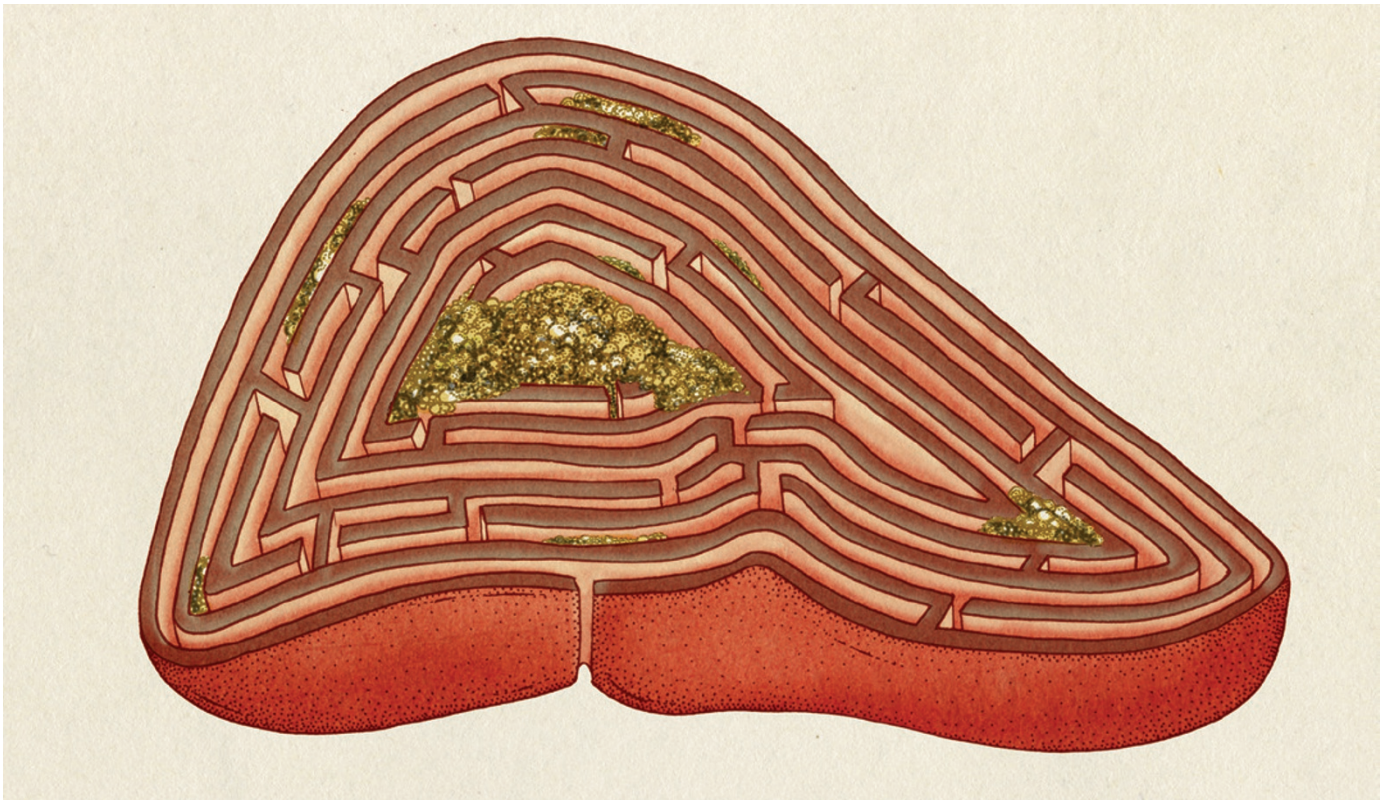

KATIE SCOTT

FATTY LIVER DISEASE

The liver labyrinth

Navigating the path that connects fatty liver disease to cancer has proved tricky.

BY BRANWEN MORGAN

The slimy-smooth, dark-red exterior of a healthy liver yields few clues about its complex nature. This 1.5-kilogram lump of tissue is so good at recovering from injury that it requires as little as one-quarter of its original bulk to fully regenerate. But the organ has its limits. Constant cell damage, such as that caused by a fatty diet, necessitates constant repair, providing the perfect setting for malignancy. Researchers are beginning to unravel how the transition to cancer occurs, with the aim of, eventually, finding more-effective ways to prevent it.

