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Review

Glucose sensing by ChREBP/MondoA–Mlx transcription factors

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ABSTRACT

The paralogous transcription factors ChREBP and MondoA, together with their common binding partner Mlx, have emerged as key mediators of intracellular glucose sensing. By regulating target genes involved in glycolysis and lipogenesis, they mediate metabolic adaptation to changing glucose levels. As disturbed glucose homeostasis plays a central role in human metabolic diseases and as cancer cells often display altered glucose metabolism, better understanding of cellular glucose sensing will likely uncover new therapeutic opportunities. Here we review the regulation, function and evolutionary conservation of the ChREBP/MondoA–Mlx glucose sensing system and discuss possible directions for future research.

Contents

1. Introduction

Multicellular animals sense and control their glucose homeostasis at several levels. Systemic regulation by insulin and glucagon maintains levels of circulating glucose constant during fluctuating nutritional conditions. Upon feeding, elevated circulating glucose is taken up by muscle, liver and adipose tissue through the actions of insulin signaling, while starvation elevates glucagon levels to promote glycogenolysis and gluconeogenesis. The intracellular glucose is rapidly converted into glucose-6-phosphate. Through a yet-unknown mechanism, glucose-6-phosphate activates two paralogous basic helix-loop-helix-leucine zipper (bHLHZ) transcription factors (TFs) ChREBP and MondoA, which heterodimerize with their common binding partner Mlx. This bHLHZ complex resembles the evolutionarily related Myc–Max complex. ChREBP/Mondo–Mlx is known to mediate a majority of the glucose-induced transcriptional response by binding to target gene promoters containing so-called carbohydrate response elements (ChoREs).

Abbreviations: ChREBP, carbohydrate response element binding protein; ChoRE, carbohydrate response element; bHLHZ, basic helix-loop-helix-leucine zipper; TF, transcription factor; G6P, glucose-6-phosphate; 2-DG, 2-deoxyglucose; Xu5P, xylulose 5-phosphate; GSM, glucose-sensing module; MCR, Mondo conserved region; LID, low-glucose inhibitory domain; GRACE, glucose-response activation conserved element; TH, thyroid hormone.

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2. Finding the transcriptional glucose sensing mechanism

While the molecular mechanisms of intracellular glucose sensing have started to emerge during the last decade, the glucose-responsive gene expression and glucose-inducible carbohydrate response element (ChoRE) were described much earlier [1–4]. Consensus ChoRE sequence comprises a tandem E-box element separated by five nucleotides (5′-CACGTGnnnnnCACGTG-3′) [5]. While the spacing displays no variation, the E-boxes are often imperfect [6]. ChoRE identification enabled biochemical purification of the glucose-activated transcription factor, which was named Carbohydrate Response Element Binding Protein, ChREBP [7,8]. Mlx was discovered through its ability to interact with Mad and Mnt proteins, which are transcriptional repressors belonging to the related Myc–Max bHLHZ network [9,10]. This was followed by identification of MondoA as an Mlx binding partner [11]. Based on its homology to MondoA, ChREBP was initially named as MondoB [11]. However, ChREBP has become an established name of this MondoA paralog. ChREBP/MondoB was also independently identified as a gene deleted in Williams-Beuren syndrome (called as WBSCR14; Williams-Beuren syndrome critical region gene 14) [12,13].

3. Regulation of ChREBP/MondoA–Mlx activity by glucose

3.1. Glucose regulates subcellular localization of ChREBP and MondoA

Regulation of ChREBP/MondoA–Mlx complexes involves shuttling between cytoplasm and nucleus (Fig. 1) [11,14–16]. MondoA–Mlx localizes to the outer mitochondrial membrane (OMM) in its inactive state [17]. While mitochondrial localization has not been demonstrated for ChREBP, it displays punctuated cytoplasmic localization upon low glucose in hepatocytes [14]. In response to elevated glucose, MondoA and ChREBP concentrate strongly into the nucleus [14,18]. Heterodimerization of ChREBP/MondoA with Mlx is required for their nuclear entry in response to glucose [15,16,19] and is a prerequisite for their binding to ChoREs [16,20,21]. ChREBP and MondoA activity is, however, regulated at several levels, since forced nuclear accumulation of ChREBP or MondoA is insufficient in target gene transactivation [15,16].

