

1           **Sugar sensing by ChREBP/Mondo-Mlx – new insight into downstream**  
2           **regulatory networks and integration of nutrient-derived signals**

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18 **Highlights**

19 -ChREBP/Mondo-Mlx is an intracellular sugar sensor of animals with conserved target  
20 genes and physiological functions

21 - ChREBP/Mondo-Mlx integrates multiple inputs through direct sensing of sugar and  
22 fatty acid-derived metabolites and cross-talk with other nutrient sensing pathways

23 -ChREBP/Mondo-Mlx controls several second-tier regulators, including transcription  
24 factors and hormones

25

26

27 **Abstract**

28 Animals regulate their physiology with respect to nutrient status, which requires  
29 nutrient sensing pathways. Simple carbohydrates, sugars, are sensed by the basic-helix-  
30 loop-helix leucine zipper transcription factors ChREBP/Mondo, together with their  
31 heterodimerization partner Mlx, which are well-established activators of sugar-induced  
32 lipogenesis. Loss of ChREBP/Mondo-Mlx in mouse and *Drosophila* leads to sugar  
33 intolerance, *i.e.* inability to survive on sugar containing diet. Recent evidence has  
34 revealed that ChREBP/Mondo-Mlx responds to sugar and fatty acid-derived  
35 metabolites through several mechanisms and cross-connects with other nutrient sensing  
36 pathways. ChREBP/Mondo-Mlx controls several downstream transcription factors and  
37 hormones, which mediate not only readjustment of metabolic pathways, but also  
38 control feeding behavior, intestinal digestion, and circadian rhythm.

39

40 **Preface**

41 Nutrient intake of animals displays a high degree of variation, which requires fine-tuned  
42 control of metabolic pathways. Animals regulate their metabolic homeostasis by  
43 continuously reading and converging signals originating from both within the organism  
44 and the outside environment. Macronutrients (sugars, amino acids and lipids) are sensed  
45 by nutrient sensing pathways that detect different dietary inputs and orchestrate an  
46 integrated adaptive response that is appropriate for that particular set of macronutrients.  
47 Simple carbohydrates, sugars, are sensed by several mechanisms, of which the so-called  
48 intracellular sugar sensing by ChREBP/Mondo-Mlx transcription factors is among the  
49 most conserved ones. Studies from mouse and *Drosophila* have shown the importance  
50 of this system in providing sugar tolerance; animals lacking ChREBP/Mondo-Mlx die  
51 rapidly on a diet containing sugars at a level, which is normally physiologically

52 tolerated [1,2]. We highlight here recent work, which has revealed several novel aspects  
53 of the ChREBP/Mondo-Mlx physiological function and regulation by nutrient-derived  
54 cues.

55

### 56 **ChREBP/Mondo-Mlx – the conserved regulator of metabolic homeostasis**

57 Carbohydrate response element binding protein (ChREBP, also known as MondoB and  
58 MLXIPL) and its paralog MondoA (MLXIP) are intracellular sugar sensors that are  
59 activated by glucose-6-phosphate (G6P) and other phosphorylated hexoses [3].  
60 ChREBP and MondoA act together with their common heterodimerization partner Mlx,  
61 a necessary step for transcriptional activation. Although both are ubiquitously  
62 expressed, ChREBP is more prominently expressed in the liver and adipose tissue  
63 whereas MondoA is most highly expressed in the skeletal muscle. Muscle breaks down  
64 glucose via the glycolytic pathway to release energy that is used for muscle contraction  
65 and in fact many of the MondoA-Mlx target genes are involved in the glycolytic  
66 pathway [4,5]. Liver is the main site for *de novo* lipogenesis (DNL), where dietary  
67 sugars are converted into triacylglycerols (TAGs) and further transported to adipose  
68 tissue for storage. ChREBP target genes include lipogenic genes, such as *fatty acid*  
69 *synthase* and *acetyl-CoA-carboxylase*, both of which possess well-established  
70 ChREBP-Mlx binding sites, known as the carbohydrate response element (ChoRE), in  
71 their promoters [6,7]. ChREBP-Mlx is also a key regulator of glycolytic genes, such as  
72 *glucokinase regulatory protein*, *glyceraldehyde-3-phosphate dehydrogenase* and *L-*  
73 *type pyruvate kinase*, in the liver and adipose tissue [6-10]. Moreover, ChREBP-Mlx  
74 regulates the glucose-induced expression of *glucose-6-phosphate dehydrogenase*  
75 (*G6PDH*), the rate-limiting enzyme of the pentose phosphate pathway (PPP) [8].

