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Editorial

# The emerging era of multidisciplinary metabolism research

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Metabolism is a chemical process that converts the energy from food in cells and organisms. In metabolic diseases, this process is not regulated properly and results in imbalanced energy production profiles. A common metabolic disease is diabetes. There are 2 types of diabetes: type 1 diabetes, which is caused by autoimmunity, and type 2 diabetes (T2D), which is not driven by autoimmunity and is much more prevalent than type 1 diabetes.

Diabetes is characterized by persistently high blood glucose levels, which can lead over time to the development of the various complications such as cardiovascular diseases, kidney failure, and ischemia. Conversely, insufficient blood glucose levels can cause brain damage, including coma, because the brain is the biggest consumer of blood glucose. Consequently, circulating blood levels are normally strictly regulated. Many organs participate in this. One is the liver, which produces glucose between meals to maintain basal glucose levels. Moreover, skeletal muscles and adipose tissues store the excess energy, and β-cells in the pancreas produce insulin, which regulates the glucose-metabolic processes in the other tissues. All of these metabolic activities are tightly coordinated. However, various factors can disrupt this intricate web and thereby induce insulin resistance. This eventually leads to T2D.

A major cause for the development of insulin resistance and T2D is obesity. However, it remains unclear how obesity induces insulin resistance. Several mechanisms have been proposed, including: low-level but chronic inflammation emanating from the adipose tissue; mitochondrial dysfunction; ectopic fat accumulation in the muscle and liver; and dysfunction in insulin-responsive tissues, including the brown fat (Roden and Shulman, 2019).

The fundamental objective of metabolism research is to determine how energy is produced and utilized. Consequently, classical metabolic diseases such as diabetes and cardiovascular diseases have long been the primary focus of this research. However, in the last 3 decades, this research focus started widening to include many other disciplines. One is the cancer field, which adopted metabolism research early because of the discovery of the Warburg effect a century ago. The Warburg effect, which is a hallmark of cancer cells, is characterized by the abnormally persistent use of the aerobic glycolysis pathway to gain energy from glucose, even when oxygen is abundant. By contrast, normal cells primarily use the β-oxidation pathway for glucose metabolism because it converts the glucose molecules into fuel more efficiently (Warburg et al., 1927). Subsequent research on cancer cell metabolism has since elucidated many other protumor and antitumor molecular mechanisms in metabolic pathways, in particular in the glycolytic pathway. This in turn has led to burgeoning research on potential therapeutic anticancer targets in metabolic pathways (Pavlova et al., 2022).

Another area that is increasingly adopting metabolism research is immunology. Interest in immune-cell metabolism was first born in the classical immunology field when the Pearce and Choi group showed that modulating fatty-acid metabolism regulates CD8 T-cell memory functions (Pearce et al., 2009). Since then, many studies have shown that metabolic changes in immune cells, including T and B cells, macrophages, dentritic cells, and natural killer cells, regulate the classical immune functions of these cells. In particular, to become activated, immune cells must shift from the β-oxidation pathway to the glycolytic pathway, similar to what is observed in cancer cells (Makowski et al., 2020).

This growth of metabolism research in the classical immunology field has been matched by reciprocal changes in the classical metabolism field, which is increasingly interested in the role that immune-cell metabolism plays in metabolic diseases. An example of this is the mechanism that was proposed above to drive obesity-induced insulin resistance. Specifically, it has been shown that obesity-induced inflammation promotes the development of insulin resistance and T2D in both animal models and humans, and that this is mainly regulated by immune cells in local tissues, particularly the epididymal adipose tissues (Lee and Lee, 2014).

Thus, the new field of immunometabolism research has 2 cross-fertilizing arms: the classical immunology arm, which studies the effect of metabolism on immune-cell functions, and the classical metabolism arm, which conversely examines the role of immune cells in metabolic diseases.

