in both the developing and regenerating livers.

These findings showed that a regenerating liver does not behave as a developing embryo. Instead, regeneration could actually be only due to an increase in cells that multiply through regular cell divisions, a process called hyperplasia.

The new results may also have important medical implications. Transcription factors are known to be more difficult to manipulate than the other identified proteins. Since the transcription factors were not present in regenerating livers, it might be easier to stimulate liver regeneration by only activating the other identified proteins.

"These results are very encouraging," Karp says. "Not only did we discover that the number of proteins involved in liver regeneration is relatively low, but they don't include transcription factors, so we may be closer to being able to stimulate liver

regeneration than we thought."

The next step will be for scientists to understand whether the regenerating cells are stem cells. Studies have shown that adult stem cells are involved in the repair of many organs, but in the case of the liver, the cells repairing it through regeneration may simply be regular cells, not stem cells.

"We think that the liver regrows through a relatively simple process, which could explain its prodigious ability to repair itself," Karp says.

Source: American Society for Biochemistry and Molecular Biology