Review

MOLECULAR METABOLISM

Transcribing β-cell mitochondria in health and disease

Hindrik Mulder*

ABSTRACT

Background: The recent genome-wide association studies (GWAS) of Type 2 Diabetes (T2D) have identified the pancreatic β-cell as the culprit in the pathogenesis of the disease. Mitochondrial metabolism plays a crucial role in the processes controlling release of insulin and β-cell mass. This notion implies that mechanisms controlling mitochondrial function have the potential to play a decisive pathogenetic role in T2D.
Scope of the review: This article reviews studies demonstrating that there is indeed mitochondrial dysfunction in islets in T2D, and that GWAS have identified a variant in the gene encoding transcription factor B1 mitochondrial (*TFB1M*), predisposing to T2D due to mitochondrial dysfunction and impaired insulin secretion. Mechanistic studies of the nature of this pathogenetic link, as well as of other mitochondrial transcription factors, are described.
Major conclusions: Based on this, it is argued that transcription and translation in mitochondria are critical processes determining mitochondrial function in β-cells in health and disease.

Keywords β-Cell; Mitochondria; Islets; Genome-wide association study (GWAS); Insulin secretion; Expression quantitative trait locus (eQTL)

1. INTRODUCTION

Mitochondria are at center stage in whole body metabolic control in health and disease. This is undisputed given their critical functions in the cellular machinery providing fuel, reducing equivalents and building blocks for basic molecular processes. This notwithstanding, how dysfunction of this system evolves and contributes to, as well as causes, common metabolic diseases is still less well understood. This review will focus on the role of mitochondria in the insulin-secreting β-cells under normal conditions and the events culminating in Type 2 Diabetes (T2D). The emphasis on β-cell mitochondria is prompted by the fact that the genome-wide association studies (GWAS) of T2D and related traits have shown that the β-cell is the main culprit in T2D [1]. A potential role for mitochondrial dysfunction in insulin target tissues is heavily debated but will not be dealt with here; excellent reviews are available elsewhere [2,3].
I will begin by outlining the critical role of mitochondria in β-cell function, with a focus on glucose-stimulated insulin secretion (GSIS). Then I will describe the fundamental processes whereby mitochondrial function is controlled, with an emphasis on transcriptional and translational regulation in mitochondria. I will highlight how dysregulation of mitochondria has been implicated in the pathogenesis of T2D. To this end, I will review human and experimental studies linking mitochondrial dysfunction causally to β-cell dysfunction and subsequently diabetes.

2. MITOCHONDRIA AND β-CELLS: STIMULUS-SECRETION COUPLING

The primary role of the pancreatic β-cell is to release insulin in response to a rise in blood glucose levels after a meal. To carry out this task, β-cells have developed an elaborate machinery that translates fluctuations in ambient glucose concentrations into cellular processes that signal to the exocytotic machinery, leading to transport, priming, fusion and emptying of insulin granules. Moreover, insulin secretion in response to a strong stimulation by glucose is biphasic, i.e., a rapid initial peak is followed by a slower but sustained second phase of insulin secretion. The critical role of mitochondria is to provide the signals controlling these processes. These signals are generated from fuel metabolism (Figure 1).

Unit of Molecular Metabolism, Lund University Diabetes Centre, Malmö, Sweden

*Unit of Molecular Metabolism, Lund University Diabetes Centre, Jan Waldenströms gata 35, SE-205 02 Malmö, Sweden. E-mail: hindrik.mulder@med.lu.se (H. Mulder).