The body needs fat for hormone production, vitamin transport and insulation, and the liver stores and breaks it down in a tightly regulated process. The accumulation of too much fat, however, can result in 'fatty liver disease', and in some people this can develop into a condition called non-alcoholic steatohepatitis (NASH), in which sections of the liver become inflamed. NASH can be accompanied by scar tissue (fibrosis) that becomes thick and hard (cirrhosis), and a few cases (2–5% each year) progress to the most common form of liver cancer, hepatocellular carcinoma (HCC).

The primary causes of cirrhosis are still alcoholism and hepatitis infection (see page S12), but NASH-based cirrhosis cases are rising fast. "The prevalence of fatty liver disease has doubled during the last 20 years, which is perhaps not surprising given the diabetes and obesity epidemic," says Geoff McCaughan, director of the Australian National Liver Transplant Unit at the Royal Prince Alfred Hospital in Sydney.

Even more troubling than the rise in NASH is another trend that McCaughan and others have identified. "Fifteen per cent of our patients with fatty-liver-associated cancers don't have cirrhosis," he says. The causes of these cases are unclear. Deciphering the patterns underlying these conditions has therefore become one of the most pressing challenges for those studying the origin and prevention of liver cancer.

As many as one in three people in developed nations might have fatty liver disease, according to the World Gastroenterology Organisation, and the condition is one of the top causes of liver disease in Western countries. But it is unknown what pushes some of those people down the path to NASH, and others even further towards HCC. "There's a very strong link between NASH and HCC, but we don't yet have large studies with the level of confidence that we have for other aetiologies," says Lars Zender, a cancer researcher at the University of Tübingen, Germany. "We need data from large, prospective, epidemiological studies that follow patients with fatty liver disease through to tumour development."

Such studies, however, can take decades and require huge amounts of money and resources, and just diagnosing fatty liver disease in the first place is difficult. Abnormal blood tests can indicate that someone might have it, but the only accurate method for diagnosis is a liver biopsy — a complicated, invasive procedure that is still subject to sampling error.

Researchers assess the amount of fat in the liver on a scale from 0 to 3: grade 0 denotes a healthy liver in which less than 5% of liver cells, or hepatocytes, contain fat; grade 1 indicates mild fatty liver disease (5–33% of hepatocytes contain fat); grade 2 is moderate disease (33–66%); and grade 3 is severe disease (more than 66%). The higher the score, the higher the

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For more on non-alcoholic fatty liver disease, see:
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likelihood of inflammation and cancer.

But the development of NASH depends on more than just the accumulation of a specific percentage of fat. "There is a tipping point, but it is different for different people," says Helen Reeves, a hepatologist and cancer researcher at Newcastle University, UK. "There are people with a score of 3 who have no inflammation and people with a score of 1 who can have quite aggressive inflammation."

THE INFLAMMATORY TRIGGER

Researchers have long known that it takes more than just fatty hepatocytes to trigger an inflammatory response and a subsequent transition to cancer. But they are only just beginning to understand what happens at a molecular level. New studies suggest that signalling molecules in and around hepatocytes determine whether prolonged high fat levels will become harmful. These molecules are produced by various tissues, as well as by bacteria that live in the gut, and they can be transported to the liver through the blood (see page S14). Furthermore, fat cells under the skin and around internal organs also release some of the signalling molecules that promote inflammation and subsequent liver damage.

These signalling molecules do not just target hepatocytes — they can also affect a different set of liver cells called hepatic stellate cells. Stellate cells produce proteins that act as a scaffold for the liver; when overactive, they deposit excessive amounts of collagen fibre in the spaces between hepatocytes, thus restricting blood flow and placing further stress on the liver.

Hepatocytes extract fat that is circulating in the bloodstream, then repackage and re-release it into the blood, store it as droplets inside the cell or break it down and use it for energy. High hormone and fat levels throw some of these processes into overdrive, and the faster they occur, the greater the accumulation of by-products, especially the reactive oxygen species commonly known as free radicals.

"The problem is, if NASH hasn't advanced to cirrhosis, nobody is looking for cancer."

Free radicals react with and bind to many cell structures, preventing normal activity and putting a cell under oxidative stress. This stress causes hepatocytes to switch on self-destruction processes and activates local immune cells, exacerbating the inflammation. "If you have inflammation and oxidative stress, you are damaging your liver all the time," Reeves says.

This sustained assault turns the liver's capacity for repair, once its saving grace, into its undoing. Continuous fat uptake means that the liver is constantly engaged in a cycle of damage, inflammation and cell death. And the constant cell division as the organ attempts to regenerate drastically increases the likelihood of cancer-causing mistakes being made during DNA replication.

