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Master at Regeneration: Learning Why the Liver Thrives

Although one may well marvel at the liver's remarkable ability to mop up alcohol and other toxins from the blood, when it comes to regeneration, the liver is the supreme star. As much as two-thirds of the liver can be removed surgically, but the remaining liver cells will piece together a fully functioning organ in just a few weeks. Researchers have now found one clue that may tell them why the liver is a master of regeneration.

In studies with developing mice, they have found that an embryonic liver will reach its full size even when there is a reduction in the number of liver progenitor cells. Meanwhile, the size of the pancreas, the liver's next door neighbor, appears to be directly affected by the number of embryonic progenitor cells. The smaller the pool of progenitors, the smaller the pancreas will be, according to the new study.

The research team, led by Howard Hughes Medical Institute investigator Douglas A. Melton, published its findings in an advance online publication on January 28, 2007, in the journal *Nature*. Ben Sanger and Akemi Tanaka, who are in Melton's laboratory at Harvard University, are co-authors of the research article.

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- Douglas A. Melton

Melton's team undertook the studies hoping to learn more about the forces that regulate the growth of organs. "It was known that the liver is very good at regenerating in adults, and the pancreas is very bad at regeneration," he said. "And that made us wonder what determines the size of these organs and why is the body so good at compensating for any loss of the liver but so bad

at rebuilding the pancreas? Since the liver and the pancreas are 'next door neighbors' during embryonic development, that made the mystery even more intriguing. Why does one compensate so well and the other so poorly?"

In their experiments with mouse embryos, the researchers used two genetic techniques to regulate the number of progenitor cells in the developing pancreas. In one set of experiments, they killed off pancreatic progenitor cells to reduce their number. In another, they added back cells in a strain of mice that is deficient in pancreatic progenitor cells. In both cases, the researchers found that the number of progenitor cells governed the ultimate size of the organ: fewer cells resulted in a smaller pancreas.

In contrast, when the researchers killed off liver progenitor cells in the embryos, the animals' livers rapidly recovered to their normal size. "We really don't understand the basis of this growth compensation," said Melton. "It could be that the liver cells are constantly paying attention to their neighbors, saying in essence 'do we have enough cells here to function optimally?' Whereas the pancreas might just designate each progenitor to produce one little 'brigade' of cells, and it doesn't even care how many other ones are nearby."

Melton admits that the experiments raise more questions than answers. Lately he's been asking himself whether it might be possible to classify organs into two groups based on their growth capacity from pools of progenitor cells. "There are organs like the liver, blood, and skin that are very good at compensating for loss. For example, everyone knows that when you donate blood your body tops the supply back up to the right amount. And, of course, when our skin is wounded, it makes new skin," Melton said.

"But then there is another class of organs, like the pancreas, which has at most a very limited capacity for compensation and in which the number of progenitors is quite important in determining the final size of the organ."

Moving from the theoretical to the practical, Melton said his group's study could have implications for efforts to use stem cells therapeutically to regenerate tissues or organs, said Melton. "Blood, liver, and skin all have adult stem cells," he said. "It could be that organs that don't have adult stem cells are just not very good at replenishing themselves. Our studies were on the pancreas, but my expectation would be that organs like the kidneys and the lungs—both of which do not regenerate themselves—may fall into this same class."

From Melton's point of view, the new findings are only the beginning of efforts to unravel the cellular and genetic properties that regulate organ size. "We would like to figure out how progenitor cells know how many cells to make in their subsequent development," he said. "Do they have some counting mechanism that predetermines the number of times they can divide, and if so, what is it? Also, is there some external signal, like the amount of

sugar in the blood or the amount of oxygen the animal receives? Right now, we haven't a clue about these mechanisms or the genes involved.”