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Glucose Metabolism Control

Henggui Zhang*

Department of Applied Chemicals and Materials Division, National Institute of Standards and Technology, Boulder, USA

Abstract

Cultured mammalian cells are the primary source of biologics. Cellular metabolism has a significant impact on the performance of these cell culture processes in terms of both productivity and product quality attributes. The primary carbon source for cellular biosynthesis and energy generation is glucose. Recent advances in our understanding of the regulation of glucose metabolism in cultured cells are summarised here. Allosteric regulation of the metabolic network, interplay between signalling pathways, and transcription factors enable cells to maintain homeostatic states in widely varying environments. Understanding metabolism regulation holds the key to changing the metabolic regulatory circuit and implementing direct metabolic control over cell culture processes.

Keywords: Cellular • Biosynthesis • Glucose • Allosteric

Introduction

In the last decade, therapeutic protein-based pharmaceuticals have grown to a billion industries. The value of these biologics will rise further over the next decade as new products are approved and demand for biosimilars grows. Almost all of those protein biologics are created in mammalian cell culture. Chinese hamster ovary cells, mouse myeloma-derived NS0 and SP2/0 cells, baby hamster kidney cells, and human embryonic kidney cells are notable examples [1].

As the demand for protein therapeutics grows, so does the need for highly productive and robust manufacturing processes. The energy metabolism of the producing cell influences its productivity and product quality. A trove of process data has linked CHO cell productivity to glucose metabolism. The glycan structure added to the protein molecule post-translationally is a major quality index of protein therapeutics. A biosimilar's glycosylation pattern, or the composition and structure of glycans attached to the protein, must be compatible with the innovative drug that it seeks to replace. Because the supply of monosaccharide precursors derived from metabolic pathways affects the glycosylation pattern of a therapeutic protein, energy metabolism can have a significant impact [2].

Glycolysis has a major entry point and two exit points at the cellular level: the transporters for glucose uptake lactate excretion (and sometimes uptake), and pyruvate entry into mitochondria. Cells divert glucose carbons to the pentose phosphate pathway (PPP) and the synthesis of serine, alanine, glycerol phosphate, and other compounds. However, the magnitude of these fluxes is less than that of lactate and pyruvate. Finally, the uptake and exit fluxes of glucose must be balanced, and the flux through glycolysis must be maintained by glycolysis enzymes. The glycolysis flux varies greatly. Cancer cells stem cells, and other rapidly growing cells have a high glycolysis rate, whereas quiescent cells have a low glycolysis rate in general [3].

***Address for Correspondence:** Henggui Zhang, Department of Applied Chemicals and Materials Division, National Institute of Standards and Technology, Boulder, USA, E-mail: hengguizhang@gmail.com*

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Literature Review

Phosphoribosylaminoimidazolesuccinocarboxamide (SAICAR), a purine biosynthesis intermediate, only stimulates the M2 isoform of PK. SAICAR accumulates in cells during acute glucose deprivation, increasing its binding to PKM2. PKM2 has a lower intrinsic activity and a higher KM for PEP than PKM1. The increased SAICAR binding reduces the KM for PEP and increases PKM2 activity, resulting in more glucose flux into mitochondria for ATP synthesis. Under glucose-limited conditions, such a mechanism has been shown to promote cancer cell survival [4].

In this review, we summarised recent advances in the regulation of glucose metabolism and attempted to provide a comprehensive view of allosteric regulation at the enzyme level as well as regulation via signalling pathways and transcription factors. Overall, it is clear that metabolic regulation is not centred on one or two enzymes, but rather is regulated at the pathway level, regardless of the type of regulation (allosteric, signalling pathway, or transcription factor). We concentrated on factors that have a significant impact on the nonlinear kinetic behaviour of glycolysis. Furthermore, due to space constraints, we were unable to address some recent advances. In response to specific physiological stimuli, some glycolytic enzymes and/or membrane transporters form supramolecular complexes [5].

Discussion

Bioprocess culture environments are far more complex than laboratory conditions. Over the last decade, process intensification efforts have increased the concentration of nutrients and metabolites to levels far above physiological levels. As a result, the response of glycolysis flux to nutrient and metabolite concentrations becomes more complex and difficult to predict. Because metabolic regulation is highly nonlinear, a systems approach is required to better understand the cellular response to a changing environment. Many researchers, including ourselves, have used systems modelling to study cell metabolism in mammalian cells [6].

All of the new insights into cellular regulation discussed in this article were obtained through the study of cultured cells. Mammalian cells used to make biopharmaceuticals express a similar set of metabolic enzymes and proteins. The regulatory mechanisms discussed in this review are most likely at work in all of these cells, but several questions remain unanswered. A better understanding of the regulation of cell metabolism in industrially important cells will almost certainly encourage the investigation of intrinsic control actions that can aid in the development of strategies for optimising cell metabolism. With recent advances in genome engineering, it will be possible to engineer these cells in order to change their metabolic regulation and increase their utility in bio-manufacturing.

Activity of kinase AMPK activation has been shown to activate catabolic pathways that generate energy. AMPK's regulatory effects are discussed in detail. Few studies have looked into the role of AMPK in mammalian cell lines used for protein production. Chong et al. discovered that when exposed to adenosine, a CHO producer cell line displayed dynamic AMPK activity. This indicates that the AMPK pathway components are present in CHO cells. Cells are almost never exposed to energy source limitation conditions in bioprocess-relevant culture conditions. As a result, the practical significance of the AMPK pathway in a bioprocessing setting is unclear [7].

Conclusion

Many cellular stimuli, such as glucose or oxygen deprivation and mitochondrial uncouples, increase ATP consumption and activate AMPK. AMPK has an antagonistic relationship with mTORC1. When ATP levels are low, AMPK phosphorylates TSC2 and Raptor, which inhibits mTORC1 activity. Suppression of mTORC1 activity inhibits anabolic processes such as cell growth, protein synthesis, and lipid synthesis. AMPK, in addition to regulating mTORC1, directly inhibits ATP-consuming anabolism by phosphorylating enzymes or regulatory proteins. For example, AMPK activation causes the fatty acid synthesis enzyme, acetyl-CoA carboxylase, the cholesterol synthesis enzyme, HMG-CoA reductive (HMGCR), and the glycogen synthesis enzyme, glycogen synthase, to be phosphorylated and inactivated.

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Conflict of Interest

There is no conflict of interest by author.

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