76

77 The physiological function and key metabolic target genes of ChREBP/Mondo-Mlx are  
78 well conserved in animals and studies in *Drosophila* have revealed new insight into the  
79 physiological roles and tissue specificity of intracellular sugar sensing. Whereas the  
80 vertebrate genome encodes for two Mondo proteins, the fruit fly, *Drosophila*, has only  
81 one Mondo protein, displaying high expression in the fat body (corresponding to liver  
82 and adipose tissue), midgut (corresponding to small intestine) and Malpighian tubules  
83 (corresponding to kidney) [2]. Mondo-Mlx mediates a substantial proportion of  
84 *Drosophila* sugar-induced transcription and it activates conserved genes involved in  
85 glycolysis, lipogenesis, and the PPP, which is the most strongly over-represented

86 Mondo-Mlx target pathway in *Drosophila* [11]. The PPP has a key role in producing  
87 NADPH reductive power, which is needed for the biosynthesis of lipids. Indeed,  
88 inhibition of the Mondo-Mlx induced activation of glucose-6-phosphate dehydrogenase  
89 leads to a dramatic reduction of TAG stores in *Drosophila* larvae [11]. The PPP is also  
90 essential for sugar tolerance. The reductive power of NADPH generated by the PPP  
91 prevents oxidative damage upon high sugar feeding through the glutathione system,  
92 which contributes to the animal's ability to tolerate a high sugar diet [11,12].

93

94 In addition to conserved metabolic pathways, studies in *Drosophila* have revealed novel  
95 tissue-specific functions for sugar sensing. Mondo-Mlx is essential for the sugar-  
96 induced regulation of digestive enzymes in the midgut. Sugar feeding represses the  
97 expression of Amylases and Maltases, which are needed for digestion of complex  
98 carbohydrates [13,14]. This mechanism might have a role in regulating glucose intake,  
99 in order to prevent glucose overload [15]. Mondo-Mlx also regulates Malpighian  
100 tubule-specific glucose transporters, possibly in order to control excretion of excess  
101 glucose [11]. Furthermore, Mondo-Mlx is essential for normal flight muscle function  
102 and structure. Muscle-specific knockdown leads to accumulation of glycogen stores,  
103 possibly reflecting reduced glucose utilization [16]. In conclusion, ChREBP/Mondo-  
104 Mlx is a conserved sugar sensor within animals, with essential roles in sugar-induced  
105 lipogenesis and coordinating whole body glucose homeostasis by controlling  
106 carbohydrate digestion and transport.

107

### 108 **ChREBP/Mondo-Mlx controls a gene regulatory network**

109 In addition to direct regulation of key metabolic genes Mondo-Mlx is emerging as a  
110 master regulator of other regulatory genes, including transcription factors (TFs) (Figure  
111 1). Mondo-Mlx directly regulates Krüppel-like factor 10 (KLF10, also known as  
112 TIEG1) and its *Drosophila* ortholog Cabut. In *Drosophila*, the *cabut* promoter has two  
113 high affinity ChoREs. *cabut* is the most strongly downregulated gene in *mlx* mutants  
114 and depletion of Cabut by RNAi induces sugar intolerance in *Drosophila* larvae [2].  
115 Similarly, in rat primary hepatocytes KLF10 expression is activated by glucose  
116 stimulation and hampered by dominant negative Mlx [17]. Elevated KLF10 expression  
117 is also observed *in vivo* in mouse following feeding on a high fat/high sugar diet [18].  
118 Adenoviral overexpression of KLF10 in primary hepatocytes suppressed the glucose-  
119 induced activation of ChREBP and several of its target genes, suggesting that KLF10

