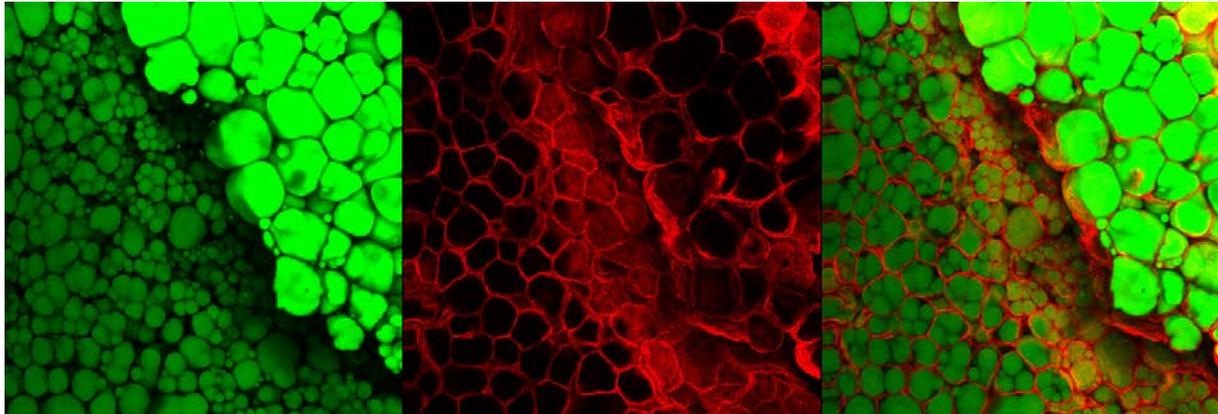


Taking out the NASH

Newsweek has called NASH “the 21st century’s looming public health threat.” Mirroring the obesity epidemic, nonalcoholic steatohepatitis — also known as nonalcoholic fatty liver disease — affects up to 25 million adults in the United States, and many will learn of the danger only when liver failure is imminent.

Jiandie Lin, Ph.D., a faculty member at the University of Michigan Life Sciences Institute, explains how he and his lab have been investigating the molecular mechanisms underlying the development and progression of NASH, and opportunities they have uncovered for potential new treatments. →



Immunofluorescent staining of brown and white fat cells.

Q: What is NASH and why is it so bad?

A: NASH is a more advanced form of nonalcoholic fatty liver disease. Not only do people who have NASH have a buildup of fat in their livers, it's reached a point where they experience inflammation, fibrosis and liver injury. Having NASH puts you at an increased risk for end-stage liver disease, cirrhosis and liver cancer — for which we really have no effective treatments.

NASH is closely tied to the obesity epidemic and metabolic disorders. About 30 percent of the Western adult population has fatty liver disease, and of those, about 20 percent develop NASH. It's also becoming increasingly prevalent in the pediatric population.

Q: What are the challenges for working on NASH?

A: There are two main problems. One is figuring out why fat accumulates in the liver.

There's been a lot of work done to figure out how fat accumulation in the liver is regulated. The liver is very interesting and complicated because it can synthesize fat, it can take up fat, it can burn fat, and it can also ship fat back to muscle or fat tissue for use. Disruptions within each of these different processes could lead to abnormal fat accumulation.

The other big question is why some people progress into NASH while others stay relatively healthy. What controls that transition? That's what's really important clinically. What determines this transition is going to really be important for how we might approach treating this disease.

There are many aspects to this transition, but ultimately it's about when liver cells start dying. And that generates this whole slew of problems like inflammation and fibrosis.

Q: What causes the cells to die?

A: That's the million-dollar question! There are a lot of theories. Oxidative stress could cause cell death, or inflammatory insults, or our immune systems could also help to kill hepatocytes that the immune cells can see are not healthy. The liver also receives blood from the gut which contains endotoxins, bacteria and so forth, and those materials may also help kill cells. Probably it's a complex combination of multiple stresses. It will be interesting and important to figure out how we can keep the cells healthier.

Part of the problem is that there's no easy way to detect NASH at the moment. You can't just draw blood from someone and say, "OK, you have NASH" or "You don't have it." You have to take a liver biopsy — and that makes it very challenging to do a large population study to look at the genetic differences in people with fatty livers who get NASH versus those who don't.

Q: When did you start studying NASH?

A: It's been about 15 years now. When I was a postdoc back in Boston, we studied nuclear hormone receptors. These are the proteins that can sense metabolites and serve as nutrient-sensitive regulators of gene transcription. Many aspects of lipid metabolism are regulated by these nuclear hormone receptors.

So at that time, I got interested in this area. Not only in the liver, but in adipocytes — fat cells. After I moved to Michigan, my research focused in on the liver and hepatocyte regulation.

There were a couple of findings along the way that moved us along this path. We developed a whole-genome functional tool to reveal key regulators of fat oxidation in the liver. And we found a molecule called BAF60a that is very important for the control of the fat oxidation program in liver cells.

More recently, we've been studying a protein called Neuregulin 4. It's a fat-derived hormone that acts on the liver, and it's able to restrict *de novo* lipogenesis — so, it really slows down new fat synthesis in the liver. And, our more recent work showed that this hormone is critically important for protecting mice from diet-induced liver injury in experimental NASH models.

Q: What's next?

A: The main focus in the pharmaceutical world has been on figuring out how to reduce the fat load in the liver. I think this is a valid idea, and there are a lot of candidates out there. A different approach is the one we're most interested in — therapeutically targeting path-

ways that affect the transition from a fatty liver to NASH. We are currently exploring the potential of targeting Neuregulin 4 as a new NASH therapy. 



Researchers aren't sure why some people develop NASH while others don't.