

PRESS RELEASE

Leibniz Research Centre for Working Environment
and Human Factors (IfADo)

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Gene modification enables more functional liver cells from stem cells

Liver cells are indispensable for research— for drug testing, to better understand diseases such as hepatitis, fatty liver, cirrhosis, or liver cancer and for development of future cell therapies. However, obtaining human liver cells from biopsies and donor organs is challenging. Therefore, research requires alternative sources of liver cells.

The perspective of obtaining bona fide hepatocytes (liver cells) from pluripotent stem cells offers enormous potential as an alternative resource. However, there has not yet been sufficient research into the processes that enable stem cells to acquire the traits of functional liver cells. A recent study by the Leibniz Research Centre for Working Environment and Human Factors in Dortmund (IfADo) now shows that the gene regulatory network of the DNA transcription factor CDX2 plays a decisive role in this problem.

Intestine and liver: cells show hybrid properties

In previous research works, the research group ‘Regulatory Networks of Stem Cell Differentiation (StemNet)’ led by Dr. Patrick Nell had demonstrated that current methods for deriving hepatocytes from stem cells resulted in so-called hybrid cells – cells that possess properties of both liver and intestinal cells.

“Hepatocytes and epithelial cells of the intestinal tract share a common origin in embryonic development, as the liver develops from a part of the primitive intestinal tract. In later development, the distinct cell types mature, which is controlled by varying levels of activity in gene regulatory networks that are associated with the respective cell types.” explains Antonia Thomitzek, doctoral student at StemNet. “Our limited understanding of and control over this process results in the generation of hybrid cells, which do not yet accurately reflect the function of physiological liver cells. “

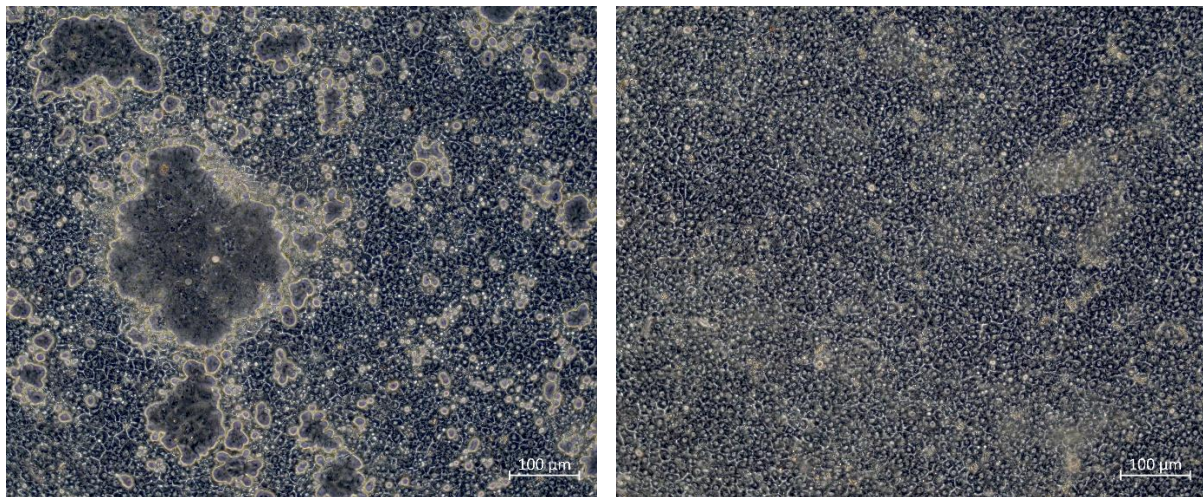
The StemNet research group has now discovered that the CDX2 network, which is unexpectedly active during the generation of liver cells from stem cells, plays a crucial role in establishing the hybrid phenotype of stem cell derived hepatocytes. By switching off CDX2 they were able to prevent the development of undesirable properties that are more typical of intestinal cells than hepatocytes.

Gene scissors enable functional liver cells

In their current study, the researchers used the ‘gene scissors’ CRISPR-Cas9 system to selectively target the CDX2 gene, which thereafter was left non-functional. CRISPR-Cas9 is a molecular biological method for cutting and modifying DNA at a selected site. If CDX2 is switched off using this method, the development of intestinal-typical characteristics is prevented almost entirely. Instead, the cells develop a clear liver phenotype. They show improved liver functions such as the correct formation of bile ducts and more efficient transport of bile acids. These characteristics are essential for functional liver cells.

“Understanding the influences of gene regulatory networks on the emergence of cellular identity is fundamental for developing reliable cell and tissue model systems based on stem cell technology” explains Dr. Patrick Nell. “This way, we advance research on suitable alternatives to animal testing and the responsible development of future cell therapies.”

The results are part of the ‘HyCell’ project, which is funded by the German Research Foundation with around 408,000 euros and will run until 2028. They mark a milestone in the development of stem cell technology, as more representative in vitro systems for liver research could make drug development more efficient and safer, and benefit applications in regenerative medicine.



Microscope images show that when the CDX2 network is active, liver cells derived from stem cells form unusually large bile ducts with intestinal enzymes (left photo). When CDX2 is turned off, the cells produce the typical bile ducts seen in liver cells (right photo). (Copyright: IfADO)



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Original publications:

Nell P., Thomitzek A., Feuerborn D. et. al. 2025. *Elimination of CDX2 restricts intestinal hybrid differentiation signatures in stem cell-derived hepatocyte like cells*. Stem Cell Research & Therapy 543. <https://doi.org/10.1186/s13287-025-04696-6>

Nell P., Kattler K., Feuerborn D. et. al. 2022. *Identification of an FXR-modulated liver-intestine hybrid state in iPSC-derived hepatocyte-like cells*. Journal of Hepatology. 77. <https://doi.org/10.1016/j.jhep.2022.07.009>

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