Retooling metabolism

Chemical methods that integrate analytical and quantitative measurements of metabolites with the ability to alter metabolic processes offer powerful tools for modulating biology and physiology.

A full understanding of metabolism requires a big-picture view of the chemical reactions of small molecules and metabolites and a perspective on the regulation of the enzymes involved in these reactions. Analytical approaches are useful for annotating and quantifying the myriad metabolites, levels of which need to be carefully controlled for normal cellular growth and differentiation. As well, chemical tools enable the detection of metabolic changes and direct manipulation of metabolic pathways with high precision. In this themed issue, we present a collection of Reviews, Perspectives and Articles that aims to showcase how chemical tools have strengthened the existing interplay of physiology, chemical biology and biochemistry — to reveal new insights into cellular regulation.

The use of analytical techniques such as untargeted metabolomics can provide an unbiased view of the changing metabolic landscape under specific cellular and biological conditions, such as in response to circadian rhythms. However, a current limitation of mass spectrometry–based metabolomics datasets is the large number of uncharacterized metabolites. Improvements in computational platforms such as MetaboAnalyst 4.0 and SIRUS4 can enable precise metabolic identification and annotation, but progress remains slow. A more focused strategy is to track the flux of a particular isotopically labeled metabolite by mass spectrometry. For example, this approach has enabled the calculation of fluxes for adipocyte NADPH, and has been used to characterize a non-conventional tricarboxylic acid (TCA) cycle. As well, examination of glycolytic thermodynamics in various organisms has revealed that the steps in glycolysis are near equilibrium, a dynamic state that enables rapid adaptation to changing environmental conditions.

Although metabolomics platforms can detect changes in metabolites in a precise and quantitative manner, they do not necessarily provide sufficient resolution to detect subcellular metabolic changes in real time. To bridge this gap, genetically encoded fluorescent sensors have been developed that monitor particular metabolites in a regionally specific manner — whether in a cellular compartment or tissue. A Perspective by Choe and Titov provides an up-to-date catalog of this toolbox and discusses the considerations required to design and apply them in various cellular contexts. The authors also highlight the use of genetically encoded tools for the manipulation of metabolism to directly modulate metabolism by altering the levels of a specific metabolite or by perturbing bioenergetics to facilitate metabolic reactions in cells. One example of such a tool was developed through the engineering of a mutant of *Lactobacillus brevis* NADH oxidase called TPNOX that modulates the NADPH/$NADP^+$ ratio in mitochondria.

Mitochondria are considered the powerhouses of the cell, containing energy-generating systems such as the TCA cycle and the electron-transport chain. In addition to their known regulatory functions, mitochondrial metabolites are now thought to be more broadly integrated into cellular metabolism, both locally and systemically. A Review from Murphy and Chouchani discusses recent findings that the TCA cycle intermediate succinate acts as a systemic metabolic signal that senses the redox state of mitochondrial coenzyme Q pools, relaying this information to the rest of the cell. Other examples of metabolites that can alter the activity of regulatory enzymes include the anti-inflammatory metabolite itaconate, which can covalently modify glycolytic enzymes, and lactate, which can modify histones and drive dysfunctional gene expression in Alzheimer's disease. Meanwhile, various lipids such as cholesterol and long- and short-chain fatty acids are critical for regulating T cell fate and function, as noted in a Review by Chi and colleagues.

Alterations in the synthesis and utilization of metabolites are associated with pathological conditions such as cancer and diabetes, which has inspired strategies to restore metabolic homeostasis. One example of altered homeostasis is the Warburg effect, whereby cancer cells exhibit a rewiring of their metabolic pathways that leads to a dependence on particular nutrients such as glucose or glutamine. Small molecules that target this dependence have high therapeutic potential. Using small molecules that target allosteric sites on metabolic enzymes, as discussed in a Perspective by Kremer and Lyssiotis, could enable rapid responses with specificities higher than those of orthosteric-mediated inhibition. Recent examples include allosteric activators of pyruvate kinase M2 that promote the formation of constitutively active tetramers and reduce tumor growth, and an allosteric inhibitor of glucose 6-phosphate dehydrogenase, which performs the first committed step of the oxidative pentose phosphate pathway.

The inability to properly produce insulin in patients with type 1 diabetes results in a failure to properly regulate blood glucose levels. Although insulin injections can restore metabolic homeostasis, the effects are transient, which has prompted efforts to identify insulin analogs with improved pharmacological properties. Inspired by cone-snail venom insulins that activate the prey's insulin receptor and rapidly reduce blood glucose levels, Xiong et al. developed a humanized cone-snail insulin that interacts with the human insulin receptor, providing a potential blueprint for the development of alternative therapeutic approaches with which to treat diabetes.

Improvements in chemical biology tools, such as those highlighted in this issue, will enable the detection and measurement of key metabolites. These measurements will guide precise manipulation of metabolic reactions to restore homeostasis and can alleviate the diseased states that come about when metabolism goes awry. ❐

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