Intermittent fasting spurs proliferation of liver cells in lab mice, study finds

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Intermittent fasting—abstaining from eating for lengthy periods of time—spurs liver cells in laboratory mice to divide rapidly, according to a study led by researchers at Stanford Medicine. The finding challenges the long-standing belief that cells in the adult liver divide rarely and, when they do, primarily to repair damage to the organ. It is also the first

to show an immediate effect of diet on liver cell biology.

"One of the most defining characteristics of the adult liver has been that it is fairly stable in terms of cell turnover," said Roeland Nusse, Ph.D., professor of developmental biology. "But we found the turnover of cells in the liver goes up dramatically after several periods of 24-hour fasting followed by refeeding. Interestingly, this type of diet mirrors the natural diet of wild animals and of early humans, before the development of agriculture, when there were periods with scarce or absent food."

It's not known what, if any, effect the increased cell replication has on the health of the animals. But the finding implies that liver biology is more dynamic and responsive to dietary changes than previously believed, and it raises the question as to how other diets might affect its biology.

Nusse, who is the Reed-Hodgson Professor in Human Biology and the Virginia and Daniel K. Ludwig Professor in Cancer Research, is the senior author of the study, which was published online Jan. 31 in *eLife*. Former postdoctoral scholar Abby Sarkar, Ph.D., is the first author of the research.

The liver's job

The liver is one of the largest organs in the body, weighing about 3 pounds in an adult human, or roughly 2% of one's body weight. In mice, it accounts for nearly 5% of body weight. The liver removes toxins from the blood for excretion, and it converts the food we eat into nutrients the body can absorb.

"Abby Sarkar wondered if an organ like the liver that is so involved in digestion would exhibit altered patterns of cell divisions, or turnover, when an animal's diet changed," Nusse said.

Laboratory mice typically have unlimited access to food at all times. But for these experiments, Sarkar withheld food from the animals for 24 hours, then allowed them to feed freely for 24 hours before another fast of 24 hours. She then analyzed cell division in the animals' livers after one week and three weeks of the intermittent fasting diet and compared it with that of animals that had been fed normally.

"We saw that the turnover of cells in the liver went up fairly dramatically shortly after refeeding began," Nusse said. "There were many more new cells than in animals that had been fed on a standard diet. This was very exciting."

The liver's role in metabolism means that the ratio between the weight of the liver and that of the body must remain constant to allow the organ to function efficiently. This is the reason the liver will regenerate to its normal size if a portion of it is removed due to injury or surgery.

Sarkar found that the cell division she observed was sparked by a decrease in the ratio of liver to body weight in the study animals after a week of intermittent fasting. She also learned that most of the cell division was localized to liver cells near the central vein of the organ.

Further investigation identified two molecular pathways responsible for maintaining appropriate liver size in the fasted animals. One is a growth factor called fibroblast growth factor, or FGF, that is produced by the intestines and travels throughout the body; another, a family of proteins called Wnts, is crucial to embryonic development and the growth and maintenance of many tissues. Wnt proteins are secreted by endothelial cells in the central vein, but, unlike FGF, they travel only a short distance. The two signals overlap on liver cells near the central vein, called pericentral hepatocytes, to stimulate their division after fasting.

"Interestingly, the Wnt pathway is not affected by intermittent fasting,"

said Nusse, who identified the first Wnt protein in 1982, "but the production of FGF is. Intermittent fasting or other changes in the food supply stimulate the production of FGF, which circulates to the liver. It wakens the liver cells from resting, then Wnt proteins give those near the central vein the signal to divide."

Sarkar next tested the effect of intermittent fasting in mice that had been genetically engineered to be unable to respond to either the FGF signal or the Wnt signal. In that phase of the research, "The effect of intermittent fasting was attenuated," Nusse said. "The cells more or less lost their ability to divide. This is a very strong indication that you need both these signaling pathways to see this effect of fasting on cell replication."

The researchers don't know whether the increased cell proliferation in the liver due to fasting has health benefits. But it's an intriguing look into how dietary changes can affect one of the largest organs in the body. They are now planning to extend their studies to include other types of diets, including ketogenic or high-fat.

"I wouldn't recommend that people start intermittently fasting to improve their liver health," Nusse said. "But it's an exciting observation—it shows that the idea that the liver is a tissue that turns over slowly should be taken with a grain of salt."

More information: Abby Sarkar et al, Intermittent fasting induces rapid hepatocyte proliferation to restore the hepatostat in the mouse liver, *eLife* (2023). DOI: 10.7554/eLife.82311

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