CELL BIOLOGY

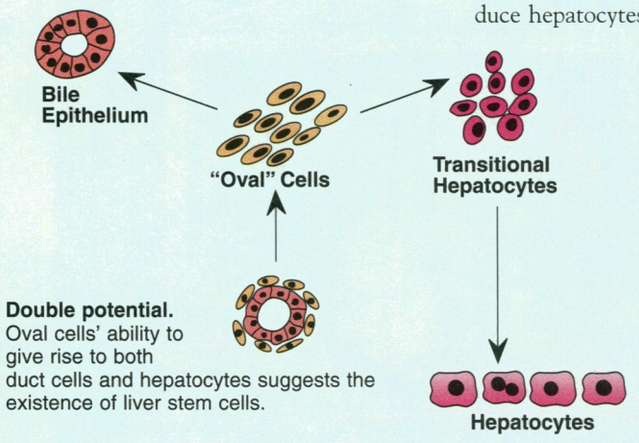
The Search for Liver Stem Cells Picks Up

In ancient times, the liver, not the brain or heart, was considered the seat of life and ruler of the emotions. Indeed, it was thought so central to life that some seers would sacrifice animals and examine their livers to check for omens. Such beliefs have long become amusing footnotes to history, but to a small group of cell biologists and pathologists, the liver remains fascinating, albeit for a more scientific reason: They believe they are on the verge of isolating cells that can give rise to the two primary cell types of the adult organ, the bile duct cells and the mature hepatocytes.

That would be a turning point in liver research, because for decades most experts on the organ didn't think such "stem" cells existed. But next week in New Orleans, researchers at Experimental Biology '93 (formerly known as the FASEB meeting) will gather for a symposium called "In Search of the Hepatic Stem Cell" that reflects a growing belief in the putative cells. "The evidence in 1993 is substantial that these cells exist," says pathologist David Safritz of the Albert Einstein School of Medicine, who will chair the symposium.

If that evidence is right, the work could have a major impact on the therapy of liver disease. Now the only way to treat people whose livers have been irreparably damaged by alcohol abuse, toxic substances, or cancer is with a liver transplant. But if they can get their hands on stem cells, physicians might be able to use them to reconstitute severely damaged livers. And liver stem cells may have potential for gene therapy as well. One of the liver's major functions is secreting proteins into the blood, and so genetically engineering liver cells to contain an active version of a defective gene might be a way of replacing a missing protein—one of the blood clotting factors whose deficiency causes the hemophilias, for example. Indeed, some researchers are already trying this with hepatocytes, but using stem cells may provide a more enduring treatment. "If you could repopulate the liver with stem cells that have a new gene, you have a long-term solution for a genetic defect," says Rhode Island Hospital pathologist Douglas Hixsom.

Liver experts had in the past rejected the notion that the adult liver maintains a stem cell population because they didn't see any need for such cells. Compared to other vital organs, the liver is remarkably resilient. As much as two-thirds of a rat's liver can be removed, and less than 2 weeks later it will be whole again, happily detoxifying noxious chemicals, storing vitamins and minerals, and secreting substances like bile, which aids in fat digestion. When such damage happens, mature hepatocytes break out of their normal quiescence and proliferate rapidly, a process that still persuades many researchers that stem cells are unnecessary. "As far as I'm concerned, there's no basis for a stem cell. What use is it?," argues University of Toronto pathologist Emmanuel Farber.



Double potential. Oval cells' ability to give rise to both duct cells and hepatocytes suggests the existence of liver stem cells.

SOURCE: SNORRI THORGEIRSSON ILLUSTRATION: H. BISHOP

But evidence hinting at the existence of stem cells came as long ago as the 1950s from studies—many of them, ironically, by Farber himself—of rats fed liver carcinogens. "The cells that formed the tumors did not look like hepatocytes," explains Brown University pathologist Nelson Fausto. Instead, he says, they came from a proliferating population of oval cells, immature cells named for their distinctive shape and located around certain bile ducts. Since the resulting cancerous nodules contained cells that had features of both duct cells and hepatocytes, some researchers surmised that the bile ducts hid a population of cells from which both types could arise.

Proving that was difficult, however, because there was then no good way to trace how the oval cells arise in the liver or to follow their fates. That began to change in the late 1980s, when new evidence emerged that oval cells could give rise to mature hepatocytes as well as to duct cells. In 1987, for example, Snorri Thorgeirsson and his colleagues at the National Cancer Institute (NCI) showed that when they treated rats with a carcinogen that prevents hepatocyte proliferation and then removed part of the animals' livers, regeneration still occurred. By labeling oval cells with a radioactive compound, the researchers then showed that during liver regeneration these cells develop into what appear to be mature hepatocytes. When hepatocytes are suppressed, suggests Thorgeirsson, "there's another system that kicks in and is able to regenerate."

In the years since, additional studies have confirmed and extended Thorgeirsson's results, although Farber still takes issue with the idea that oval cells can ordinarily produce hepatocytes. "These are ductular cells and there is no evidence they are anything more," he says, contending that the oval cell proliferation caused by carcinogens is an aberrant phenomenon unrelated to the normal liver. Other researchers, however, disagree and have already started an intense effort to screen various cell populations, taken from normal livers, that might be oval cell precursors and thus stem cells.

In New Orleans, for example, Joe Grisham, a pathologist at the University of North Carolina in Chapel Hill, will discuss experiments that make use of the bacterial gene beta-galactosidase, a so-called reporter gene that allows researchers to tag cells and follow them and their progeny when transplanted back into animals. His research team was able to track cells that originated in the bile duct as they integrated back into the liver and assumed the size and nuclear structure of normal hepatocytes. A cautious Grisham would only call the cells "stem-like."

Yet even while Grisham and others work to isolate hepatic stem cells, a new argument has erupted among the researchers involved in the search. The question now dividing many is no longer whether stem cells exist, but what their exact role is in the liver. The majority support the notion of a facultative stem cell, a small dormant population of cells that multiply only when the liver suffers extreme damage that impairs the normal regenerative ability of mature hepatocytes. A minority, however, have embraced a "streaming liver" hypothesis, says Albert Einstein cell biologist Lola Reid, which suggests that the liver is similar to other organs like the skin and intestine in that it has an active stem cell population that continuously replenishes mature cells that have lost their ability to divide.

The evidence for this controversial theory is sketchy, however, and liver experts are having enough difficulties accepting the existence of a stem cell population, let alone an active one. There's much they still don't know, admit researchers. "I think you're going to see a lot of papers coming out in the next few years," predicts NCI's Thorgeirsson. Reid agrees: "This is a field in its infancy, but its going to snowball in the years to come."

–John Travis