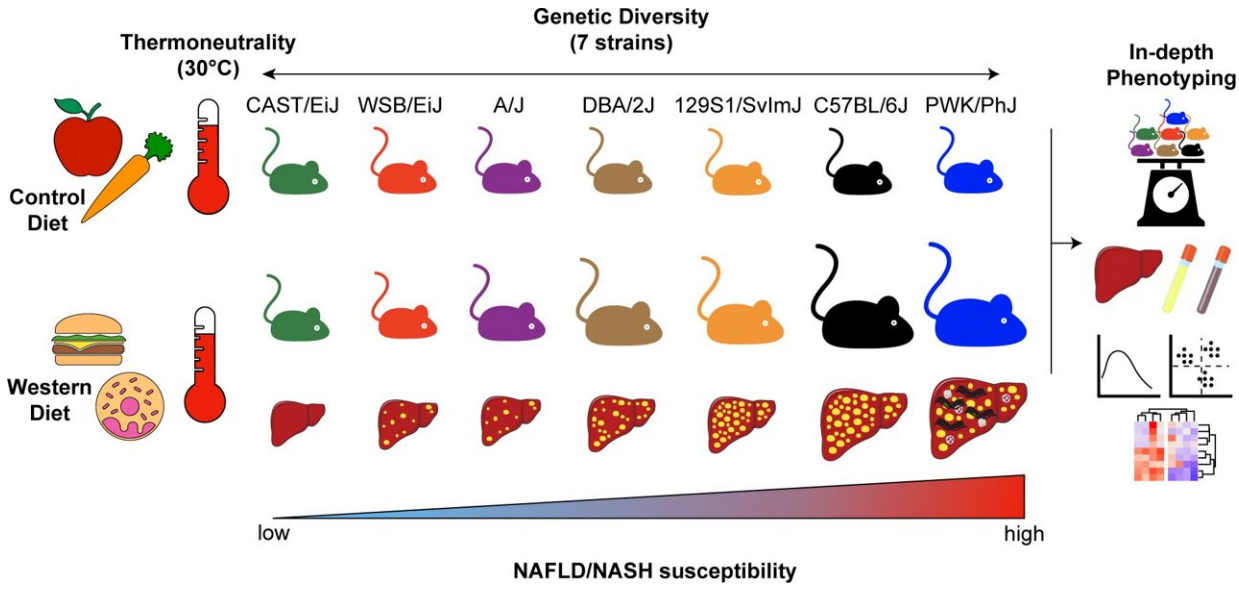
Finding the best models for liver and kidney disease

February 21 2023, by Nik Papageorgiou



Graphical abstract. Credit: *Journal of Experimental Medicine* (2023). DOI: 10.1084/jem.20221738

In two separate studies, researchers at EPFL have carried out extensive tests to develop the best mouse models for studying kidney and liver diseases. The findings provide crucial insights into both conditions, and are expected to open up new avenues of research and treatment.

"In these two studies we investigated how the mouse's genetic background affects the susceptibility to fatty liver disease and the

transition from acute kidney injury to chronic kidney disease," says Professor Johan Auwerx at EPFL. "These diseases affect millions of people worldwide and have currently no treatment, having faithful disease models will speed up drug development in these therapeutic areas."

From kidney injury to kidney disease

Kidney disease is a major global health issue, affecting over 20% of people worldwide with acute kidney injury and 10% with chronic kidney disease. Despite being largely preventable, kidney disease is both a direct cause of morbidity and mortality and a significant risk factor for cardiovascular diseases.

Auwerx's group, with scientists at Janssen Pharmaceuticals, carried out a study to establish the response of seven mouse models of kidney injury, and compare both their susceptibility to acute kidney injury and the transition to chronic kidney disease. The aim was to establish a baseline for the response of the mouse strains to kidney injury.

The approach uncovered a "strain-specific response", whereby one of the mouse strains was completely resistant to the transition from acute kidney injury to chronic kidney disease, while one strain, the so called "PWK/PhJ strain", was highly sensitive.

This particular strain of mice comes from wild mice as opposed to mice raised in the laboratory. Being genetically distinct from their lab counterparts, PWK/PhJ mice are valuable tools for genetic mappingof determinants of renal disease.

The sensitivity of PWK/PhJ mice, the study found, was linked to lower-than-normal mitochondrial function, persistent inflammation, and pronounced fibrosis—all of which accelerated the transition from acute

to chronic kidney disease.

By comparing the findings of this study with human kidney diseases, the researchers discovered critical metabolic changes that are common across species; specifically, that modulation of immune and mitochondrial pathways, including NAD+ metabolism, during the initial recovery was predictive of long-term remission.

Liver disease

In the second study, Auwerx's group and their colleagues at Janssen, focused on non-alcoholic fatty liver disease (NAFLD), the most prevalent chronic liver disease. NAFLD affects around 25% of people in the western world. NAFLD is really an umbrella term for a number of liver diseases that range from practically benign conditions all the way to severe non-alcoholic steatohepatitis (NASH), a progressive liver disease characterized by steatosis (fatty liver), inflammation and even liver fibrosis.

"Despite significant efforts to model human NASH in mice, good mouse models are still lacking," says Giorgia Benegiamo, the study's first author. "Here, we explored the susceptibility to NASH in mice from seven different genetic backgrounds, under a diet and environmental conditions that mimicked human lifestyle as much as possible."

The study found that, despite being exposed to the same environment, each mouse strain responded very differently. Once again, mice from the PWK/PhJ strain proved to be the most sensitive to NAFLD/NASH, and also the only strain to show progression to fibrotic NASH.

"We were surprised to find such a wide range of phenotypic responses in mice exposed to exactly the same metabolic challenges," says Benegiamo. "The most important outcome of our study is the

identification of a novel mouse model of NASH that closely mimics the human disease and that will be extremely helpful to develop and test novel therapeutic strategies."

The PWK/PhJ strain is a novel NASH mouse model that shows symptoms of the metabolic syndrome and develops liver steatosis, inflammation and fibrosis. It therefore successfully models several aspects of NASH in humans. At the molecular level PWK/PhJ mice develop severe mitochondrial dysfunctions.

"In both studies we found that mitochondrial dysfunction underlies disease progression, and identified very sensitive and very resistant mouse strains," says Johan Auwerx. "Having better models will speed up drug development for these diseases, which are huge unmet medical needs."

The research is published in the *Journal of Experimental Medicine* and *JCI Insight*.

More information: Giorgia Benegiamo et al, The genetic background shapes the susceptibility to mitochondrial dysfunction and NASH progression, *Journal of Experimental Medicine* (2023). DOI: 10.1084/jem.20221738

Jean-David Morel et al, Mitochondrial and NAD+ metabolism predict recovery from acute kidney injury in a diverse mouse population, *JCI Insight* (2023). DOI: 10.1172/jci.insight.164626

Provided by Ecole Polytechnique Federale de Lausanne