Molecular Immunology 68 (2015) 513–519

Contents lists available at ScienceDirect

Molecular Immunology

journal homepage: www.elsevier.com/locate/molimm

Glucose, glycolysis and lymphocyte responses

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ARTICLE INFO

Article history:
Received 5 June 2015
Received in revised form 15 July 2015
Accepted 26 July 2015
Available online 7 August 2015

Keywords:
Glycolysis
Metabolism
Lymphocyte
Natural Killer cell
T cell
B cell
mTORC1
c-Myc
HIF1-α
Oxidative phosphorylation
Glucose
Galactose
IFNγ
Granzyme B
GAPDH
review

ABSTRACT

Activated lymphocytes engage in robust growth and rapid proliferation. To achieve this, they tend to adopt a form of glucose metabolism termed aerobic glycolysis. This type of metabolism allows for the use of large amounts of glucose to generate energy, but also to support biosynthetic processes. This review article will discuss how aerobic glycolysis supports the biosynthetic demands of activated T cells, B cells and Natural Killer cells, and the emerging concept that glycolysis is integrally linked to the differentiation and function of these lymphocyte populations.

1. Introduction

Immune responses involve highly dynamic changes in immune cell function, which often encompass robust cellular growth and proliferation. Therefore, it is not surprising that there are corresponding changes in metabolism that match the dynamic nature of immune cells. Recent research has begun to characterise the metabolic alterations occurring in immune cells, which deciphers how metabolic reprogramming facilitates changes in cell fate and function during the course of an immune response. This article will discuss the emerging evidence that effector lymphocyte populations have a substantial appetite for glucose to fuel cellular biosynthetic processes that also impacts upon lymphocyte differentiation and function. Understanding why glucose is of particular importance for lymphocyte responses is an exciting area of active research.

2. Cellular metabolism: energy versus biosynthesis

2.1. Glycolysis, oxidative phosphorylation and efficient ATP production

Adenosine Triphosphate (ATP) is the key molecule that provides energy for cellular processes. Maintaining cellular ATP levels is essential for bioenergetic homeostasis and the survival of all cells, including lymphocytes. Glycolysis and Oxidative Phosphorylation (OxPhos) are two metabolic pathways that together efficiently convert the simple sugar glucose, the principal fuel source for mammalian cells, into ATP (Fig. 1). Glucose is metabolised to pyruvate by glycolysis, which involves a series of enzymatic steps that

Abreviations: OxPhos, oxidative phosphorylation; NK, natural killer; mTOR, mammalian target of rapamycin; NAD+ or NADH, nicotinamide adenine dinucleotide; FAD+ or $FADH_2$, flavin adenine dinucleotide; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; CTL, cytotoxic T lymphocytes; HIF1α, hypoxia-inducible factor 1α; 2DG, 2-deoxyglucose; BCR, B cell receptor; G6P, glucose-6-phosphate; UTR, untranslated region; IRP1, iron regulatory protein 1; PDK1, phosphoinositide dependent kinase 1.

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http://dx.doi.org/10.1016/j.molimm.2015.07.034
0161-5890/

