REGENERATIVE BIOLOGY

The versatile and plastic liver

There is conflicting evidence about which cell type is responsible for liver regeneration following damage. It emerges that duct-like progenitor cells arise from hepatocytes after liver damage, a finding that reconciles previous data.

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Prometheus, a Titan in Greek mythology, is said to have been condemned by Zeus to have his liver plucked out by an eagle every day for eternity, only to have the organ grow back each night. In real life, as in the myth, the liver has remarkable regenerative potential, but the precise mechanism by which liver cells repopulate the tissue following damage remains unknown. Writing in *Cell Stem Cell*, Tarlow *et al.*[1] report that, following liver damage, transplanted liver cells called hepatocytes are converted into another liver cell type, the ductal progenitor cell, which then proliferates and differentiates back into a functional hepatocyte to replenish the tissue.

The liver is the largest internal organ in the human body, and is responsible for many metabolic and detoxification activities. It is composed mainly of bile-duct cells and hepatocytes, which work in conjunction with other, less-populous cell types. But the cell type responsible for repopulation of the tissue after damage has been an area of active debate.

Some studies[2,3] in mice have indicated that hepatocytes are the major drivers of liver regeneration. However, other studies in mice[4], rats[5] and zebrafish[6] have found that, following blockade of hepatocyte regeneration, damage activates a response that involves progenitor cells[7]. These liver progenitor cells have been shown to derive from ductal cells[7] or to arise from an as-yet-unidentified cell[8,9]. To add complexity to this already conflicting set of reports, a stream of bile-duct cells with progenitor features is seen in almost all cases of human liver disease that involve cell loss[10]. Tarlow and colleagues sought to shed light on the issue by combining two gold-standard methods to assess stem-cell potential: cell transplantation and lineage labelling. In the latter technique, cell types are indelibly labelled and their descendants traced, even if they give rise to different cell types.

The authors first addressed the question of whether hepatocytes are the source of the progenitor cells that replenish damaged livers by using mice lacking the *Fah* gene, which encodes fumerylacetoacetate hydrolase. Hepatocytes lacking this enzyme accumulate intermediate metabolites and undergo programmed cell death. Because of this, transplanted wild-type hepatocytes have a selective advantage over host hepatocytes, and so can engraft — that is, successfully integrate into the host tissue — and repopulate the liver.

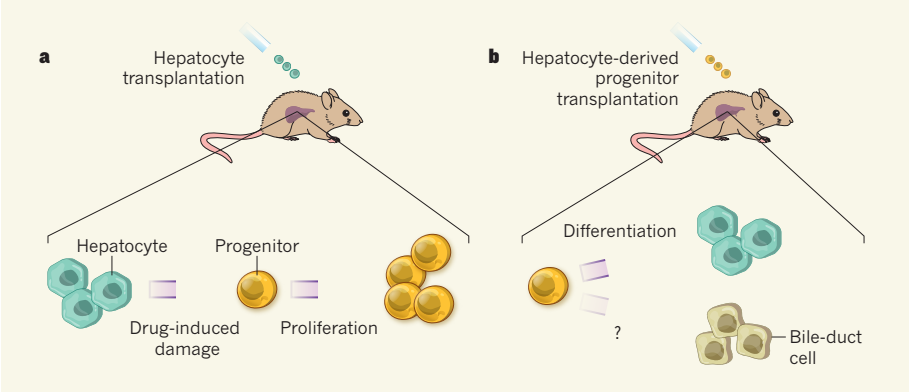

Figure 1 | Regeneration of the liver. The cell type that promotes liver regeneration following damage is a subject of much debate. **a**, Tarlow *et al.*[1] transplanted liver cells called hepatocytes into mice that were deficient in the enzyme fumerylacetoacetate hydrolase and so model liver disease. The authors then damaged the host liver and observed that the transplanted donor hepatocytes became progenitor cells with the characteristics of bile-duct-cell progenitors, which proliferated and replenished the liver. **b**, If these hepatocyte-derived, duct-like progenitor cells are taken from the host liver and engrafted into a second mouse, they can differentiate back into functionally mature hepatocytes and populate the liver. Whether they can also produce mature bile-duct cells is unknown.

