Health & Medicine ︱ Philipp Kalds

Metabolic dysfunction

The liver and beyond

The liver is the principal organ for all metabolic needs, including glucose and lipid metabolism. Professor Philipp Kalds of Lund University, Sweden, has collaborated with fellow researchers to understand metabolism and its links to diseases, such as liver disease and type 2 diabetes. Despite extensive study, the mechanisms underlying these pathologies remain largely unexplained. Professor Philipp Kalds of Lund University, Sweden, has collaborated with fellow researchers to understand metabolism and its links to diseases, such as liver disease and type 2 diabetes (T2D). These diseases have both genetic and environmental causes (behavioural causes or alterations in metabolism due to the environment). The liver is central to this pathology, but other tissues and organs are believed to be involved as well.

Grasping the ‘crosstalk’ or signalling between organs could be pivotal in deciphering the pathophysiology of metabolic diseases. Advances in laboratory technologies, such as mass spectrometry, provide a tool to identify metabolites – biproducts yielded from cell metabolism – and biomarkers implicated in such diseases. Yet, scientists suspect there are still many metabolites and biomarkers not yet identified and still have not fully elucidated the underlying mechanisms involving these molecules in metabolic diseases.

Unravelling the complexity of metabolic dysfunction is a tall order. However, by identifying the mechanisms underlying their observations in animal studies, Kalds and colleagues hope to translate their research into therapies that will one day benefit patients.

LIVER CELL REGENERATION

Metabolism refers to the substantial number of biochemical reactions in our cells that break down food into energy enabling cell, organ, and whole-body functions. It is a complex process involving multiple organs, tissues, and a plethora of metabolites, enzymes, and biomarkers. As the centre of metabolism, the liver consistently suffers a barrage of insults from toxins causing liver cell (hepatocyte) damage. However, hepatocytes have the remarkable ability to renew and regenerate following an injury. Initial stages of regeneration involve hypertrophy (increase in size) of hepatocytes, whereas in the latter stages, cell division dominates. This regeneration requires cell proliferation and regulation of metabolism, but little is known about the metabolic requirements during liver regeneration.

In their 2018 paper, ‘Metabolic remodeling during liver regeneration’, the researchers explored the metabolic requirements using a novel approach, combining functional MRI imaging, metabolomics (the study of metabolites in cells), transcriptomics (study of RNA transcripts), and cell biology. They emphasised the metabolic changes at various times during regeneration and addressed hepatocyte metabolic needs along with the mechanisms and pathways involved.

The researchers’ experiments demonstrated that stopping hepatocytes from dividing results in mitochondrial dysfunction and downregulation of oxidative pathways. Consequently, alanine transaminase (ALT) was increased, and metabolic remodelling ensued. This signalled liver damage, but importantly also regulated metabolism by reducing oxidation, impairing mitochondrial functions, and increasing amino acid metabolism to aid regeneration. This prior work by the team provided a deeper understanding of metabolic events that occur during liver regeneration, acting as a starting point in the development of liver regeneration biomarkers.

THE IMPORTANCE OF CELL DIVISION IN LIVER DISEASES

Recently there has been a major increase in patients suffering from non-alcoholic fatty liver disease (NAFLD), making it the most prevalent liver disease worldwide. Pathological features include fat build up in hepatocytes, abnormal metabolism, and cell division. Recognising the contribution of metabolic dysfunction within the disease, the new term – metabolic dysfunction-associated fatty liver disease (MAFLD) – is increasingly used. Marked by release of metabolites and signalling molecules, such as organokines (proteins secreted by organs that regulate metabolism) and hormones, this metabolic dysfunction is a driving cause of fat buildup in the liver. These molecules enable communication between metabolic organs to coordinate crosstalk between the liver and other tissues.

Liver disease can be progressive, worsening from NAFLD to NASH due to non-alcoholic steatohepatitis (NASH) where fatty liver co-exists with inflammation. These diseases can eventually lead to hepatic fibrosis/cancer (HCC), the most common type of liver cancer. The inability of hepatocyte to divide is a hallmark of such liver diseases, prompting investigation into both the underlying causes and consequences of this inability. The protein family of cyclin-dependent kinases orchestrates cell cycle progression, therefore acting as a key factor in understanding diseases marked by abnormal cell division. Cyclin-dependent kinase 1 (CDK1) is one such protein and previous studies have shown that when CDK1 is deleted, hepatocytes become senescent and are unable to undergo cell division. Instead, they become hypertrophic, causing changes in glucose metabolism.

Phospholipids form the plasma membrane of new daughter cells. This implies that lipid metabolism is essential for cell division. However, by investigating the impairment of hepatocyte cell cycle regulatory gene CDK1, the team proposed that the loss of this cell cycle regulator could be both a cause and a contributor to liver disease. In their in-depth analyses revealed that a consequence of CDK1 activity loss is dysfunctional fatty acid oxidation, resulting in increased free fatty acids in the blood and subsequently elevated blood insulin and insulin resistance. Increased blood glucose levels conclude in a diabetic-like phenotype along with liver disease.

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Another consequence of CDK1 activity loss is increased storage of free fatty acids in adipose tissue, leading to additional fat mass in the mice. CDK1 knockout mice also suffer hepatic steatosis and fibrosis, distinct features of NASH. The team proposed the loss of hepatocyte CDK1 activity as both a cause and an outcome of liver disease. They also suggest that therapeutics targeting senescent cells could help in the treatment of metabolic diseases of the liver.

The team acknowledge there is no known mutation of CDK1 in liver disease and T2D. However, other studies indicated increased abundance of senescent cells and reduced CDK1 activity in NAFLD; possibly due to elevated levels of the cyclin-dependent kinase inhibitor – p21 (CDKN1A). Combining the results of the studies, the
Behind the Research
Professor Philipp Kaldis

Philipp Kaldis and colleagues have conducted extensive research to elucidate the mechanisms of liver diseases, focusing on metabolism and interorgan crosstalk.

Research Objectives

The team has dedicated years to elucidate the mechanisms of these diseases, unveil metabolites at the centre of this pathology, and unpick the complexities of organ crosstalk.

Detail

Bio

Philipp Kaldis received his PhD from ETH, Zurich, Switzerland and did his postdoctoral work at Yale University, USA. He founded his laboratory at the National Cancer Institute, National Institutes of Health. After being promoted to Senior Investigator, he moved to work at the Institute of Molecular and Cell Biology, Singapore. He currently works as a professor at Lund University, Sweden and is a vice-coordinator for the Lund University Diabetes Centre.

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Collaborators

- Hyungwon Choi (National University of Singapore)
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References

Are there any things that have surprised you during your work in this field?

The biggest surprise was to uncover that cell division of hepatocytes is not required for liver regeneration and that this caused alterations in metabolism. This was completely unexpected and contradicted the previously held beliefs.

What is the next step to take this research forward in identifying and better understanding metabolites involved in both liver and type 2 diabetes pathophysiology?

The first step is to be able to detect more metabolites – at least 10,000 (up from the current 1,000, but in the long-term 100,000 would be even better). This is not going to be easy and will require possibly new approaches in several steps of the metabolomics process. The other step is to painstakingly study as many metabolites as possible to determine their functions in several organs in fatty liver disease and T2D.

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