Abbreviations: ATGL, adipocyte triglyceride lipase; AMPK, AMP-dependent protein kinase; COX, Cytochrome *c* oxidase; CYTB, Cytochrome *b*; ERR-α, Estrogen-related receptor-α; eQTL, Expression quantitative trait locus; GDH, Glutamate dehydrogenase; GSIS, Glucose-stimulated insulin secretion; GWAS, Genome-wide association study; HSL, Hormone-sensitive lipase; ICD_c, Cytosolic isocitrate dehydrogenase; K_{ATP}, ATP-dependent K^+-channel; MTERF, Mitochondrial transcription termination factor; ND, NADH dehydrogenase; NRF, Nuclear respiratory factor; NSUN4, NOP2/Sun RNA methyltransferase family member 4; OXPHOS, Oxidative phosphorylation; PC, Pyruvate carboxylase; PDH, pyruvate dehydrogenase; PGC, Peroxisome proliferator-activated receptor-γ co-activator; POLγ, DNA polymerase-γ; POLRMT, Mitochondrial RNA polymerase; PPARγ, Peroxisome proliferator-activated receptor-γ; PRC, PGC1-related coactivator; SENP1, Sentrin/SUMO-specific protease-1; SNP, Single Nucleotide Polymorphism; SUR1, Sulphonylurea receptor-1; T2D, Type 2 Diabetes; TCA, Tricarboxylic acid; TEFM, Mitochondrial transcription elongation factor; TFAM, Transcription factor A mitochondrial; TFB1M, Transcription factor B1 mitochondrial; TFB2M, Transcription factor B2 mitochondrial

Received February 6, 2017 • Revision received May 13, 2017 • Accepted May 22, 2017 • Available online xxx