To demonstrate this emerging trend of combining metabolism research with other areas of research, the current issue of *Molecules and Cells* includes 4 review papers on the intersection of metabolism with cancer, mitochondria, neurology, and immunology, which will complement previously published review papers for the metabolism field in this journal (Chae et al., 2023; Kim et al., 2023; Lee et al., 2022; Sa et al., 2022).

In one of these reviews, Kim and Hyun (2024) focus on liver cancer. The liver is a key metabolic player because it regulates many metabolic processes, including basal glucose production and lipid metabolism. When insulin resistance develops, the

liver becomes steatotic and eventually develops metabolic dysfunction-associated steatotic liver disease (MASLD) (formerly known as nonalcoholic fatty liver disease) and eventually hepatocellular carcinoma. Kim and Hyun summarize what is known about the pathophysiology of MASLD, especially with regard to the altered lipid metabolism in the liver and how it promotes the development of cancer cells. In particular, they show that in MASLD, the premetastatic liver cells and cancer cell subpopulations communicate with each other via extracellular vesicles and particles. These communications are strongly driven and shaped by the altered lipid metabolism in the liver and promote tumor progression and metastasis, including by suppressing immune cells in the liver microenvironment. Finally, the potential of targeting lipid metabolism for treating metastatic liver cancer is discussed.

The review by Lee and Yoon (2024) describes the role of mitochondrial metabolism in tumorigenesis, with a particular focus on the mitochondrial sirtuins (SIRTs). The 7 SIRT family members are nicotinamide adenine dinucleotide $(NAD)^+$-dependent protein deacetylases that are involved in many cellular functions, including metabolism, inflammation, and tumorigenesis. SIRT3, SIRT4, and SIRT5 are predominantly localized in the mitochondria. Lee and Yoon describe the specific roles of these SIRTs in regulating cellular metabolism and their impact on $NAD^+$ consumption. They also discuss how these SIRTs shape cancer cell survival and proliferation and provide insights into the development of anticancer therapies that target the mitochondrial SIRTs or $NAD^+$ biology.

The review by Mishra and Townsend (2024) explores the role of sensory nerve activities in adipose-tissue functions. Brown and white adipose tissues are highly innervated and many studies show that neuronal systems shape adipose functions. In particular, sympathetic nerves and their neurotransmitter norepinephrine have been shown to regulate thermogenesis in brown fat and lipolysis in white adipose tissues. However, much less research has been conducted on other neural systems, including sensory nerves. Mishra and Townsend discuss the roles of these nerves, and particularly their neuropeptides, in adipose-tissue metabolism.

Finally, Kang and Lee (2024) examine the heterogeneity of adipose tissue macrophages (ATMs) in obesity. It is now well accepted that ATMs play a critical role in the development of obesity-induced inflammation, insulin resistance, and T2D. The current paradigm states that this role is mediated by obesity-induced repolarization of ATMs from the anti-inflammatory M2 phenotype to the proinflammatory M1 phenotype. Kang and Lee revisit ATM heterogeneity from the perspective of the single-cell genomics studies that are recently available. They summarize and compare ATM subclusters from literatures, none of which can be classified as purely M1 or M2 macrophages. Thus, to improve our understanding of the roles of ATMs in obesity, it is necessary to move away from the dichotomous M1/M2 macrophage classification. Lee and Kang also discuss the many noninflammatory ATM subclusters, which include lipid-associated macrophages, and detail some future directions of immunometabolism single-cell genomics studies.

Thus, these 4 review papers provide tantalizing insights into just a few of the many metabolism-research fields that have emerged recently. They also demonstrate the power of incorporating metabolism research into other research fields. It is likely that this multidisciplinary approach will expand to many other areas, including neuronal biology, degenerative diseases, and stem-cell biology. The resulting data will greatly enhance our understanding of these fields, thus increasing our ability to develop new classes of drugs for not only classical metabolic diseases such as T2D but many other conditions as well.

## DECLARATION OF COMPETING INTERESTS

The author declares that he has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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