ADVERTISEMENT FEATURE

UNCOVERING THE SECRETS OF METABOLIC DISORDERS

Mouse models are proving invaluable for studying how fat tissue and the liver are linked to DISRUPTIONS TO NORMAL METABOLISM.

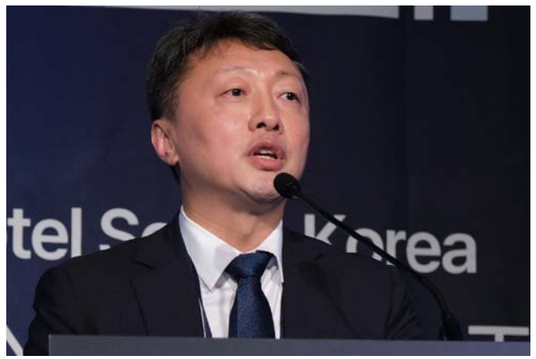
Metabolic disorders such as type 2 diabetes and obesity are rising at alarming rates in both developed and developing countries, presenting an ever-growing global health burden. Gaining a better understanding of the biology behind these conditions will help inform their prevention and treatment.

Mouse models are one of the most powerful tools researchers have for investigating metabolic disorders, and have been used by the International Mouse Phenotyping Consortium (IMPC) to identify key genes associated with them.

Bioresources for genomic medicine, such as mouse models, were the focus of the IMPC–INFRAFRONTIER Seoul Meeting 2022, hosted by the Korea Mouse Phenotyping Center (KMPC), on 8–10 May 2022 in Seoul, South Korea. More than 610 people from 17 countries participated in the meeting in person and online, including principal investigators, researchers, industry experts and government officials.

A special session on 'Genetic Mouse Models in Metabolic Research' — held on 9 May as a hybrid event — was jointly organized by Nature Portfolio and KMPC, and was chaired by Christoph Schmitt, the chief editor of *Nature Metabolism*.

In his keynote talk on mouse models for adipose tissue, Philipp Scherer, a professor at the Touchstone Diabetes Center and the University of Texas Southwestern Medical Center in Dallas, noted that clinical data from people can often only indicate correlation, not causation, and that mouse models are needed to glean more insights into the underlying biology. As one example, he cited the strong correlational data that exists between obesity and diabetes, but commented that the jury is still out about all the biological mechanisms driving this connection.



▲ Je Kyung Seong, director of the Korea Mouse Phenotyping Center, noted that ongoing work to build a comprehensive, functional catalogue of a mammalian genome will accelerate understandings of gene function.

THE ROLE OF IRON

Scherer's group is seeking to address the question of where adipocytes, or fat cells, fit into metabolism — principally by using mouse models. This is made difficult by several complicating factors. One is that cells sometimes jettison tiny capsules of their contents known as exosomes, so that even when a gene for a protein in adipocytes is knocked out in one cell type, the protein can be replenished by other cell types. "We saw very active 'exosomal trafficking' in adipose tissue — it was quite amazing," Scherer said.

Using mouse models, Scherer and his team have uncovered the critical role that iron plays in the development of type 2 diabetes. Specifically, they found that excess iron in adipose tissue leads to insulin resistance, whereas lowering the iron content resulted in much healthier adipose tissue. If this finding holds for humans, it could lead to new ways to manage the condition.

RESPONSE TO THE COLD

Not all adipose tissue is bad for metabolic health; brown adipose tissue is associated with cardiometabolic health in humans. Yu-Hua Tseng, a professor at Joslin Diabetes Center and Harvard Medical School in Boston, Massachusetts, and her team have been investigating the complex interactions that occur between brown adipose tissue and the mechanism regulating metabolism in the liver.

Exposure to low temperatures has been shown to activate brown adipose tissue. This is a so-called thermogenic fat that animals use to generate heat in cold conditions, and which secretes signalling molecules. Hypothesizing that exposure to cold ameliorates obesity-induced inflammation and insulin resistance, Tseng and her co-workers set out to determine the link between the two. After a series of mouse experiments, they discovered that cold exposure reduced obesity-induced inflammation and insulin resistance via the molecule Maresin 2, which is produced by brown fat.

David Guertin, a professor at the University of Massachusetts Chan Medical School in Worcester, is also looking at how model mice respond to the cold. His team is studying adipose and liver organ biology, including how these tissues use nutrients and communicate to maintain energy balance. As part of this work, they have used mice to study metabolic adaptations that drive thermogenesis in adipocytes. Guertin noted that brown adipose tissue is a key factor in energy balance, but its role as a critical regulator of metabolic homeostasis in adult humans has only recently been recognized. His team has found that the breakdown of nutrients in the process of catabolism drives thermogenesis via the mitochondrial protein UCP1 and that cold adaptation also increases a set of metabolic pathways involved in building molecules from smaller units that support thermogenesis.

▲ Genetic mouse models, such as those bred at the Korea Mouse Phenotyping Center (above), assist metabolic disorder studies, said Christoph Schmitt, chief editor of *Nature Metabolism* (top right). Harvard's Yu-Hua Tseng (bottom right) talked about the links between brown adipose tissue and the liver.

Yun-Hee Lee, an associate professor at Seoul National University in Seoul, South Korea, has also been studying fat. With an eye to future treatments for metabolic disorders, she talked about her team's exploration of the potential remodeling of adipose tissue to be a therapeutic target. In particular, they have identified the inhibition of the Hippo kinases STK3/4, key components of the Hippo signaling pathway that regulates cell proliferation and death, as a promising therapy for metabolic disorders since it improves metabolism and the balance of insulin and glucagon to maintain blood sugar levels through promoting adipocyte browning. This leads to improved survival and restoration of the quality-control mechanism for mitochondria.

A HUMAN SHIFT

As a reminder that, as valuable as they are, mouse studies are only a means to a more important end, Kirsty Spalding, a senior researcher at the Karolinska Institutet in Stockholm, Sweden, discussed the contribution of adipose cells to metabolic disorders in humans. Her lab is exploring the origin and turnover of adipocytes, their progenitor cells, and lipid stores in lean and obese individuals. As part of this work, Spalding's team has been exploring what induces adipocytes to enter the senescent state, in which cells cease dividing but remain metabolically active. Using the analogy of the brake and accelerator in a car, they hypothesized, and then confirmed, that insulin acts as an accelerator, while cellular stress functions as a brake.

A MODEL-MOUSE LIBRARY

Finally, Je Kyung Seong, director of KMPC, noted the big gap between the wealth of gene sequencing data and knowledge of gene function. "The function of most genes still remains unknown," he said. IMPC is seeking to redress this situation by "building the first truly comprehensive, functional catalogue of a mammalian genome," Seong explained. They are systematically phenotyping 20,000 knockout mouse strains — one for each protein-coding gene — and have already passed the 8,500 mark. Researchers everywhere can benefit from this remarkable bioresource, as the data is being made freely available, while mouse production can be supported by IMPC members.

Overall, the session provided fascinating glimpses into the latest work being conducted on the roles of liver biology and adipose tissue in metabolic diseases, and it highlighted the importance of mouse models in this field. It's an area where rapid progress is being made, but where many questions still remain to be resolved — questions that are all the more urgent in light of the rapid proliferation of metabolic disorders. ■

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