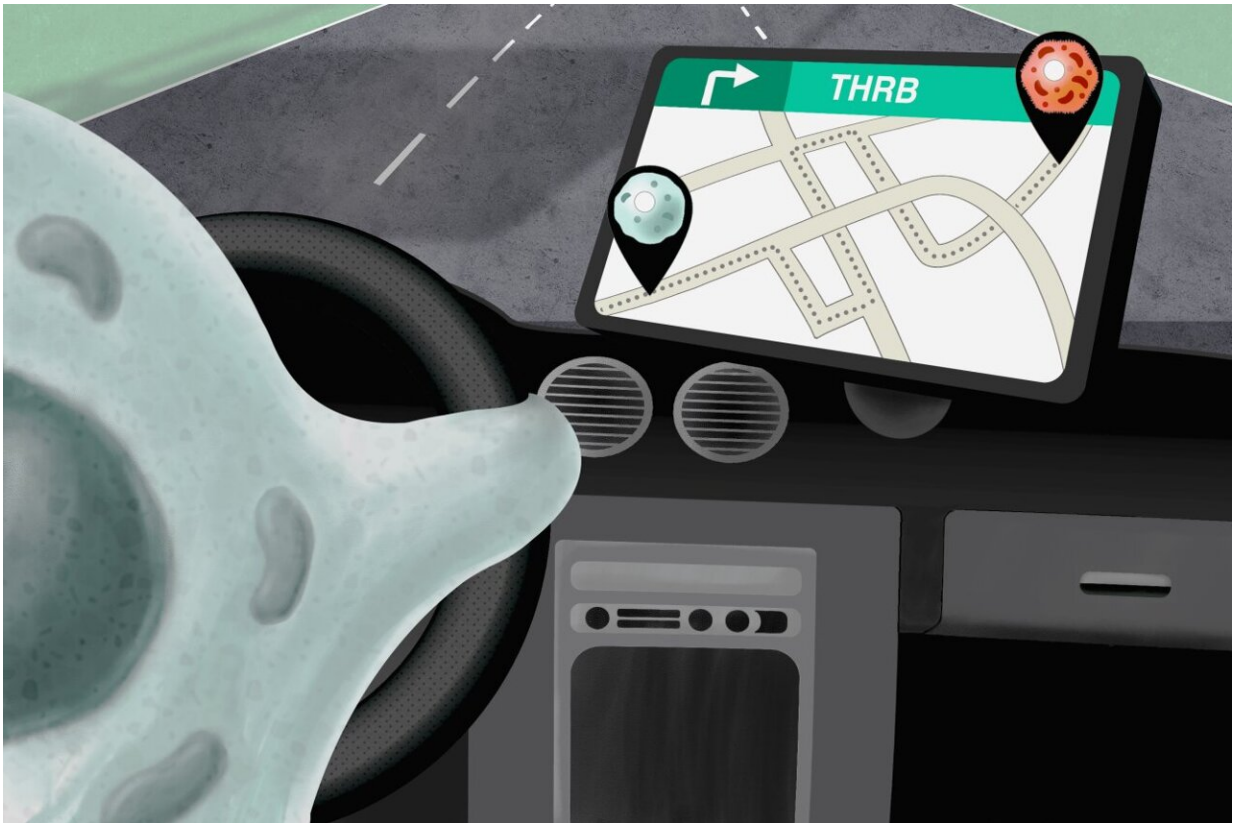


# Thyroid hormone found to be a missing ingredient in lab-made liver cells

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Thyroid hormone receptor beta (THRB) helps an immature liver cell get to its destination, a mature state. Credit Andrew Tubelli

Stem cells are the versatile building blocks from which every cell type in the body—from neurons to skin cells to blood cells—is ultimately

descended. Researchers have also figured out how to turn stem cells into different cell types in the lab, which has been helpful for studying health and disease in their normal cellular contexts, and could be used to generate cells for medical transplants. Whitehead Institute Founding Member Rudolf Jaenisch not only uses these cells in his research, but has spent much of his career discovering and improving the methods for making accurate laboratory models out of stem cell-derived cells.

