Clinica Chimica Acta 461 (2016) 53–58

Contents lists available at ScienceDirect

Clinica Chimica Acta

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

Review

The Warburg effect: A new story in pulmonary arterial hypertension

Hongyan Peng [a,1], Yunbin Xiao [b,1], Xicheng Deng [c], Jingfei Luo [a], Chenliang Hong [a], Xuping Qin [a,*]

[a] Institute of Pharmacy and Pharmacology, University of South China, Hengyang, Hunan 421001, China
[b] Department of Cardiology, Hunan Children's Hospital, Changsha, Hunan 410007, China
[c] Department of Cardiothoracic Surgery, Hunan Children's Hospital, Changsha, Hunan 410007, China

ARTICLE INFO

Article history:
Received 1 April 2016
Received in revised form 19 July 2016
Accepted 23 July 2016
Available online 27 July 2016

Keywords:
The Warburg effect
Pulmonary arterial hypertension
Pulmonary arterial vascular smooth muscle cells
Pulmonary arterial endothelial cell

ABSTRACT

Pulmonary arterial hypertension (PAH) is a rare yet fatal condition that is characterized by a continuous and notable elevation of pulmonary arterial pressure (PAP), resulting in right heart failure and death. Pulmonary arterial remodelling does not result from abnormal proliferation of pulmonary arterial vascular smooth muscle cells (PASMCs) but from pulmonary arterial endothelial cell (PAEC) dysfunction. However, the pathological mechanism of these two types of vascular cells in pulmonary artery remodelling is unclear. The Warburg effect describes aerobic glycolysis wherein cells commonly reprogram their energy metabolism to preferentially utilize glycolysis over oxidative phosphorylation for ATP production. Recent research has demonstrated that the Warburg effect plays a significant role in the development of PAH, which involves the abnormal proliferation of PASMCs and endothelial dysfunction. This review attempts to illustrate the functions of the Warburg effect in PAH, which may provide a new therapeutic target for PAH treatment.

Contents

1. Introduction

The Warburg effect, a metabolic abnormality, was observed by Otto Warburg in the 1920s; hence, the metabolic abnormality was named the Warburg effect [1]. The Warburg effect, also known as aerobic glycolysis, was identified as central to malignant transformation in a number of tumour types and was characterized by the production of lactate to form an acid environment that creates a protective effect for cancer cells [1] (Fig. 1). Pulmonary arterial hypertension (PAH) is a pulmonary vascular remodelling disease with a continuous and notable elevation of pulmonary arterial pressure (PAP) and pulmonary vascular resistance (PVR), resulting in right heart failure and death [1]. Researchers have reported that pulmonary arterial hypertension (PAH) and cancer share the same metabolic pathway that constitutes the Warburg effect [2,3]. Recently, numerous studies have reported on the pathology of PAH, and a number of treatment options have markedly

* Corresponding author at: Institute of Pharmacy and Pharmacology, University of South China, No. 28 Changsheng Road, Zhengxiang District, Hengyang, Hunan 421001, China.
E-mail address: qinxp333@hotmail.com (X. Qin).
[1] These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.cca.2016.07.017
0009-8981/

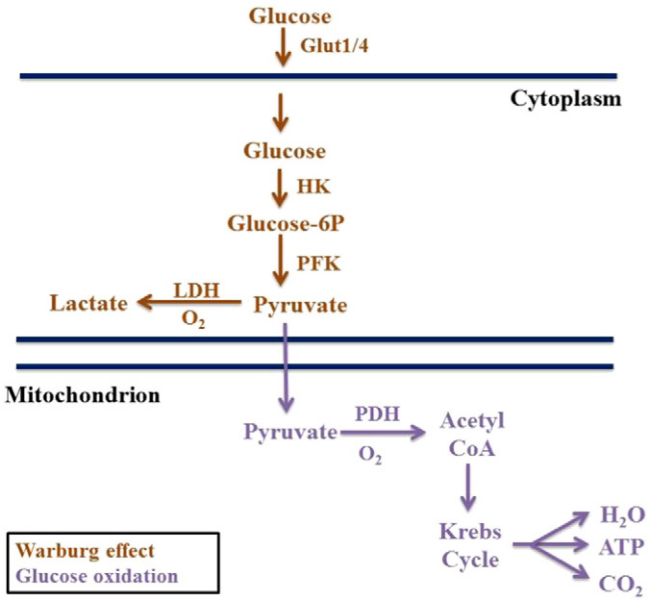

Fig. 1. A diagram of the metabolic shift. Glucose is transported to the cytoplasm by glucose transporter 1/4 (GLUT1/4) and converted to pyruvate via hexokinase (HK) and phosphofructokinase (PFK). Then, pyruvate is catalysed into acetyl-CoA by PDH with sufficient oxygen in the mitochondrion. Finally, acetyl-CoA is completely oxidized to CO_2, H_2O, and ATP in the mitochondrion through the Krebs cycle. However, the metabolic shift, also named the Warburg effect, involves pyruvate being catalysed into lactate by LDH with adequate oxygen in the cytoplasm. Finally, lactate is transported to the extracellular environment by MCT4.

improved overall quality of life and survival in PAH. However, whether the Warburg effect is involved in the pathological process of PAH or initiates this condition with its subsequent progressive pulmonary vascular obstruction remains unknown.