120 can act as a negative feedback regulator of ChREBP [17]. A different outcome was  
121 observed in loss-of-function experiments in *Drosophila*, where Cabut mediated  
122 downregulation of a gene set in response to sugar feeding [19]. Among the most  
123 strongly repressed Cabut target genes was *phosphoenolpyruvate carboxykinase*  
124 (*pepck*), which is a direct Cabut target and also a target of KLF10 in mouse [19,20].  
125 PEPCK is the rate-limiting enzyme of cataplerotic flux from the TCA cycle to mediate  
126 channeling of carbon towards gluco- and glyceroneogenesis. Consistent with high  
127 expression of *pepck*, *Drosophila mlx* mutants display high levels of glycerol and  
128 trehalose (a circulating form of glucose in insects), which could be suppressed by  
129 simultaneous loss of *pepck* [19]. Interestingly, Cabut also links sugar sensing to  
130 regulation of circadian rhythm. Deregulation of Cabut has a dramatic impact on the  
131 cycling of circadian metabolic gene output, while having no impact on the cycling of  
132 core clock genes [19]. Notably, in rat hepatocytes ChREBP-Mlx also directly regulates  
133 BHLHB2/DEC1, which has a well-established role in circadian regulation [21,22]. In  
134 conclusion, through direct regulation of downstream transcription factors,  
135 ChREBP/Mondo-Mlx-mediated sugar sensing appears to be closely coupled to the  
136 circadian clock. Considering the observations on re-setting of the peripheral circadian  
137 clock through timed feeding [23], it will be interesting to further explore the  
138 physiological importance of the observed interplay between these TFs.

139

140 ChREBP/Mondo-Mlx also controls the expression of TFs involved in lipid  
141 homeostasis. The Gli-similar (GLIS) transcription factor Sugarbabe has been long  
142 known as the earliest and strongest sugar-responsive gene in *Drosophila* [14]. Recently,  
143 *sugarbabe* was found to be a direct target of Mondo-Mlx. Loss- and gain of function  
144 analyses revealed that Sugarbabe contributes to the lipid homeostasis *in vivo*. It  
145 regulates fatty acid synthesis downstream of Mondo-Mlx by inducing the expression of  
146 lipogenic genes *ACC*, *FAS*, *AcCoAS* and *ATPCL* in response to sugar feeding [11]. Gli-  
147 similar transcription factor 2, the closest human homologue of Sugarbabe, was  
148 originally identified as a bifunctional transcription factor, regulating both the activation  
149 and repression of its target genes involved in kidney development [24]. Interestingly,  
150 variants of another *sugarbabe* homolog, GLIS3, are now established as one of the  
151 strongest known genetic risk factors for both type 1 and type 2 diabetes [25]. In addition  
152 to direct regulation of other TFs, ChREBP-Mlx also regulates downstream effectors  
153 indirectly. One such example is the fatty acid responsive nuclear receptor PPAR $\gamma$  [26].

154 ChREBP expression is elevated during adipocyte differentiation and ChREBP activity  
155 is needed to maintain maximal transcriptional output of adipogenic PPAR $\gamma$ .  
156 Consequently, ectopic activation of ChREBP promotes adipocyte differentiation.  
157 ChREBP likely affects PPAR $\gamma$  indirectly through lipid biosynthesis as the activating  
158 effects of ChREBP depend on functional Fatty acid synthase [26]. In conclusion,  
159 ChREBP/Mondo-Mlx contributes to lipid homeostasis through its direct targets as well  
160 as through secondary TFs.

161

### 162 **New hormonal targets of ChREBP/Mondo-Mlx**

163 In addition to downstream transcription factors, ChREBP/Mondo-Mlx contributes to  
164 systemic regulation through hormonal signals, including FGF21. In cultured  
165 hepatocytes ChREBP-Mlx regulates the expression of *FGF21* in a glucose-dependent  
166 manner [8,27]. Levels of circulating FGF21 are rapidly increased in response to  
167 fructose in humans as well as mice [28,29]. Interestingly, both baseline and fructose-  
168 stimulated levels of FGF21 are significantly elevated in subjects with metabolic  
169 syndrome [28]. This is consistent with findings showing elevated activation of hepatic  
170 ChREBP in obese individuals [30]. Loss of FGF21 in turn leads to impaired *de novo*  
171 lipogenesis in mouse liver, which is accompanied by liver fibrosis following prolonged  
172 fructose exposure [29]. In addition to metabolic regulation, FGF21 also regulates sugar  
173 feeding. Mice lacking FGF21 consume elevated levels of sucrose, whereas ectopic  
174 FGF21 suppresses the intake of sugar in mice as well as cynomolgus monkeys [31,32].  
175 The liver-derived FGF21 suppresses sugar feeding in mice by acting through the FGF21  
176 receptor complex in the paraventricular nucleus of the hypothalamus [31]. A similar  
177 regulatory system likely exists in humans, since variants of *FGF21* are strongly  
178 associated with sweet preference, as judged by the consumption of candy [33].

