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New concepts in feedback regulation of glucose metabolism

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Abstract

Glycolysis, the breakdown of glucose, is one of the most conserved and extensively studied biochemical pathways. Designing principles from chemistry and thermodynamics allow for energy production, biosynthesis and cellular communication. However, the kinetics or metabolic flux through the pathway also determines its function. Recently, there have been numerous developments that establish new allosteric interactions of glycolytic enzymes with small molecule metabolites and other mechanisms that may cooperate to allow for addition complex regulation of glycolysis. This review surveys these newfound sources of glycolysis regulation and discusses their possible roles in establishing kinetic design principles of glycolysis.

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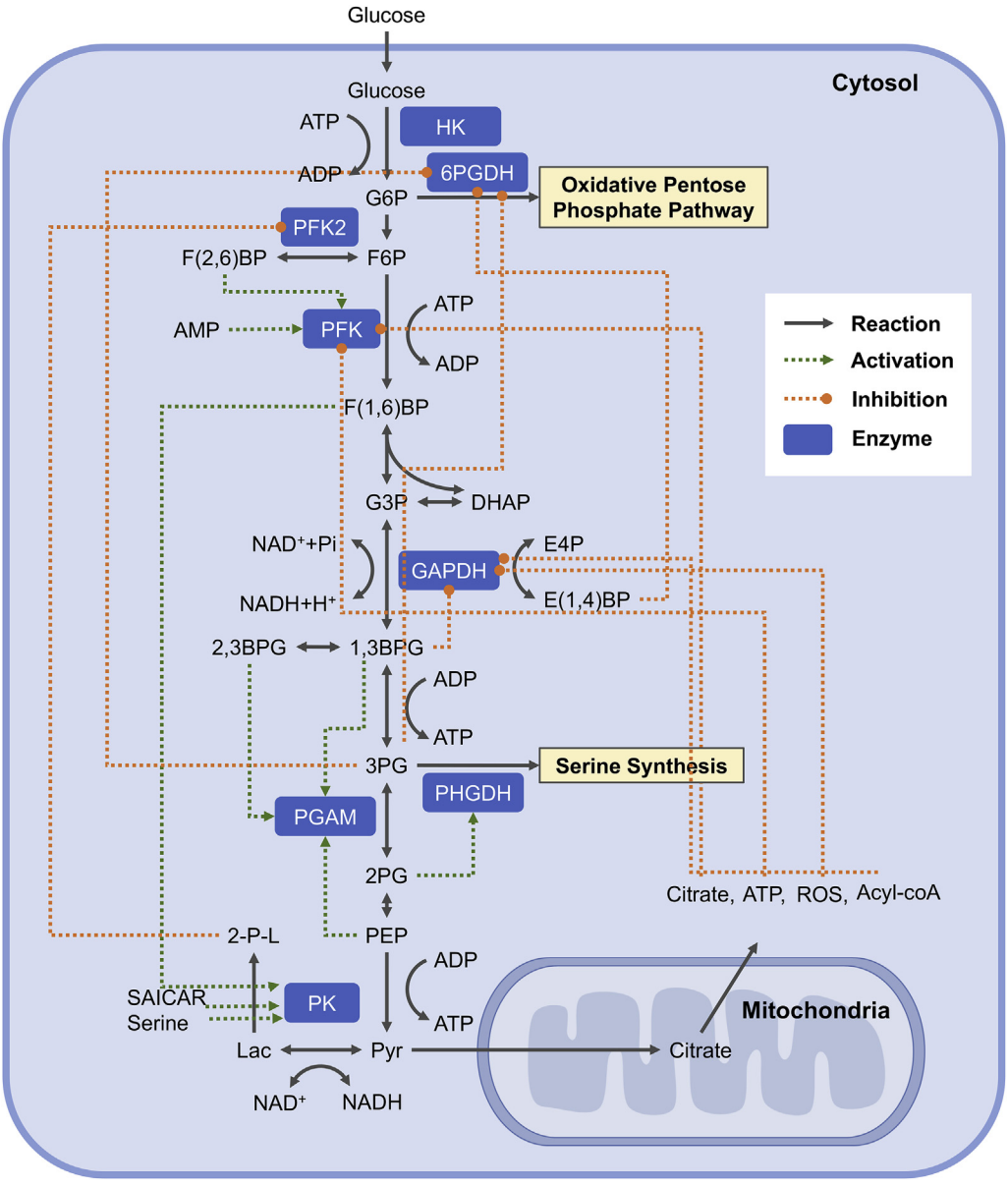
Glycolysis: structure and function