One challenge on which Jaenisch's lab is focusing is how to eliminate the differences among cell types as they are found in the body and their stem cell-derived equivalents. In particular, they have found that stem-cell derived cells are often immature, more closely resembling the cells found in fetuses rather than in adults. These differences can make the cells less accurate research models and prevent them from being medically useful as functional transplant cells. Stem cells in the body receive complex cocktails of molecular signals as they transform into different cell types. The challenge for researchers lies in figuring out which of the many molecular signals in the body are relevant and then getting the recipe exactly right in their recreations.

Postdoctoral researcher Haiting Ma in the Jaenisch lab decided to tackle this problem for hepatocytes, the main type of cell in the liver. In work published in *Cell Stem Cell* on April 21, Jaenisch and Ma share their findings on why stem cell-derived [liver cells](#) resemble fetal liver cells, and what's needed to make them mature—including an important role for a thyroid hormone.

The liver filters everything that enters the body through the digestive system. It helps to store and modify nutrients, safely break down toxins and waste, process medications and more. There is still a lot to learn about how the liver functions and what goes wrong in a number of liver-associated diseases, and accurate stem cell-derived models will help with that research. Liver cells are also needed to treat end-stage liver disease,

and if researchers could mass-produce stem cell-derived liver cells that would function safely in an adult liver, this could help to meet the demand for liver cell transfusions.

For this study, Jaenisch and Ma grew liver cells from stem cells in two setups: a typical 2D culture, in which the cells were grown in a dish, and a 3D spheroid, in which cells that started out in the normal culture were then allowed to grow into three-dimensional balls of cells. The spheroids can be designed to mimic some aspects of the cells' natural environment in ways that a 2D culture cannot. In each case, the researchers exposed the cells to a carefully timed mixture of signals to prompt them to develop into liver cells. The researchers then analyzed cells from both the 2D and 3D cultures and compared them to primary liver cells, or cells from a body, using a variety of techniques to look for differences related to DNA and gene expression. They found that the cells cultivated in the 3D system were closer to cells from the adult body than those in the 2D system.

"The 3D culture not only contributes to maturation of the liver cells, but it can also be used to scale up production of the cells, which could be very useful for cell therapies in the future," Ma says.

However, both sets of lab-derived cells lacked important features of adult liver cells. The analyses pointed to one important missing factor in particular: In the adult liver cells, a hormone receptor called thyroid hormone receptor beta (THRB) binds to a number of places in the DNA. THRB then senses the presence or absence of thyroid hormones, and regulates a variety of gene expression processes accordingly. However, the researchers found that while the stem cell-derived liver cells made the right amount of THRB, something was preventing it from binding where it should and performing its function.

Normally, THRB has a partner that helps it bind to DNA, the [thyroid](#)

[hormone](#) T3. When the researchers added T3 to their 2D and 3D cultures, this led to more typical binding of THRβ, which in turn made the cells—especially the cells from the 3D culture—more closely resemble adult liver cells in a number of ways. Improved THRβ binding increased the expression of key liver genes, restored the activity of regulatory elements in the DNA that modify gene expression, and reduced the expression of a fetal liver gene. The researchers also gained insights into the molecules with which THRβ interacts and the mechanisms by which it affects liver maturation, painting a more complete picture of its key roles in liver cells.

Altogether, this work led to a better recipe for making adult liver cells from [stem cells](#) in the lab—using the 3D spheroid culture and adding T3. When cells developed with this approach were incorporated into the livers of mice, the cells integrated successfully and the liver maintained normal function long term.

The new and improved stem cell-derived liver cells are still not a perfect match for adult liver cells—the researchers have ideas about which missing characteristics they could tackle next—but the current cells' ability to seamlessly integrate into the liver, as well as indicators from the analyses that they would be good models for liver-associated diseases, suggest that they will be useful in a variety of projects.

"As we improve the authenticity of our stem cell-derived cell types, we open up new opportunities for research," Jaenisch says. "We can build more accurate models in which to study high-impact diseases, such as [liver](#) diseases, diabetes, and chronic viral infections, and using those models we can develop strategies for treatment and prevention."

**More information:** Haiting Ma et al, The nuclear receptor THRβ facilitates differentiation of human PSCs into more mature hepatocytes, *Cell Stem Cell* (2022). [DOI: 10.1016/j.stem.2022.03.015](https://doi.org/10.1016/j.stem.2022.03.015)

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