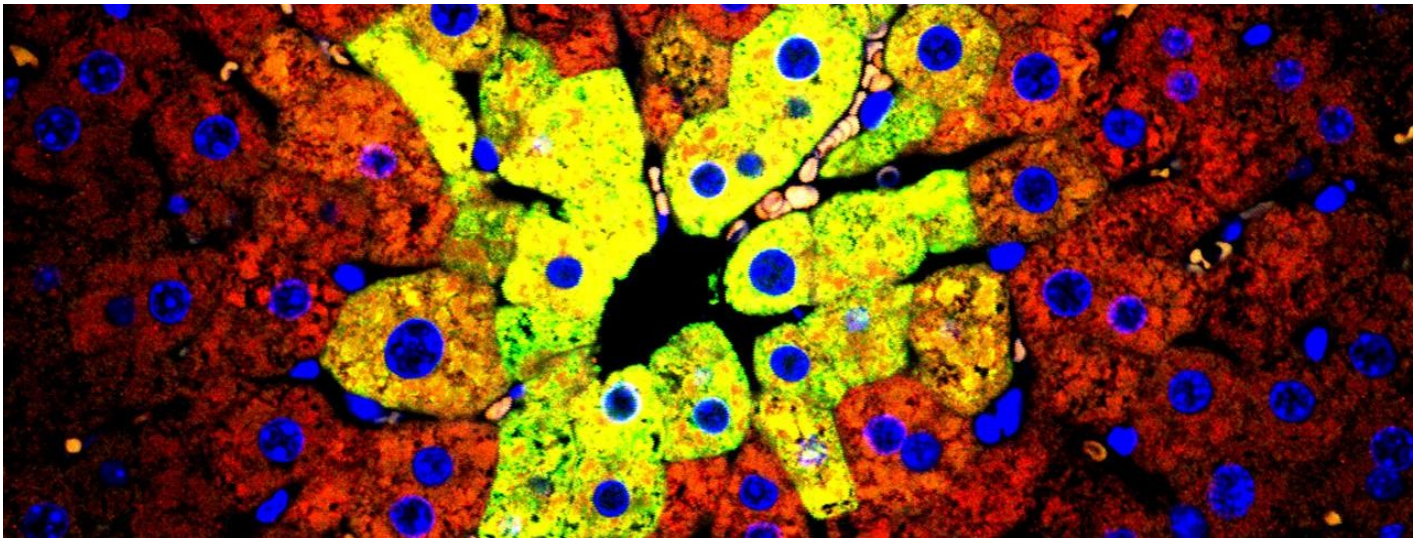
NOVARTIS

Factory foreman keeps liver's line workers on task



A complex protein module keeps the liver's biochemical factory running smoothly and at capacity.

By Elizabeth Dougherty | Apr 18, 2016

The human liver is a complex biochemical factory. It flows blood through an assembly line that produces sugars and fats and clears toxins, like an oil refinery, a food processing facility and a water treatment plant all rolled up in one.

Given all this complexity, a tour of the liver might sound involved, but in reality it's pretty straightforward. This is because the liver is little more than a repetitive three-dimensional grid of identical microscopic hexagons.

While the microstructure of the liver's chemical plant has been known for a long time, exactly what runs the factory has remained a mystery. But new research from Novartis has revealed that a complex module made of multiple proteins acts as a factory foreman that keeps the liver operating smoothly. Without this module, called RSPO-LGR4/5-ZNRF3/RNF43, liver cells stop doing their jobs. Further, the liver stops filling in empty spaces on the assembly line as workers drop out. In fact, without this module the factory doesn't even get fully built. The findings are described in a recently published *Nature Cell Biology* paper.