179

180 Research in *Drosophila* has revealed new connections between Mondo-Mlx and  
181 hormonal metabolic regulation via TGF- $\beta$ /Activin signaling. TGF- $\beta$ /Activin ligand  
182 Dawdle is highly expressed in the *Drosophila* fat body, from where it is secreted [15].  
183 Sugar feeding strongly elevates *dawdle* expression, while loss of *mlx* leads to impaired  
184 *dawdle* activation [11,15]. Moreover, Mondo-Mlx directly binds to a ChoRE at the  
185 *dawdle* promoter [11]. Dawdle is essential in metabolic regulation as mutants of *dawdle*  
186 show elevated circulating trehalose and glucose as well as high levels of glycogen and

187 triacylglycerol [34]. Dawdle acts through multiple target tissues, for example it acts on  
188 *Drosophila* insulin producing cells to promote insulin-like peptide secretion [34].  
189 Moreover, Dawdle activates its receptor Baboon in intestinal enterocytes and  
190 suppresses the expression of genes encoding carbohydrate digestive enzymes,  
191 Amylases and Maltases, thus inhibiting carbohydrate digestion in response to excess  
192 systemic glucose [15]. Interestingly, Dawdle functionally cooperates with the Mondo-  
193 Mlx target TF Sugarbabe, which also contributes to the sugar-induced repression of  
194 amylase expression [11]. In conclusion, studies in mammals and *Drosophila* have  
195 opened new insight into the role of ChREBP/Mondo-Mlx on the systemic regulation of  
196 metabolism via hormones secreted by the liver and fat body, respectively.

197

### 198 **Direct regulation of ChREBP/Mondo-Mlx by nutrient-derived cues**

199 ChREBP/Mondo TFs respond to sugars via their N-terminal Glucose sensing module  
200 (GSM), which can be functionally divided into low-glucose inhibitory domain (LID)  
201 and glucose response activation conserved element (GRACE) [35]. Although direct  
202 structural evidence about ChREBP/Mondo activation mechanism is still missing, ample  
203 indirect evidence suggests that direct binding of G6P, and possibly other  
204 phosphorylated hexoses, lead to loss of intramolecular inhibition of GRACE by LID  
205 [36,37]. Subsequently activated ChREBP/Mondo-Mlx dissociates from 14-3-3,  
206 translocates to the nucleus, and binds to the ChoRE to activate its target genes (Figure  
207 2A) [38-40]. Furthermore, glucose-responsive dephosphorylation as well as acetylation  
208 have also been shown to contribute to ChREBP activation [41,42]. A detailed  
209 representation of ChREBP/Mondo-Mlx activation has been presented elsewhere [3].  
210 This core activation mechanism allows ChREBP/Mondo-Mlx to control gene  
211 expression in response to sugar availability. However, additional regulatory  
212 mechanisms and functional interplay with other nutrient-responsive TFs to integrate  
213 other nutrient-derived signals are beginning to emerge. One such signaling mechanism  
214 is O-GlcNacylation. The synthesis of the substrate for O-GlcNacylation, UDP-GlcNAc,  
215 through the hexosamine biosynthesis pathway (HBP), depends on availability of  
216 nutrients, such as glucose and glutamine [43]. Thereby, O-GlcNacylation is considered  
217 as a nutrient sensing mechanism. ChREBP is O-GlcNAc modified [44-46] and recent  
218 mass-spectrometric analysis have revealed multiple target sites [47]. Consistent with  
219 the glucose sensitivity of the HBP, the levels of ChREBP O-GlcNAc modification are  
220 increased upon exposure to high glucose [44,45]. O-GlcNAc modification increases

221 ChREBP protein stability and increases the expression of ChREBP target genes [44].  
222 Pancreatic  $\beta$ -cells have an inherent glucose sensing capacity and ChREBP activation  
223 seems to involve a distinct mechanism in this setting. ChREBP forms a cytoplasmic  
224 complex with a Calcium binding protein Sorcin [48]. Calcium influx in response to  
225 high glucose releases ChREBP allowing its nuclear localization. In conclusion,  
226 ChREBP activity is regulated by sugars through multiple parallel mechanisms.

