Strength in numbers: Phosphofructokinase polymerization prevails in the liver

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Strength in numbers: Phosphofructokinase polymerization prevails in the liver

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Numerous metabolic enzymes assemble into filamentous structures, which are thought to serve additional regulatory functions. In this issue, Webb et al. (2017. J. Cell Biol. https://doi.org/10.1083/jcb.201701084) show that the liver-specific isoform of phosphofructokinase-1 forms filaments in vitro and localizes as puncta in cells along the plasma membrane. This suggests spatial organization of glycolysis in higher organisms.

Glycolysis is the core of central carbon metabolism; its intermediates provide precursors important for generating ATP through glucose oxidation, serine for one carbon metabolism, sugars for protein glycosylation, and building blocks for nucleotide synthesis through the pentose phosphate shunt (Fig. 1 A). Although glucose metabolism is highly studied, spatiotemporal aspects of glycolysis remain largely unexplored. Polymerization of metabolic enzymes is one means of spatially regulating cellular processes, and it has been observed for numerous enzymes including acetyl-CoA carboxylase (ACC), cytidine triphosphate (CTP) synthase, glutamate dehydrogenase, and β-glucosidase (O’Connell et al., 2012). A recent study has shown that PFK1, the rate-determining step of glycolysis that converts fructose 6-phosphate (F6P) to fructose 1,6-bisphosphate (F1,6BP) to glucose, is regulated by metabolites. PFK1 is distinct, however, because it most enzymes involved in glucose metabolism is allosterically regulated by metabolites. PFK1 is distinct, however, because it is not reversible, and it is the rate-determining step of oxidative glucose metabolism (Fig. 1 A).

PFK1 has two states of quaternary structure: the inhibitory T state and the activated R state (Fig. 1 B; Webb et al., 2015). ATP, citrate, and phosphoenolpyruvate bind PFK1, stabilizing the T state and therefore inhibiting catalytic activity. These metabolites are elevated in a cell when there is sufficient energy production through TCA cycle flux and glycolysis, respectively. Alternatively, metabolites such as AMP and F2,6BP stabilize the PFK1 R state, activating it to increase glycolytic flux in low-energy conditions. In addition to allosteric modifications, PFK1 is regulated by posttranslational modifications such as glycosylation. Glycosylation inhibits PFK1 activity and rewires glucose metabolism to the pentose phosphate pathway (Yi et al.,...
Metabolic enzymes have evolved to rapidly respond to ever-changing cellular conditions. Therefore, a high order of regulation is required to fine-tune their activity. Advances in metabolomics have allowed us to assess global changes in cellular metabolic profiles, and yet the spatiotemporal aspects of metabolism are still largely unexplored and represent an exciting area for future studies. The existence of metabolic enzyme filaments implies the importance of localized metabolism and suggests an additional layer of complexity and regulation of glycolysis.

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References