DAMAGE CONTROL

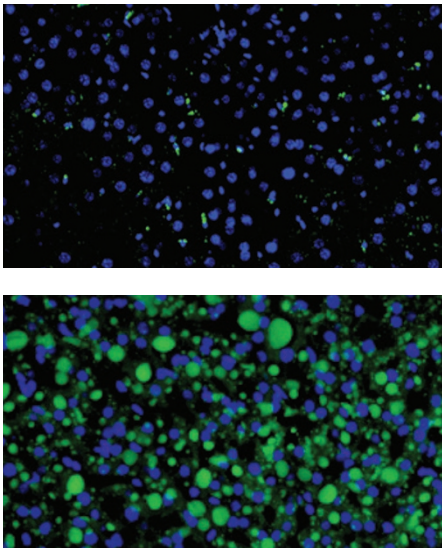
A better understanding of how cancer emerges from NASH requires a better monitoring system — one that does not rely solely on detecting cirrhosis. "The problem is, if NASH hasn't advanced to cirrhosis, nobody is looking for cancer," Reeves says.

Beyond that, researchers also need to pay more attention to the molecular profiles of diseased livers, says Zender. Examining tissue samples from affected and unaffected sections of someone's liver could show which genes or genetic pathways are triggering or perpetuating abnormal cell growth. Comparing the data with that of other patients with NASH could also reveal what cell-death-promoting molecular pathways are being activated in the presence and absence of cirrhosis. Such insight could help researchers to find future therapeutic targets against NASH, with the hope that treating the condition early will prevent progression to cancer.

Finding a way to treat NASH should have benefits beyond cancer prevention. Indeed, there is a strong association between NASH and cardiovascular disease, so a treatment for NASH could reduce the mortality due to this associated condition. Eventually, many patients with NASH require surgical removal of part of their liver or a liver transplant (see page S17), so treating the disease early could reduce the number of operations and thereby lessen the need for scarce donor organs.

The past few years have seen a substantial change in the NASH therapeutic landscape. The lack of animal models has stymied the development of new treatments for fat-related liver cancer[1] because normal mice typically develop liver cancer without fibrosis or cirrhosis as intermediary steps. But new mouse models could remove this hurdle. Cancer researcher Michael Karin at the University of California, San Diego, recently described a mouse model of NASH that progresses to human-like HCC in 40 weeks[2]. He and his colleagues then showed that interfering with a key inflammatory protein prevented NASH and the progression to liver cancer. The protein, called tumour-necrosis factor, is already targeted by a psoriasis and rheumatoid arthritis drug called etanercept; when Karin gave the drug to his mice, it prevented NASH and HCC. He hopes to convince companies that make anti-inflammatory drugs such as etanercept to test them in patients with NASH and NASH-driven HCC — failing that, he will organize such tests himself.

Thomas Burris, a pharmacologist at St Louis University, Missouri, feeds normal mice a diet similar to that of people in Western countries: full of saturated fat and cholesterol and high in sugar in the form of fructose (which is abundant in soft drinks). He then studies how the animals progress from mild to severe fatty liver disease to NASH. The mice develop a fatty liver within weeks, with NASH emerging over a couple of months. A number of the older NASH mice even progress to HCC.



THOMAS BURRIS AND KRISTINE GRIFFETT, SAINT LOUIS UNIV. SCHOOL OF MED.

Lipids (green) in liver tissue from normal mice (top) and mice with fatty liver disease (bottom).

Burris's mouse models have been used to find several therapeutic targets for the treatment of NASH, as well as drug candidates. One of these candidates, SR9328, has been shown to suppress fat production, eliminate inflammation and reverse fat accumulation in mouse livers[3]. But researchers do not yet know how effective this drug will be in the presence of fibrosis and cirrhosis, which do not develop in these mice. A phase II clinical trial of a drug with a similar mode of action — obeticholic acid — showed the medication to be so effective that its developer, Intercept Pharmaceuticals, based in San Diego, California, halted the trial early.

The need for therapies such as this is dire: current global projections suggest that in some countries NASH will overtake hepatitis as the main need for liver transplantation by 2025. The increase in NASH is also likely to lead to a rise in rates of HCC, but researchers are still unsure of the mechanisms — genetic or otherwise — that trigger the progression to cancer[4]. "I'm sure we'll know the answer in 20 years' time, but we don't know it now," Reeves says. ■

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