227

228 In addition to posttranslational modifications, ChREBP/Mondo-Mlx is also regulated  
229 at the transcriptional level. In mammals, the *ChREBP* gene encodes two isoforms,  
230 *ChREBP- $\alpha$*  and *ChREBP- $\beta$* , which are transcribed from different promoters [49].  
231 ChREBP- $\alpha$  contains the N-terminal GSM and is thus directly activated by G6P.  
232 ChREBP- $\alpha$  stimulates the expression of the shorter ChREBP- $\beta$ , which lacks inherent  
233 glucose sensing ability, but has a 20-fold higher transcriptional activity than ChREBP-  
234  $\alpha$ . The promoter of *ChREBP* contains a binding site for Liver X receptor (LXR), and it  
235 has been shown that LXR regulates the expression of *ChREBP* in the liver [50,51].  
236 However, the effect of LXR on *ChREBP* expression appears to be independent of  
237 nutrient as the expression of *ChREBP* is not altered in high-sugar fed LXR mutant mice  
238 [52]. Hepatocyte nuclear factor 4 alpha (HNF-4 $\alpha$ ) in turn has been shown to activate  
239 the expression of both *ChREBP* isoforms in response to glucose [53]. Moreover, HNF-  
240 4 $\alpha$  has been also shown to physically interact with ChREBP, and this interaction is  
241 promoted by glucose [53,54].

242

243 While ChREBP is activated in the liver of animals on a high sugar diet, a high lipid diet  
244 has an inhibitory effect. Furthermore, administration of fatty acids inhibits nuclear  
245 translocation and activation of ChREBP (Figure 2B) [55,56]. Fatty acids are oxidized  
246 into ketone bodies, such as  $\beta$ -hydroxybutyrate and acetoacetate. By using an *in vitro*  
247 binding assay with purified ChREBP and 14-3-3 as well as protein-free hepatocyte  
248 extracts, Nagakawa and coworkers showed that  $\beta$ -hydroxybutyrate and acetoacetate  
249 increase the binding between ChREBP and 14-3-3 [57]. This increased binding anchors  
250 ChREBP to the cytoplasm, preventing its target gene activation. Fatty acid  
251 administration also significantly elevates the levels of intracellular AMP [55]. AMP  
252 activates the AMP-activated protein kinase (AMPK), which phosphorylates ChREBP  
253 on Ser568 and inhibits its transcriptional activity, while having no impact on the nuclear



254 localization [55,58]. Interestingly, a recent study suggests that AMP can also inhibit  
255 ChREBP directly, through an allosteric mechanism. AMP binds to ChREBP and  
256 increases its affinity to 14-3-3, which prevents ChREBP nuclear translocation [58]. In  
257 conclusion, recent studies suggest that ChREBP acts as a direct sensor for several fatty  
258 acid-derived metabolites, thus integrating multiple nutrient-derived cues.

259

### 260 **Cross-talk between ChREBP and other nutrient sensing pathways**

261 In addition to nutrient sensing through direct allosteric regulation and posttranslational  
262 mechanisms, ChREBP/Mondo acts in close synergy with other nutrient sensing  
263 systems, including insulin signaling. A well-established example is SREBP, a target of  
264 insulin signaling, which controls synergistically lipogenic gene expression with  
265 ChREBP [59]. In *Drosophila*, Mondo was shown to act synergistically with Salt-  
266 inducible kinase 3 (SIK3), which is also a target of the insulin signaling pathway  
267 [12,60]. Mondo and SIK3 act cooperatively to activate the PPP upon sugar feeding [12].  
268 Similarly to Mondo, SIK3 is essential for sugar tolerance and animals with reduced  
269 expression of both Mondo and SIK3 display extremely low tolerance towards dietary  
270 sugars [12]. Moreover, ChREBP O-GlcNacylation is inhibited by Foxo1, which is an  
271 inhibitory target of insulin signaling, thus providing additional cross-talk between  
272 insulin-mediated systemic glucose homeostasis and intracellular glucose sensing [46].  
273 ChREBP also likely modulates insulin signaling, since genome-wide analysis of  
274 ChREBP chromatin binding in mouse liver and adipose tissue revealed significant  
275 enrichment in ChREBP binding near genes encoding components of the insulin  
276 signaling pathway [61].