Glycolysis, the breakdown of glucose, is a pathway that exemplifies the core principles of how metabolic biochemistry can achieve biological function [1,2] (Figure 1). It is the oldest studied biological pathway with much of its discovery dating back to the 1950s. Thus, it is remarkable and speaks to the complexity of biology that almost 70 years later, there is still much to learn about both its biochemical makeup and biological function. Recently, several studies have discovered new elements of biochemistry within the pathway that may function to create feedback and feedforward forms of interaction throughout the pathway. How these newfound interactions confer regulatory principles for glucose metabolism is largely unknown. This review will provide a brief overview of glycolysis and mention, non-exhaustively, some classic forms of glycolysis regulation. It will next discuss recent developments in defining new aspects of the structure of the pathway, through allosteric interactions and other means, and speculate on the possible roles for these additional layers of wiring. These mechanisms likely confer numerous additional properties to glycolysis regulation but our knowledge is still in its infancy. I ultimately hope to give the reader a sense of the new possibilities for glycolysis regulation that may be present in certain contexts.

Glycolysis involves the uptake and metabolism of glucose through a set of chemical reactions that together constitute one of the oldest and most broadly studied biochemical pathways. As a result, energy in the form of ATP is generated and electrons are passed from glucose to the cofactor NADH. The intermediates in the pathway can undergo additional chemistry to generate biomass in the form of nucleic acids, proteins, and lipids. The product of glycolysis, pyruvate, can be further oxidized in the mitochondria or reduced and thus fermented to produce lactic acid or lactate. The lactate produced rapidly exchanges with pyruvate to enter the mitochondria as well [3,4]. Furthermore, the process of metabolizing glucose also signals to other aspects of the cellular milieu such as the chromatin state by affecting histone acetylation or the activation of receptor tyrosine kinase pathways by changing the redox state that leads to oxidation of the catalytic cysteine and thus catalytic inactivation of protein phosphatases [5–7]. Altogether each of these fates of glucose confers numerous essential functions to cells many of which are evolutionarily conserved from the most primitive of organisms to the most complex of multicellular species.

The biochemical setup of glycolysis contains several design principles that allows for each step in the pathway to achieve a specific outcome. This topic has been reviewed and analyzed extensively [2,8,9]. These goals either achieve thermodynamic favorability, satisfy physiochemical constraints such as membrane permeability, or allow for the creation of intermediates that can initiate biosynthesis from enzymatically feasible chemistry. As a result, much and in some cases, all demand for biomass and energy can be met from the breakdown and chemical conversion of sugar alone.

Figure 1



New concepts of regulation in glycolysis. Overview of glycolysis and new mechanisms of feedforward and feedback regulation. The pathway of glycolysis begins with the uptake of glucose and ends with the production of lactate of CO_2 in the mitochondria. Classic and newly identified feedback and feedforward interactions in the pathway are highlighted. Abbreviations: G6P - Glucose-6-phosphate, F6P - Fructose-6-phosphate, F(1,6)BP - Fructose-1,6-bisphosphate, DHAP - Dihydroxyacetone phosphate, G3P - Glyceraldehyde-3-phopshate, 1,3BPG - 1,3-bisphosphoglycerate, 2,3BPG - 2,3-bisphosphoglycerate, 3PG - 3-phosphoglycerate, 2PG - 2-phosphoglycerate, PEP - phosphoenolpyruvate, PEP - phosphoenolpyruvate, Pyr - pyruvate, Lac - lactate, SAICAR - 2-[5-Amino-1-(5-phospho-D-ribosyl)imidazole-4-carboxamido] succinate), NAD^+ – Nicotinamide adenine dinucleotide (oxidized), NADH - Nicotinamide adenine dinucleotide (reduced), ATP - Adenosine triphosphate, ADP - Adenosine diphosphate, AMP - Adenosine monophosphate, ROS - Reactive oxygen species, Acyl-coA - Acyl coenzyme A, 2-P-L 2-phospholactate, E4P - 4-phosphoerythronate, E(1,4)BP - 1,4-bisphosphoerythronate, HK - hexokinase, PFK - phosphofructokinase, PFK2 - phosphofructokinase 2, 6PGDH - 6-glucose-6-phosphate dehydrogenase, GAPDH - glyceraldehyde phosphate dehydrogenase, PHGDH - phosphoglycerate dehydrogenase, PGAM - phosphoglycerate mutase, PK - pyruvate kinase.

While the structure (i.e. the chemical reactions and thermodynamic properties) of glycolysis enables numerous cellular functions, metabolism is never in thermodynamic equilibrium and the kinetic properties of metabolism determine the function of the pathway. For example, during normal tumor development, cells exhibit larger rates of glycolysis and this leads to overflow metabolism such as fermentation of lactate (i.e. the Warburg Effect). As a result, cells carrying out this Warburg Effect have dramatically different phenotypes