The Role of Mondo Family Transcription Factors in Nutrient-Sensing and Obesity

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In the past several decades obesity has become one of the greatest health burdens worldwide. Diet high in fats and fructose is one of the main causes for the prevalence of metabolic disorders including obesity. Promoting brown or beige adipocyte development and activity is regarded as a potential treatment of obesity. Mondo family transcription factors including MondoA and carbohydrate response element binding protein (ChREBP) are critical for nutrient-sensing in multiple metabolic organs including the skeletal muscle, liver, adipose tissue and pancreas. Under normal nutrient conditions, Mondo family transcription factors directly regulate glucose and lipid metabolism in brown and beige adipocytes or modulate the crosstalk between metabolic organs. In this review, we aim to provide an overview of recent advances in the understanding of MondoA and ChREBP in sensing nutrients and regulating obesity or related pathological conditions.

Keywords: MondoA, ChREBP, nutrient-sensing, obesity, brown and beige adipose tissue

INTRODUCTION
The epidemic of obesity has emerged as a worldwide public health issue. In 2017, the Global Burden of Disease Study estimated that high body mass index (BMI), one of the leading risk factors, accounted for 4.72 million deaths and 148 million disability-adjusted life-years (DALYs) (1). Excessive caloric intake mainly derived from the high-fat and high-fructose diet is a major cause for obesity (2–4). The urgent need for weight-loss treatments has given rise to multiple attempts to target cellular metabolism and restore systemic energy homeostasis, among which is the strategy of promoting brown and beige adipocyte activity and development. Brown adipocytes are essential for thermogenesis in mammals with their characteristic expression of uncoupling protein-1 (UCP1) in mitochondria, while beige adipocytes are inducible to express thermogenic genes in response to stimulus (5). Enhancing activities of brown and beige adipocytes not only promotes energy expenditure through heat generation, but also enhances glucose metabolism and protects against insulin resistance (6–11), which provides promising therapeutic effects to counteract obesity and related diseases.

The Mondo family transcription factors, comprised of MondoA (also known as MLXIP) and carbohydrate response element binding protein (ChREBP, also named MondoB and MLXIPL),
belong to the basic helix-loop-helix leucine zipper (bHLH/LZ) family (12, 13). Upon binding to their heteromeric partner MLX (Max-like protein X), Mondo and MLX translocate to the nucleus where they bind to carbohydrate response elements (ChoREs) on target gene promoters, and stimulate a transcriptional response to nutrients (12–14). As a structural basis of their nutrient-sensing and responsiveness, the glucose-sensing module (GSM) of Mondo proteins consists of a low-glucose inhibitory domain (LID) and a glucose-response activation conserved element (GRACE) (Figure 1). Under basal conditions, GRACE is repressed by the LID domain, which is relieved by alterations in nutrient levels such as the elevation of glucose concentration (15). An isoform of ChREBP, ChREBPβ, lacks the LID domain and is induced by the activation of the canonical isoform ChREBPα (16). Upon activation, MondoA and ChREBP bind to importin-α which mediates their nuclear entry (17), while their nuclear export and cytoplasmic retention are regulated by chromosome region maintenance protein 1 (CRM1) and 14-3-3 proteins (18–20). Though similar in structure, MondoA and ChREBP have distinct tissue distribution patterns, with MondoA predominantly in skeletal muscle and immune cells and ChREBP in liver and adipose tissue (12, 13), and our unpublished data.

Initially identified as glucose sensors, Mondo family has more extensive regulatory functions in metabolic homeostasis. Therefore, their role in physiological and pathological conditions has gained growing interest. In this review, we will discuss how MondoA and ChREBP sense and respond to nutrient availability, focusing on the involvement of Mondo family in obesity and related diseases.

**NUTRIENT-SENSING BY MONDOA AND CHREBP**

**ChREBP in Metabolic Organs**

ChREBP is widely expressed in metabolic organs, predominantly in liver, also in adipose tissues, pancreas, intestine, kidney, relatively low in skeletal muscle (21).

ChREBP is regulated by multiple nutrient molecules, among which glucose and its metabolites are major determinants. In the presence of high glucose, glucose 6-phosphate (G6P), the first intermediate in glycolysis binds to the GRACE domain of ChREBP (22, 23). Moreover, xylulose 5-phosphate (Xu5P), the metabolite generated through the pentose phosphate pathway, activates protein phosphatase 2A (PP2A), and the sequential

![FIGURE 1](image_url)
dephosphorylation of several residues activates ChREBP (24). Furthermore, fructose-2,6-bisphosphate (F2,6-BP) derived from fructose-6-phosphate (F6P) has been identified as another signaling metabolite responsible for glucose-induced recruitment of ChREBP to its target genes (25). On the other hand, when glucose is limited, branched chain keto-amino acids (BCKA) and fatty acids (FA) inhibit ChREBP activity (26, 27) (Figure 2).