277

278 Evidence about cross-talk between sugar sensing and amino acid sensing is also  
279 emerging (Figure 2C). Glutamine is a critical metabolic intermediate, acting as a carbon  
280 and ammonium carrier. Glutaminolysis is critical in replenishing the TCA cycle, when  
281 TCA cycle carbon is channeled to biosynthesis. Interestingly, glutamine modifies  
282 glucose sensing by inhibiting the transcriptional output of MondoA [62]. Consequently,  
283 glutamine inhibits the glucose-induced activation of *TXNIP*, a negative regulator of  
284 glucose transporter GLUT1 [63], thus increasing cellular glucose uptake [62].  
285 Glutamine has no impact on MondoA nuclear localization or DNA binding, but it likely  
286 impacts MondoA cofactors [62]. MondoA can also control the uptake of glutamine. In  
287 endothelial cells infected with Kaposi's Sarcoma-associated Herpesvirus, glutamine

288 transporter SLC1A5 is activated in a MondoA-Mlx-dependent manner to facilitate  
289 glutaminolysis [64]. In conclusion, MondoA coordinates the intracellular balance of  
290 glucose and glutamine catabolism.

291

292 The mechanistic target of rapamycin (mTOR) is a conserved intracellular amino acid  
293 sensing system, which also has been shown to modulate the output of ChREBP/Mondo-  
294 Mlx. mTOR inhibitors increase the expression of MondoA-Mlx target gene *TXNIP*  
295 [65]. mTOR physically interacts with MondoA and sequesters it from forming an active  
296 complex with Mlx [65]. Similarly to MondoA, ChREBP is inhibited by mTOR through  
297 protein-protein interaction [66]. mTOR inhibition leads to increased expression of  
298 *TXNIP*, which causes death of pancreatic  $\beta$ -cells [66]. Interestingly, the levels of  
299 *TXNIP* are strongly elevated in diabetic islets, further suggesting that retaining the  
300 interaction between cellular amino acid and glucose sensing is essential for normal  $\beta$ -  
301 cell homeostasis. Recent evidence from *C. elegans* implies that Mondo-Mlx has a  
302 capacity to modulate mTOR signaling, since loss of *C. elegans* homolog of Mondo and  
303 Myc, MLL-1, leads to mTOR activation [67]. MLL-1 represses the expression of  
304 leucyl-tRNA synthetase *lars-1*, whose activity promotes mTOR activation via RAG-  
305 GTPases [67,68]. Through the regulation of mTOR signaling, MLL-1 is essential for  
306 promoting longevity [67]. In sum, mTOR and ChREBP/Mondo pathways appear to be  
307 closely interconnected, which potentially provides cross-coordination between  
308 phenotypic outputs of dietary sugars and amino acids.

309

### 310 **Concluding remarks**

311 To conclude, recent work in the field has revealed that ChREBP/Mondo-Mlx regulates  
312 a large regulatory network, including transcription factors and hormones, which  
313 controls not only metabolic pathways, but also feeding activity and intestinal digestion.  
314 In addition to intracellular sugar sensing, ChREBP/Mondo-Mlx integrates multiple  
315 nutrient-responsive inputs, placing it at the very heart of an interlinked regulatory  
316 system mediating physiological re-adjustment in response to nutrient intake. Such  
317 integrated control allows animals to flourish in highly variable nutrient landscapes.

