Cell
Leading Edge

Editorial

50 years of metabolism research at *Cell*

Metabolism is fundamental to biology. How organisms obtain, produce, store, and use energy and associated chemical cofactors is connected to many other pathways and processes. We learn more about these connections every day, as well as what happens when aspects of metabolism go awry. As part of our ongoing 50th Anniversary celebrations at *Cell*, we and our colleagues at *Cell Metabolism* and *Trends in Endocrinology and Metabolism* have collaborated to bring you special content on metabolism and its connections to disease and aging. This collaboration is most visible through the related covers for each journal, which come together to form a single image.

Metabolism research has evolved significantly in the past 50 years. It was classically focused on describing changes in metabolites and enzyme activities as well as isotopic labeling of pathways across cells and in different tissues. The advent of genetic and molecular technologies in the 1970s facilitated a shift in the field, particularly by enabling molecular cloning of the key players and their regulators in metabolic and hormone signaling pathways. This trend is clear in papers published in *Cell* between the 1970s and 1990s, including several landmarks such as a series of studies uncovering mechanisms for cholesterol regulation, the discovery of hormone receptors and their regulatory elements, and the identification of molecular crosstalk between different metabolic pathways. New technologies also made it possible to perform genetic manipulations in mice, leading to models that recapitulated metabolic disorders and significantly boosted research into the pathophysiology of metabolic diseases. This is reflected in the marked increase in publications focused on obesity, diabetes, muscle biology, liver disease, hypertension, and hypercholesterolemia between the 1980s and 1990s.

It wasn't just technical breakthroughs that brought change to metabolism research; it was also changes to how people live and what they eat. With more sedentary lifestyles and processed diets, worldwide adult obesity has more than doubled since 1990, and adolescent obesity has quadrupled. The public's increasing concerns about obesity sparked a surge in research on body weight control. Accordingly, starting from 2000, *Cell* witnessed a significant increase in the number of submissions and publications on adipogenesis, energy metabolism, obesity, and its complications, such as diabetes, heart disease, osteoarthritis, fatty liver diseases, and certain cancers. Many of these publications extended our understanding of the fundamental biology underlying metabolism and provided foundations for disease treatments—for example, the discovery of beige adipocytes and their unique gene expression signatures in mice and humans, the endocrine role for bone and adipose tissue and their functions in energy metabolism, how leptin regulates bone mass, and a link between diet and obesity to MASH and liver cancer.

While rodents have served as powerful preclinical models for metabolic studies, not all findings in mice can be translated to humans. Differences between rodent models and humans exist at multiple levels, ranging from eating behavior, energy expenditure, and thermogenesis to nutrient partitioning. Given these differences, metabolic research, especially with a focus on diseases, is expanding from model organisms to humans. The completion of the first draft of the human genome in 2003 galvanized efforts to understand the genetic basis of prevalent metabolic diseases, and concomitantly, we have seen more human genetic data integrated into metabolic research publications. These studies have characterized genes associated with mouse and human metabolic disease and highlighted the complexity of metabolic disorders. For example, the common genetic variants identified by GWAS only modestly contribute to the risk of type 2 diabetes (most loci contribute less than 15%), indicating that interactions between genetic, social, and environmental influences shape the disease. Sadaf Farooqi and Yong Xu discuss the limitations and benefits of studies in mice and humans investigating energy homeostasis and underscore the increasing importance of human studies in discovering disease mechanisms and identifying therapeutic targets. Carrying this point further, in this issue, Dale Abel and colleagues summarize the pathophysiology of type 2 diabetes. They also explore the intricate relationships between genetic susceptibility and social and environmental determinants, highlighting how these factors influence type 2 diabetes development among individuals and populations.

Our global society is a complex tapestry of different cultures, each distinguished by its traditions, belief systems, lifestyle practices, and dietary habits, thereby contributing to the rich diversity of human populations. In that spirit, we asked pioneers in metabolism research to share their views on metabolic heterogeneity at multiple levels. Of course, it's not just cultures that are different—it's also the individuals within those cultures. In *Cell Metabolism*, Bret Goodpaster and colleagues give us a summary on how variation in exercise responses guides personalized physical activity, and Amy Nichols and colleagues explore gender differences in metabolism, offering a comprehensive view of the contribution of female reproductive risk factors to later metabolic dysfunction.

Metabolic heterogeneity is also abundant at the cellular level. Different cell types within tissues exhibit distinct metabolic enzyme expression patterns. Cellular metabolism also varies under healthy and disease conditions. One hundred years ago, in 1924, Otto Warburg observed that cancer tissue slices ferment glucose to lactate even with sufficient oxygen available. Since then, aerobic glycolysis has been extensively studied in cancer, immunity, pluripotency, and infection. Sarah-Maria Fendt highlights the history of the Warburg effect and how those findings advanced cancer metabolism and many other fields.

Basic research paved the way to the FDA-approved drug Resmetirom, a liver-targeted THR-β agonist that is a landmark breakthrough in treating metabolic-dysfunction-associated steatotic liver disease (MASLD) and fibrosis. And who hasn't

heard of Ozempic and Wegovy? These GLP-1 drugs, which work by reducing gastric emptying, food intake, and body weight while improving glucose tolerance, have brought hope to individuals with obesity and type 2 diabetes. Philipp Scherer and colleagues review the success of the GLP-1R agonists for obesity treatment; their favorable effects on glycemia, fatty liver, and kidney diseases; and the potential side effects of mono- and multi-receptor agonists.

Advances in medical treatments have significantly improved the clinical management of metabolic diseases, but it is clear that drugs aren't the only answer. Our lifestyles are critically important, too. Over the past two decades, we've seen increasing publications on exercise, nutrition, and dietary interventions. These include studies on the molecular links between exercise interventions and disease treatment and prevention and on the interplay between diet and the microbiome. Specific gut microbes are associated with specific nutrients and foods. Furthermore, the composition of the microbiome is associated with health outcomes. In their Review, Peter Turnbaugh and colleagues summarize the progress in dietary interventions that alter the microbiome and the energy balance.

Our understanding of human metabolism and interventions for metabolic diseases shapes societal structures and, in turn, impacts the focus of research. Improvements in nutrition, disease control, and public health measurements have reduced mortality rates and steadily increased the world's life expectancy. By 2030, 1 in 6 people in the world will be aged 60 years or over, which has brought up new challenges in terms of how to adequately support longevity. We want to live longer and live better. Age-related diseases such as cardiovascular disease, cancer, and Alzheimer's disease demand increasing attention. Looking to the future, we invited 10 experts to share their perspectives on cardiometabolic health. In addition, in the latest issue of *Trends in Endocrinology and Metabolism,* Dwight Towler reviews parathyroid hormone signaling in cardiovascular pathophysiology.

The progress in metabolic research highlights the mutual reinforcement of social change and scientific progress. Simultaneously, these dynamics substantially impact modes of science communication. We are now living in an age of information explosion where facilitating timely and accurate dissemination of scientific knowledge is essential for both the scientific community and the broader public. In a Conversation with Giles Yeo, we discuss key elements for promoting science and simplifying complex concepts for the general audience.

Walking down the memory lane of *Cell*'s metabolic research content with our authors and Cell Press colleagues, we are inspired by the milestones that have broadened the horizons and possibilities of the field. We look forward to continuing to work closely with all of you in this field to step up the exciting frontiers of metabolism research and contribute to human health for the next 50 years and beyond.

The *Cell* editorial team

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