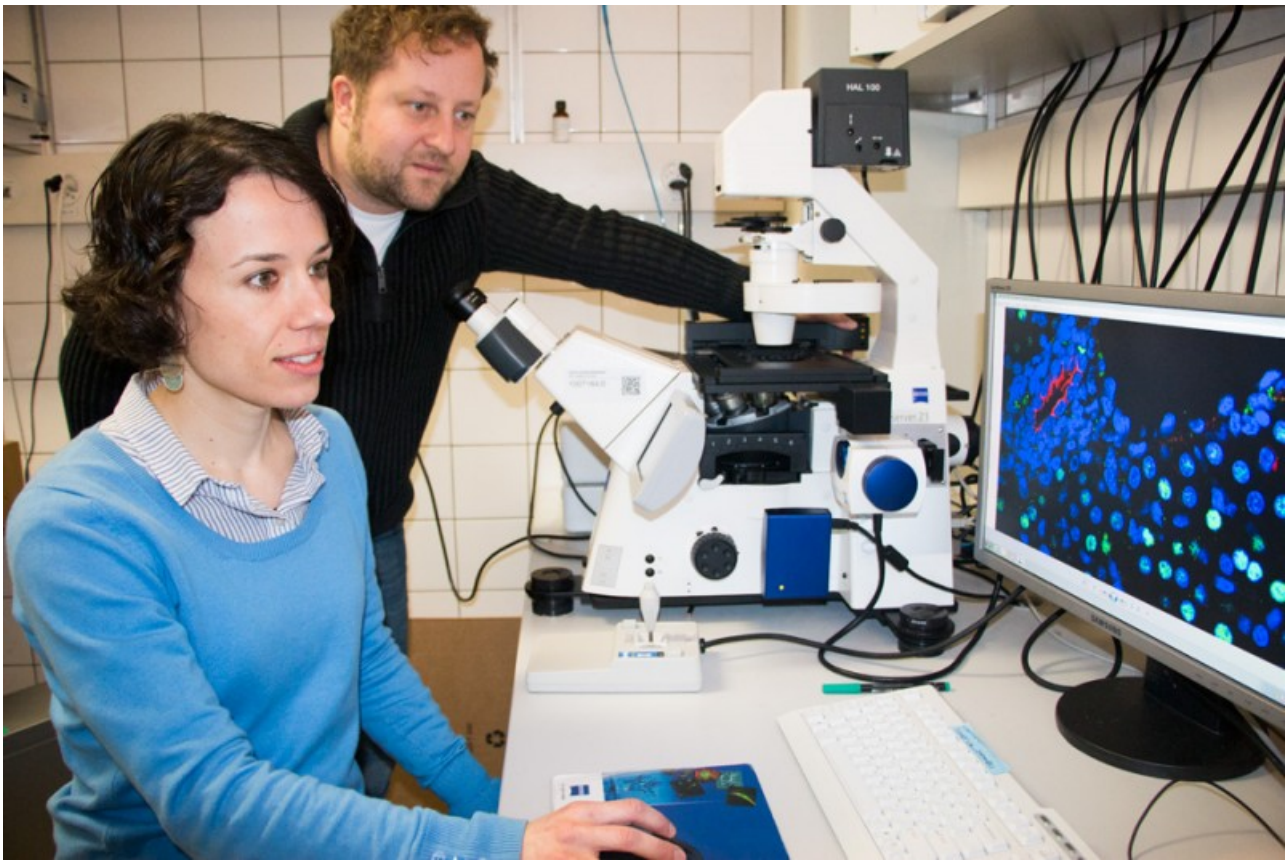
"Activating this pathway encourages liver growth, while reducing its activity slows it," says Jan Tchorz, an investigator in the Developmental and Molecular Pathways group at the Novartis Institutes for BioMedical Research (NIBR). "These findings highlight the potential for the development of drugs that encourage liver cell proliferation to improve liver regeneration or that slow growth to treat liver cancer."

The Novartis team, led by Tchorz, began looking at this module because proteins in it, such as LGR4/5, are seen in cells with regenerative capabilities in other tissues. They were also interested in the division of labor inside the liver. Inside each of the liver's tiny hexagons, called lobules, is a micro-factory in which hepatocytes, liver cells that act as factory line workers, separate into three zones that perform a series of distinct chemical manufacturing and processing jobs.

The team started by knocking out LGR4/5 in the livers of mice. To their surprise, knocking out LGR4/5 impaired the formation of the liver lobule microstructure and the development of specialized metabolic

capabilities in liver cells. In later experiments, the team engineered mice in which the factory foreman module could be activated with injections, such as injections of R-spondin (RSPO), or de-activated. When the foreman was activated, liver cells gained specialized metabolic capabilities, but when deactivated, those capabilities were lost.

“It was as if, without the factory foreman, these workers forgot how to do their jobs,” says Lara Planas-Paz, a postdoctoral researcher in Tchorz’s group. “The cells were still there, but they lost all their metabolic enzymes.”2



Postdoctoral researcher Lara Planas-Paz and Investigator Jan Tchorz discover what runs the liver’s complex biochemical factory. Photo by Marta Sanchez-Oro

The team also found that the module controls liver size. Not only did mice without LGR4/5 develop smaller livers than control mice, but also in adult mice in which livers were partially removed, those without LGR4/5 grew back smaller livers than control mice. Similarly, in adult mice in which the module could be activated and deactivated, liver growth increased with activation, and slowed with deactivation.

These findings provide researchers with a key to learning more about how the liver works and could provide insights into new therapeutics to treat liver damage caused by toxins or disease. A better picture of whether and how this module controls the regenerative capacity of the liver could also provide clues about how to encourage liver regeneration in damaged livers, or to stop abnormal growth in liver cancer.

“The therapeutic potential might not specifically be about this module,” says Chinwe Ukomadu, a senior translational medicine expert at NIBR. “Our thinking continues to evolve on the processes that control liver metabolism, regeneration and repair.”

In terms of liver regeneration, the Novartis team showed that it isn’t specialized cells that respond to the call for growth. Liver cells have highly specialized metabolic functions depending on where they are in a lobule, but when it comes to producing new line workers, all liver cells are ready to fill the need. “We found that cells in all three liver zones had the capacity for regeneration,” says Planas-Paz.

While this research does not point directly to potential new liver interventions, it does provide a way in.

“I learned about the liver’s microarchitecture years ago in medical school,” says Ukomadu. “But we still don’t completely understand how the liver operates and maintains itself. Whenever we learn new things about how this organ forms and operates, it allows us to dive in more deeply in search of something useful.”

Main image: The liver is a repetitive three-dimensional grid of identical microscopic hexagons called lobules. In the lobule shown here, a metabolic enzyme called CYP2E1 is stained red. A second metabolic enzyme called glutamine synthetase is stained green, and yellow shows cells with both enzymes. DNA is stained blue. Image by Lara Planas-Paz/Novartis.