ChREBP regulates many enzyme genes in glycolysis and lipogenesis, including liver type pyruvate kinase (L-PK), acetyl-CoA carboxylase (ACC), fatty acid synthase (FAS), ATP-citrate lyase (ACLY), stearoyl-CoA desaturase-1 (SCD1) and glycerol-3-phosphate dehydrogenase (GPDH) (28–30). In addition, ChREBP may control very low-density lipoprotein (VLDL) export by regulating microsomal triglyceride transfer protein (MTTP) transcription (31) (Figure 3).

Mouse models with knockout or overexpression of the ChREBP gene provide direct evidence for its role in glucose and lipid metabolism (Table 1). ChREBP global knockout mice show down-regulated pyruvate production and inhibited glycolysis, with lower mRNA levels of ACC, FAS, ACLY and SCD1 in liver than wild-type mice, leading to a significant decrease in lipids converted from glucose (32). ChREBP liver-specific knockout mice showed dysregulation of glucose response and impaired glucose homeostasis (34). Moreover, adenoviral overexpression of ChREBP caused higher liver triglyceride contents with increased FAS and ACC expression (35, 46). It is now believed that ChREBP and sterol regulatory element binding protein-1c (SREBP-1c) play a synergistic role in the regulation of lipogenesis in liver (47). Moreover, the expression of the ChREBPβ isoform is associated with the respective increase and repression of branched chain alpha-keto acid dehydrogenase kinase (BDK) and protein phosphatase Mg2+/Mn2+-dependent 1K (PPM1K) transcript levels in liver (48). In addition, the transcription of fibroblast growth factor 21 (FGF21) is regulated by ChREBP (49). FGF21 is involved in energy metabolism by regulating carbohydrate intake (50). Fructose ingestion increases FGF21 production in a ChREBP-dependent manner while FGF21 knockout attenuates ChREBP expression and de novo lipogenesis following fructose consumption, indicating that ChREBP and FGF21 constitute a signaling axis which mediates an adaptive hepatic metabolic response to fructose ingestion (51).

**MondoA in Metabolic Organs**

As another transcriptional biosensor of intracellular glucose concentration, MondoA contributes to more than 75% of glucose-induced transcription signature in HA1ER epithelial

![Figure 2](image-url)
cells (52). By shuttling between mitochondria and nucleus, MondoA bridges cytoplasmic nutrient level to transcriptional adaptations. MondoA localizes to the outer mitochondrial membrane under basal conditions, and accumulates in the nucleus in response to nutrient signals such as high glucose (52, 53). In addition to nuclear accumulation, glucose triggers MondoA-MLX binding to target promoters, and activates gene expression through recruitment of histone H3 acetyltransferase as coactivators (54).

Similar to ChREBP, MondoA senses levels of G6P and F2,6-BP (52, 55) (Figure 2). Meanwhile, MondoA is responsive to non-glucose hexoses including allose and glucosamine (56). Intriguingly, glutamine recruits a histone deacetylase-dependent corepressor to MondoA, turning MondoA-MLX into a transcriptional repressor. Moreover, cellular acidosis drives MondoA transcriptional activity since low pH promotes the production of mitochondrial ATP, with which mitochondria-bound hexokinase generates G6P from cytoplasmic glucose (57). This finding has justified the special localization of MondoA-MLX and unraveled the mechanisms underlying the activation of MondoA by lactic acidosis. Other molecules reported to be sensed by MondoA include adenine nucleotides and other adenosine-containing molecules (58, 59). Furthermore, mTOR (mammalian target of rapamycin), another key nutrient sensor, interacts with MondoA with a suppressive effect on its transcriptional activity (60). Nonetheless, so far there is no report on fatty acids or amino acids regulating MondoA level or activity.

Different from ChREBP, MondoA is predominantly expressed in skeletal muscle and immune cells (12), and our unpublished data. MondoA-deficient mice show enhanced glycolytic rates probably because loss of MondoA in skeletal muscle increases glucose uptake (43) (Table 1). In response to glucose and fructose, MondoA activates transcription of thioleodxin interacting protein (TXNIP) and arrestin domain-containing 4 (ARRDC4), which inhibits glucose uptake (Figure 3) (56, 61). TXNIP, a dynamic sensor that modulates the energy demand of cells, plays a crucial role in the homeostasis of glucose.
As a direct and glucose-responsive target of MondoA, TXNIP is upregulated when G6P level increases and concomitantly restricts glucose absorption, thus providing a negative feedback loop to prevent energy overload. Mechanisms underlying inhibition of glucose uptake regulated by TXNIP include the suppression of glucose transporter (GLUT) expression, GLUT vesicle transport and insulin signaling (44, 62–64). Moreover, MondoA enhances glycosgen synthesis by activating the transcription of phosphoprotein phosphatase 1 regulatory subunit 3A (PPP1R3A), phosphoprotein phosphatase 1 regulatory subunit 3B (PPP1R3B) and genes encoding the glycolgen targeting subunits of protein phosphatase 1 (PP1) promoting glycosgen synthesis (65, 66). Muscle-specific MondoA knockout decreases glycosgen level in the skeletal muscle of mice (62) (Table 1). Hence, under physiological conditions, glucose homeostasis is maintained by the downstream effects of MondoA activation.