318

319 However, several questions remain to be addressed. These include elucidating the  
320 structural basis of the function of the Glucose sensing module. This would allow better

321 understanding of the “nutrient sensor” mechanism of ChREBP/Mondo and possibly to  
322 enable design of new pharmaceuticals to modulate its activity. Given the availability of  
323 animal models, understanding of the physiological roles of ChREBP/Mondo in  
324 different tissues and cell types will certainly arise. Moreover, a wider perspective is  
325 needed to understand the natural variation in dietary sugar intake, and the variation  
326 between species and individuals with respect to their healthy nutrient landscape. As  
327 ChREBP/Mondo-Mlx is a key determinant in sugar tolerance in mice and *Drosophila*,  
328 it will be interesting to analyze its function in animals with differential sugar intake -  
329 and perhaps differential inherent sugar tolerance. Understanding the genetic factors  
330 predisposing humans to disease on a high sugar diet would allow disease prevention  
331 through personalized nutrition.

332

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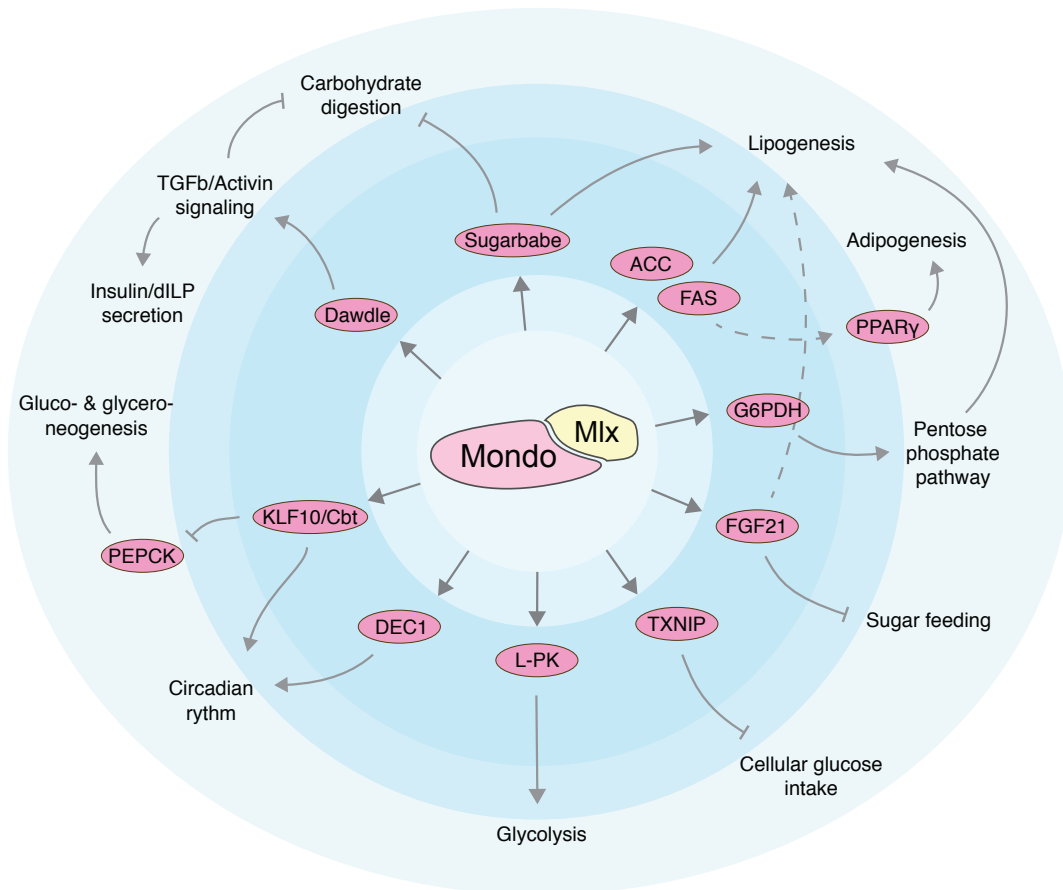
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356 **Figures**

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360 **Figure 1. ChREBP/Mondo-Mlx is a master regulator of a sugar-induced gene**

361 **regulatory network.** In response to sugars, ChREBP/Mondo-Mlx activates the

362 expression of a number of metabolic genes, but also other regulatory genes involved in

363 the control of carbohydrate and lipid metabolism, sugar feeding and circadian rhythm.