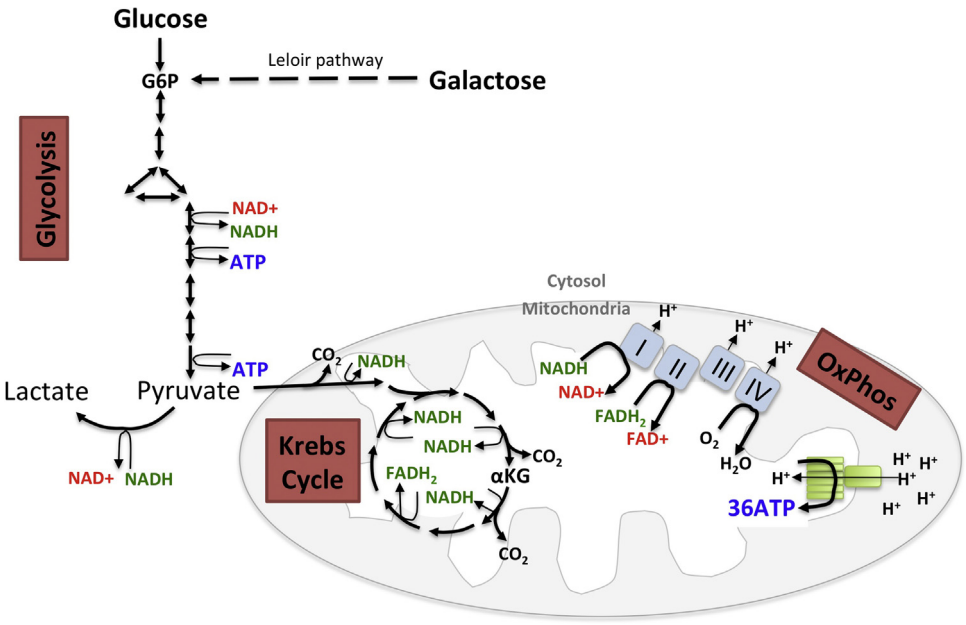

Fig. 1. ATP production by glycolysis and oxidative phosphorylation.
Glucose is an important fuel for the generation of ATP to satisfy the bioenergetics demands of the cell. The first step of glycolysis involves the phosphorylation of glucose by hexokinase to generate glucose-6-phosphate (G6P). Glycolysis then proceeds as a series of enzymatic reactions that ultimately generate the final product, pyruvate. Depending on cellular activity, pyruvate can have multiple fates in the cell, one of which is to be completely oxidised to CO_2 in the mitochondria for the efficient production of ATP. Alternatively, under anaerobic conditions, pyruvate can be converted to lactate which is secreted out of the cell. Pyruvate is also converted to lactate during aerobic glycolysis, a metabolic signature adopted by cells engaging robust growth and proliferation. The alternative fuel galactose can be metabolised by the Leloir pathway to generate G6P that is then further metabolised by glycolysis.

produces 2 molecules of ATP per molecule of glucose. Pyruvate can then be fully oxidised to CO_2 by the Krebs cycle, following its transport into the mitochondria. The Krebs cycle generates reduced nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide ($FADH_2$). These two key reducing agents fuel OxPhos by feeding electrons into complex I and II of the electron transport chain respectively, leading ultimately to the reduction of O_2 to H_2O. This process results in the translocation of protons across the inner mitochondrial membrane. The proton gradient that is generated is used to drive ATP synthase, an enzyme that converts ADP to ATP, to generate a net of approximately 36 molecules of ATP per molecule of glucose. Relatively inert cells, such as naïve T lymphocytes that are not engaging in cellular growth or proliferation, have little demand for biosynthetic processes other than for basic housekeeping purposes. For this reason ATP alone is largely sufficient to sustain these cells. For this reason naïve T lymphocytes have relatively low rates of glucose uptake, which they metabolise by glycolysis followed by OxPhos to efficiently generate ATP. However, effector lymphocytes have entirely different bioenergetic and biosynthetic demands compared to naïve lymphocytes, hence it is not surprising that effector lymphocytes adopt a distinct metabolic signature (Gerriets and Rathmell, 2012; Pearce and Pearce, 2013).

2.2. Aerobic glycolysis fuels biosynthetic pathways

It was first recognised by Otto Warburg in 1956 that the metabolism of cancer cells is distinct to that of normal tissue (Warburg, 1956). It is now well accepted that this altered metabolism serves to facilitate the robust growth and proliferation, characteristic of these cells (Vander Heiden et al., 2009). Malignant cells take up large amounts of glucose that is metabolised to pyruvate by a highly active glycolytic pathway. However, Warburg observed that cancer cells do not have high rates of OxPhos. Instead the pyruvate generated by glycolysis is converted to lactate, which is secreted from the cell. This is the type of glucose metabolism is adopted by cells in anaerobic conditions where there is no oxygen available to facilitate OxPhos (Fig. 1). However, cancer cells, and other metabolically active and proliferative cells, also metabolise glucose to lactate even in the presence of abundant oxygen; a metabolic signature termed aerobic glycolysis. Indeed, Otto Warburg also observed that activated lymphocytes become highly glycolytic producing large quantities of lactate (Warburg et al., 1958).

It has long been recognised that aerobic glycolysis is adopted by cells engaging in robust growth and proliferation because it provides the biosynthetic precursors that are essential for the synthesis of nucleotides, amino acids and lipids, i.e. the molecular building blocks essential for increasing the biomass of the cell (Hume et al., 1978; Wang et al., 1976). Many of the intermediates of the glycolytic pathway act as a source of carbon that feeds into a range of biosynthetic pathways (Fig. 2). For instance, glucose-6-phosphate, which is generated by the first step of glycolysis, can be used by the pentose phosphate pathway to generate ribulose-5-phosphate that can be used for the synthesis of nucleotides. Therefore, for cells engaged in aerobic glycolysis the primary function of glucose has shifted from a fuel to generate energy, i.e. ATP, to a source of carbon that can be used for biosynthetic purposes (Hume et al., 1978). If this is the case it seems rather wasteful to secrete large quantities of lactate, a source of carbon. In fact, the secretion of lactate is essential to maintain high rates of glycolysis for a number of reasons. Firstly, glycolysis can generate pyruvate much faster than the mitochondria and the Krebs cycle can use it. Intuitively, this will lead to a build up of pyruvate resulting in product inhibition of the final enzyme of glycolysis, pyruvate kinase. Through a knock-on effect upstream in the glycolytic pathway, the net result would be an inhibition of glycolytic flux. Therefore, one reason to convert pyruvate to lactate is to prevent a build up of pyruvate and allow glycolysis to operate at a higher rate to OxPhos (Vander Heiden et al., 2009). Secondly, NAD+ is an essential cofactor for the enzymatic reaction catalysed by the glycolytic enzyme Glyceraldehyde-3-phosphate