http://dx.doi.org/10.1016/j.molmet.2017.05.014

Review

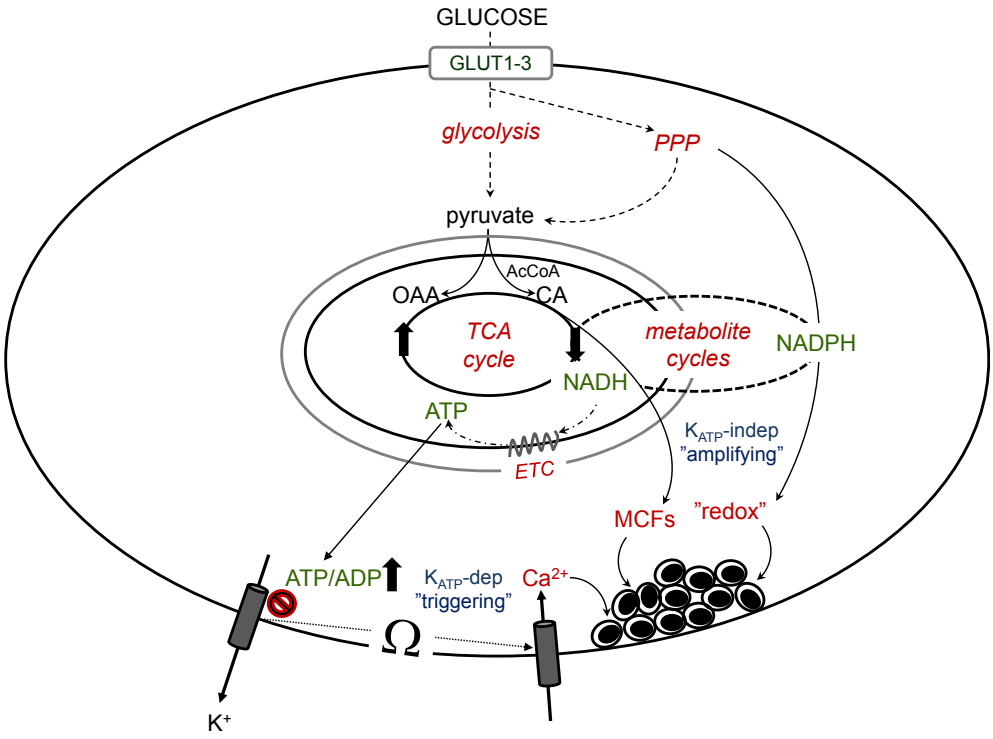

Figure 1: Stimulus-secretion coupling in the pancreatic β-cell. Glucose is transported into the β-cell via facilitated diffusion in proportion to its extracellular concentration. Metabolism in glycolysis and the tricarboxylic acid (TCA) cycle ensues. This leads to a rise in the ATP/ADP ratio and closing of an ATP-dependent K^+-channel (K_{ATP}) in the plasma membrane. A voltage-dependent Ca^{2+}-channel opens and triggers exocytosis of insulin. In addition, metabolic coupling factors (MCF) amplify insulin secretion. These are thought to be generated by metabolite cycles associated with the TCA cycle and the pentose phosphate pathway (PPP). MCFs may be NADPH, perhaps mediating its effect via cellular redox, glutamate or lipid moieties. AcCoa — acetyl-CoA; CA — citrate; ETC — electron transport chain; GLUT — glucose transporters; OAA — oxaloacetate; Ω — membrane polarization.

2.1. Triggering phase of insulin release

The consensus model of β-cell stimulus-secretion coupling holds that glucose is transported into the β-cell by facilitated transport in proportion to its extracellular concentration [4,5] (Figure 1). This is carried out by GLUT2 in rodents [6] and predominantly by GLUT1 and 3 in humans [7]. After phosphorylation by glucokinase, glycolysis ensues, resulting mainly in production of pyruvate; lactate formation occurs, if at all, at a slow rate owing to very low expression of lactate dehydrogenases under normal conditions [8—10]. Pyruvate enters the mitochondria and is either decarboxylated by pyruvate dehydrogenase (PDH) or carboxylated by pyruvate carboxylase (PC); hence, acetyl-CoA and oxaloacetate are formed, respectively, adding carbons to the tricarboxylic acid (TCA) cycle in the mitochondrial matrix. Oxidation of citrate back to oxaloacetate generates two molecules of CO_2, the reducing equivalents NADH, as well as one molecule GTP. NADH donates electrons to the electron transport chain in the inner mitochondrial membrane. A proton-motive force is created, driving extrusion of protons through complexes I, III, and IV into the intermembrane space. Hereby, an electrochemical proton gradient is generated. The ATP synthase allows flow of protons back into the matrix. The energy harnessed by this flow drives phosphorylation of ADP to ATP — oxidative phosphorylation (OXPHOS).

The ATP formed is the critical energy required in any cell. It is transported out of the mitochondria by the adenine nucleotide transporter. In addition to energizing the major functions of the cell, ATP serves a specialized function in the β-cell. A rise in the cellular ATP/ADP ratio is sensed by sulphonylurea receptor-1 (SUR1) [11]. SUR1 controls an outward-rectifying K^+-channel in the plasma membrane, which maintains a negative resting membrane potential in the β-cell [12]. When this ATP-dependent K^+-channel (K_{ATP}) is closed by increased ATP production in the β-cell, i.e., a rise in the ATP/ADP ratio, the plasma membrane depolarizes [13]. This activates voltage-gated Ca^{2+}-channels, leading to a rapid rise in intracellular Ca^{2+}, and consequently triggering of exocytosis of insulin granules. This mode of stimulus-secretion coupling is sometimes referred to as the K_{ATP}-dependent or triggering pathway of insulin secretion [14] (Figure 1). Clearly, mitochondrial function is of paramount importance for this process [4,15].

2.2. Amplifying phase of insulin release

Raising intracellular Ca^{2+} by other means, e.g., via depolarization of the plasma membrane by KCl, produces a rapid, but transient, release of insulin [16]. This observation led to the recognition of processes required to sustain and amplify secretion of the hormone [14]. Importantly, it was found that some of these processes work independently of the K_{ATP}-channel [17]; they are referred to as K_{ATP}-independent or amplifying pathways of insulin secretion (Figure 1).

Arguably, the most important K_{ATP}-independent stimulator of insulin secretion is glucose itself [18]. A seminal discovery was that the hexose exerts a stimulatory effect on insulin release in the presence of high extracellular K^+ levels (depolarizes the plasma membrane) and diazoxide (maintains the K_{ATP}-channel in an open state) [17]. It was suggested that this amplifying effect on insulin release is exerted by a direct effect on the exocytotic machinery by signals generated in cellular metabolism, i.e., metabolic coupling factors [19,20]. Although widely accepted, this paradigm has recently been challenged, largely