3.2. Activation of ChREBP/MondoA–Mlx by glucose-6-phosphate

Several lines of evidence imply that ChREBP/MondoA–Mlx activation is induced by intracellular glucose-6-phosphate (G6P), the immediate metabolite of glucose (Fig. 1) [18,22,23]. The formation of G6P is catalyzed by hexokinases or glucokinase, which also localize to the OMM [24]. The responsiveness of MondoA–Mlx to G6P was shown elegantly by the use of a glucose analog 2-deoxyglucose (2-DG). 2-DG is phosphorylated into 2-deoxyglucose-6-phosphate (2-DG6P), but it cannot be processed further, leading to 2-DG6P accumulation [18]. In response to 2-DG treatment, MondoA–Mlx translocates into the nucleus and strongly transactivates target genes [18].

Although ChREBP was the first component of the network to be identified as a glucose-responsive factor, the molecular mechanism of its activation has been a matter of debate. Early studies on ChREBP activation pointed to xylulose 5-phosphate (Xu5P), an intermediate of the pentose phosphate pathway, as an activating signal [25]. Xu5P was shown to activate protein phosphatase 2A (PP2A), which lead to dephosphorylation and activation of ChREBP–Mlx [25]. However, the role of PP2A as the primary activator of ChREBP has been questioned in several studies [23,26–28]. Also subsequent studies have provided evidence in favor of G6P, instead of Xu5P, as the main ChREBP-activating metabolite [22,23]. Levels of G6P and Xu5P can be modulated by manipulating expression of glucose 6-phosphate dehydrogenase (G6PDH). Overexpression of G6PDH, which decreases levels of G6P increasing levels of Xu5P, suppresses ChREBP activity and ChREBP target gene expression [23]. Knockdown of G6PDH has the

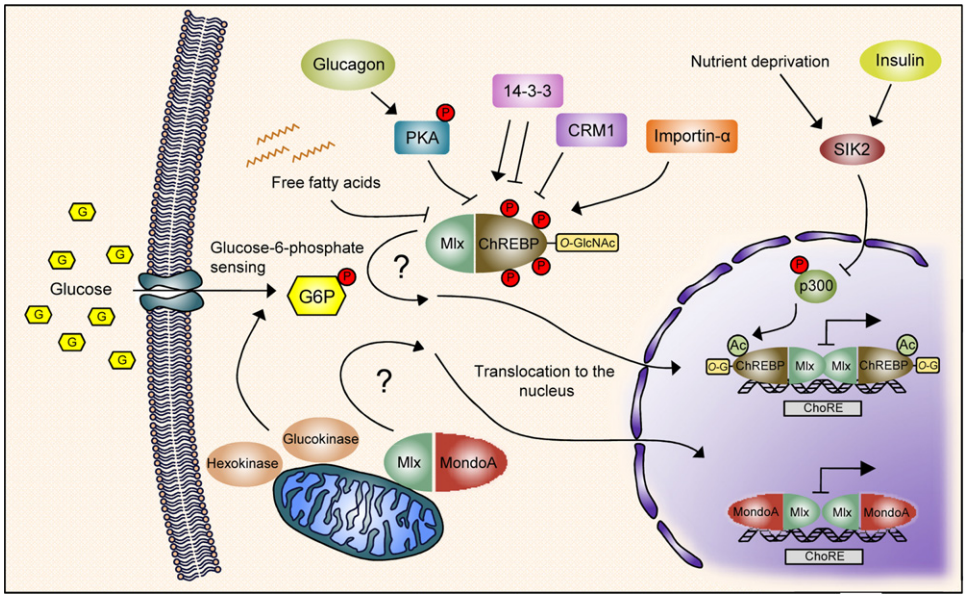

Fig. 1. Regulation of ChREBP/MondoA–Mlx activity. ChREBP/MondoA–Mlx is activated and translocated into nucleus in response to elevated glucose-6-phosphate (G6P) [18,22,23], while free fatty acids suppress ChREBP activity [72,73]. Heterodimerization between ChREBP/MondoA and Mlx is a prerequisite for their nuclear entry and transcriptional activity [15,16,18–21]. MondoA–Mlx is known to shuttle between mitochondria and nucleus [17]. ChREBP–Mlx is phosphorylated by PKA at Ser196 in response to glucagon [23,39]. Also other phosphorylation sites have been implicated in regulating the activity of ChREBP–Mlx [14,35,37]. ChREBP nuclear import is mediated by importin-α, and ChREBP is exported from nucleus by the nuclear export factor CRM1 [32,33,35]. ChREBP and MondoA associate with 14-3-3, which promotes cytoplasmic localization and is needed to keep ChREBP glucose responsive [19,31,34,35]. O-GlcNAcylation increases the transcriptional activation of ChREBP–Mlx [42,43]. The binding of ChREBP to the ChoREs of its target promoters is enhanced by acetylation by p300, which is regulated by SIK2 [36,44,45].