Tarlow and colleagues transplanted hepatocytes labelled with a red fluorescent protein into *Fah*-deficient mice. Once the host liver had been repopulated with the red-labelled donor cells, the authors used toxic drugs to induce a type of liver injury that prevents hepatocyte proliferation and leads to the production of duct-like progenitor cells that repopulate the damaged area. They found that many of the duct-like progenitors were labelled red, indicating that they had arisen from the transplanted hepatocytes, in agreement with previous results in rats[11]. Then the authors isolated these duct-like progenitors from the damaged livers and showed that the cells could engraft and repopulate a liver in a second animal, giving rise to fully mature hepatocytes (Fig. 1). These results indicate that hepatocyte-derived, duct-like progenitors are at least partially responsible for repopulating the liver following damage.

The experiments raise questions about whether conversion between different cell states happens in undamaged livers, and whether transformation from hepatocytes to duct-like progenitors and back again is a common phenomenon in human liver disease. Tarlow *et al.* observed a similar conversion of hepatocytes into duct-like progenitor cells when they transplanted human hepatocytes into *Fah*-deficient mice, confirming observations from tissues derived from people with acute liver failure[12].

It is not known whether duct-like progenitors from humans or mice can convert into mature bile-duct cells because of a lack of markers to distinguish donor duct cells from those derived from the mouse host. One possible way around the problem would be to grow progenitor duct cells in culture, then fluorescently label and transplant the cells. This strategy has been successfully used in mice in a study in which duct-like progenitor cells that had been grown *in vitro* engrafted into the host mouse liver after transplantation, albeit at low efficiency[9].

Not all of the duct-like progenitor cells that arose following damage were labelled red, indicating that some were not derived from hepatocytes. Tarlow and co-workers did not assess the fate of this cell population. Do these cells make fully mature ducts after their engraftment? In humans, primary biliary cirrhosis and biliary atresia, which affect the biliary-duct system, are among the most common reasons both for liver transplants and for transplant rejection[13]. Therefore, identifying cells that can repopulate the bile-duct compartment is a priority. Could duct-like progenitors — those either derived from or independent of hepatocytes — be engrafted into mouse models of biliary diseases? Because *Fah*-deficient mice have a hepatocyte defect that does not allow duct engraftment, animal models of biliary disease will be needed to answer this question.

Part of the controversy over liver regeneration has now been reconciled. Tarlow and colleagues' finding that drug-induced damage causes hepatocytes to give rise to duct-like progenitors that then differentiate back into hepatocytes explains much of the conflicting evidence reported. Maybe Proteus, the Greek sea god who could mutate into different forms, is a more appropriate mythological reference for the versatile liver than Prometheus. ■

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NEUROSCIENCE

A three-dimensional neural compass

The discovery that the neural navigation system of the mammalian brain acts in three dimensions sheds light on how mammals orient themselves in complex environments. **See Article p.159**

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All mammals face the challenge of navigating in complex, three-dimensional (3D) environments, whether they are swinging from branch-to-branch in forests or burrowing underground tunnels. How does the brain maintain a sense of place and direction in 3D? In a beautiful study on page 159 of this issue, Finkelstein *et al.*[1] report that bats have an internal neural compass that tracks direction in 3D during both surface locomotion and flight.

The hippocampal–parahippocampal region of the brain contains four neural cell types that together make up the core of the mammalian navigational system: place, grid, border and head-direction cells. Place, grid and border cells provide information about position, distance and the geometry of the surrounding environment, respectively. Head-direction cells provide information about bearing in the environment — they are considered to be the brain's compass. The classical head-direction cell, discovered in 1984 in the dorsal presubiculum of the rat parahippocampal region[2,3], responds whenever the animal faces a particular direction in the horizontal plane (an azimuth).

Finkelstein *et al.* first recorded neural activity in the dorsal presubiculum of bats as the animals crawled upright on flat surfaces. The authors used a standard recording protocol for identifying head-direction cells in rats, but with one major technical advance — a tracking device that allowed them to resolve the orientation of the head in 3D. As with rats[2,3], they found many cells that responded to the animal's orientation in azimuth, but they also found cell types that responded to pitch (vertical orientation), roll and combinations of two or three axes. Relatively few cells responded to roll, and, perhaps not coincidentally, bats rarely rotate in the roll axis during flight. Therefore, the researchers focused primarily on azimuth and pitch.

Next, the authors inverted the bats. To understand why this is important, consider a typical landing manoeuvre in which the bat begins flying towards the eastern side of a cave, inverts itself and lands facing west (Fig. 1a). If head-direction cells merely respond to the orientation of the animal with respect to external landmarks, then when the bat passes through the point at which its direction in the horizontal plane changes from east to west, the population of active cells would instantly switch from those representing east to those representing west, resulting in an unstable cellular network. Surprisingly, Finkelstein and co-workers discovered that a cell that was tuned to the east when the animal was upright