364 The figure summarizes key targets of mammalian ChREBP and MondoA as well as

365 *Drosophila* Mondo. Abbreviations: ACC: acetyl-CoA carboxylase, Cbt: Cabut, DEC1:

366 deleted in esophageal cancer 1, FAS: fatty acid synthase, FGF21: fibroblast growth

367 factor 21, G6PDH: glucose-6-phosphate dehydrogenase, KLF10: krüppel-like factor

368 10, L-PK: L-type pyruvate kinase, PEPCK: phosphoenolpyruvate carboxykinase,

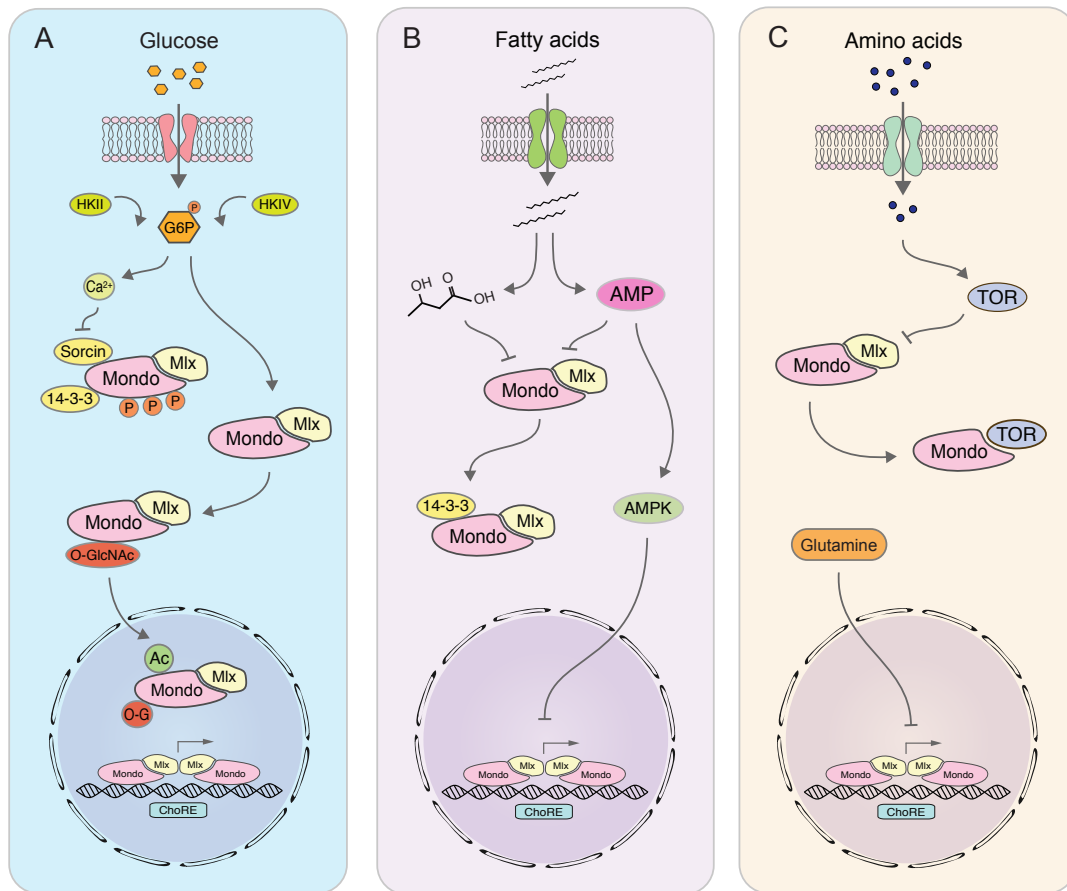
369 PPAR $\gamma$ : peroxisome proliferator-activated receptor gamma, TXNIP: thioredoxin-

370 interacting protein.

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375 **Figure 2. ChREBP/Mondo-Mlx activity is regulated by many nutrient-derived**  
376 **cues. ChREBP/Mondo-Mlx is activated by glucose-6-phosphate (G6P) (A) and**  
377 **inhibited both by ketone bodies and AMP, whose levels depend on fatty acids (B).**  
378 **Direct binding of TOR to MondoA and ChREBP inhibits their function and glutamine**  
379 **inhibits the transcriptional activity of ChREBP-Mlx (C).**

380

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416 *Of outstanding interest \*\**  
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