Moreover, PAH is a pulmonary vascular remodelling disease, where the process of pulmonary vascular remodelling involves all layers of the vessel wall and is complicated by cellular heterogeneity within each compartment of the pulmonary arterial wall [3]. Indeed, each cell type, including pulmonary arterial endothelial cells (PAECs), pulmonary arterial vascular smooth muscle cells (PASMCs), and fibroblasts, as well as inflammatory cells and platelets [3], may be involved in PAH. Nevertheless, PAECs and PASMCs play a more significant role in PAH because abnormal proliferation of PASMCs and PAECs are a central component of pulmonary arterial remodelling. In fact, an effective therapy of PAH is to decrease pulmonary vascular resistance (PVR) by inhibiting abnormal proliferation and migration of PASMCs and by improving PAEC functions. However, existing therapies or drugs for PAH do not mainly aim to improve abnormal proliferation of pulmonary artery cells.

In recent decades, many researchers have found that cancer and PAH share not only a similarly poor prognosis but also a major pathophysiologic mechanism, including increasing cell proliferation and an emerging metabolic shift. Interestingly, studies have reported that the animal model of PAH [4] and extravascular tissue of PAH patients exhibit the Warburg effect [5], which indicates that the pathophysiologic mechanism of PAH may be the same as cancer. However, it remains unclear whether the Warburg effect is involved in PASMC proliferation and endothelial dysfunction. In addition, how to initiate proliferation or dysfunction of pulmonary arterial cells remains unclear. Thus, the purpose of this review is to introduce a new story about the significant roles the Warburg effect plays in PASMC proliferation and endothelial dysfunction.

2. The signalling pathway involved in the Warburg effect in PASMC hyperproliferation

The vascular wall of pulmonary arteries is considered to be a proliferative and anti-apoptotic microenvironment [6]. PASMCs are part of the pulmonary vascular wall and play a central role in pulmonary vascular remodelling. Increased PASMC proliferation and apoptosis resistance have been observed in PAH. Accordingly, the up-regulation of growth factors [7] as well as a metabolic shift [8] are also present in PAH. This metabolic shift may involve immune or inflammatory cell recruitment [9], increase cytokine or chemokine expression [10], and cause mitochondrial membrane hyperpolarization, which eventually leads to increasing PASMC proliferation and decreasing PASMC apoptosis. However, how the Warburg effect mediates PASMC proliferation and apoptosis remains unclear. However, signalling pathways have been reported that involve Warburg effect-mediated PASMC proliferation.

2.1. Sirt3/STAT3/NFATc2

Sirtuins, a family of NAD^+-dependent histone deacetylase (HDACs) in mammalian cells, are associated with a wide range of physical processes, including cell survival, apoptosis and metabolism [11]. Mammals have seven Sirtuins, including Sirt1, Sirt2, Sirt3, Sirt4, Sirt5, Sirt6, and Sirt7, that are distributed throughout the cell [12]. Sirt3 is the best characterized mitochondrial Sirtuin; it regulates many levels of mitochondrial function through deacetylation activity that activates multiple electron transport chain (ETC) complexes and enzymes, leading to impaired oxidative phosphorylation and a compensatory increase in glucose uptake and glycolysis [13]. Furthermore, Sirt3 is a critical regulator of metabolic homeostasis in PASMCs, and a lack of Sirt3 function promotes the development of PAH via increasing acetylation of mitochondrial enzymes and ETC complexes, which suppresses mitochondrial oxidative phosphorylation [14] and inhibits mitochondria-dependent apoptosis [13].

Additionally, downstream mitochondrial signalling promotes the activation of proliferative and antiapoptotic transcription factors that are important in human and animal PAH, including the signal transducer and activator of transcription 3 (STAT3) [15] and the nuclear factor of activated T cells (NFAT) [16].

STAT belongs to the signal transducers and activators of transcription protein family that regulates diverse cellular processes, including growth and survival, and is frequently deregulated in cancer [17]. The STAT protein family consists of 7 isoforms, including STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6, with STAT3 being the most important in cardiovascular diseases [17]. Recent studies have indicated that STAT3 localizes to mitochondria [18]; in particular, mitochondrial STAT3 increases the activity of complexes I and II of the respiratory chain in a transcription-independent manner [19]. The research has shown that PASMCs from Sirt3 knock out (Sirt3KO-PASMCs) mice exhibited activated STAT3 by increasing STAT3 phosphorylation at tyrosine 705 and by promoting STAT3 nuclear translocation, which decreases ETC complex activity [15]. Furthermore, a STAT3 target gene, the provirus integration site for Moloney murine leukaemia virus (Pim1), has been shown to contribute to PAH pathogenesis by increasing PASMC proliferation and resistance to apoptosis [17,21].

Interestingly, the nuclear factor of activated T cells isoform 2 (NFATc2) can be enhanced by Pim1 activation. NFATc2, a master activator of T cells, belongs to the nuclear factor of activated T cells (NFAT) family and increases the transcription of multiple inflammatory mediators and activates T and B cells [20]. NFATs were originally identified as transcription regulators in lymphoid cells, but it has since been shown that they play a critical role in a variety of cells, including PASMCs [21]. NFATc2 is related to glycolysis and regulates the transcription of numerous glycolytic enzymes, promotes proliferation and inhibits apoptosis in PASMCs of PAH [13]. Moreover, the NFATc2 target gene KCNA5 encodes the voltage-gated potassium channel Kv1.5, and KCNA5 mRNA levels are reduced in Sirt3-KO PASMCs [13]. As Kv1.5 regulates the resting plasma membrane potential in PASMC, its loss or inhibition causes plasma membrane depolarization and Ca^{2+} influx [22], which lead to an increase in Ca^{2+} that further enhances NFATc2 activation within a positive feedback loop, contributing to its sustained activation.