In addition to glucose metabolism, MondoA diverts nutrients to lipid metabolic pathways, including fatty acid thioesterification [acyl-CoA synthetase 1, 4 (ACSL1, 4)], desaturation [fatty acid desaturase 1, 2 (FADS1, 2, SCD1, 5)], elongation [elongation of very long chain fatty acids protein 5, 6 (ELOVL5, 6)], and triglyceride synthesis [diacylglycerol acyltransferase 1, 2 (DGAT1, 2)] (44) (Figure 3). Taken together, as a nutrient-regulated transcription factor, MondoA not only decreases glucose import but also diverts nutrients to storage in skeletal muscle. Although various posttranslational modifications of ChREBP have been revealed to regulate its activity in different conditions (67–69), there is so far no report on how MondoA is posttranslationally modified. Therefore, further mechanistic studies are needed to elucidate the interacting protein network of MondoA in response to nutrient level alterations.

### THE ROLE OF MONDOA AND ChREBP IN OBESITY

#### ChREBP: From White to Brown and Beige Adipocytes

Obesity is the excessive accumulation of fat caused by imbalance between energy intake and consumption. It is the major risk factor for many metabolic disorders such as type 2 diabetes, fatty liver and cardiovascular diseases (70). Regarded as a crucial target for the prevention and treatment of obesity, the adipose tissue consists of white adipocytes which store energy, and brown and beige adipocytes which consume energy and produce heat (71). Inducing beige adipocytes from white adipose tissues (WAT) is known as browning, a process which improves glucose metabolism and insulin sensitivity (11). Various transcription and endocrine factors participate in this process by directly or indirectly stimulating UCP1 expression in adipose tissues, including peroxisome proliferator-activated receptor γ (PPARγ), PPARγ coactivator-1α (PGC-1α), silent information regulator type 1 (SIRT1) and FGF21 (72). The activation of brown and beige adipocytes is considered to be an attractive therapeutic strategy for obesity and its comorbidities. Brown and beige adipocytes serve as a sink for excessive nutrients by promoting energy expenditure in mitochondria (73).

ChREBP promotes lipogenesis in adipose tissues (36, 74). For high-carbohydrate diets, excessive fructose and glucose are converted to fatty acids, in which a series of enzymes including ACLY, ACC and FAS participate (75). The predominant destiny of the newly synthesized fatty acids is to become triglycerides for storage, which helps to maintain energy homeostasis (76). Adipocyte de novo lipogenesis is also involved in the regulation of systemic insulin sensitivity and thermogenesis, both of which

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**TABLE 1 | Roles of Mondo family on body weight, hepatic steatosis and insulin sensitivity according to mouse models, depending on nutritional status, genetic background and drug administration.**

| Mondo family | Context | Modulation in Mouse Models | Body Weight | Fat Mass | Hepatic Steatosis | Insulin Sensitivity | Reference |
|--------------|---------|-----------------------------|-------------|---------|------------------|--------------------|-----------|
| ChREBP       | Standard diet | Global knockout            | =          | \(\)    | =                | =                  | (32, 33)  |
|              | Liver-specific knockout | \(\) \(\) \(\) \(\) \(\) | =          | \(\)    | =                | =                  | (34)      |
|              | Liver-specific overexpression | \(\) \(\) \(\) \(\) \(\) | =          | \(\)    | =                | =                  | (35)      |
|              | AT-specific knockout | \(\) \(\) \(\) \(\) \(\) | =          | \(\)    | =                | =                  | (36)      |
|              | AT-specific overexpression | \(\) \(\) \(\) \(\) \(\) | =          | \(\)    | =                | =                  | (37)      |
|              | Pancreatic β-cell-specific overexpression | \(\) \(\) \(\) \(\) \(\) | =          | ND      | ND               | =                  | (38)      |
|              | Standard diet in ob/ob mice | Global knockout | =          | \(\)    | =                | =                  | (39)      |
|              | background | Liver-specific knockout | \(\) \(\) \(\) \(\) \(\) | =          | \(\)    | =                | (34)      |
|              | High-fat diet | Liver-specific knockout | =          | \(\)    | =                | =                  | (34)      |
|              | Liver-specific overexpression | \(\) \(\) \(\) \(\) \(\) | =          | \(\)    | =                | =                  | (36)      |
|              | AT-specific knockdown | \(\) \(\) \(\) \(\) \(\) | =          | ND      | ND               | (41)      |
|              | AT-specific overexpression | \(\) \(\) \(\) \(\) \(\) | =          | ND      | ND               | (41)      |
|              | Western diet | Global knockout | \(\) \(\) \(\) \(\) \(\) | =          | \(\)    | =                | (42)      |
|              | High-carbohydrate diet | Liver-specific knockout | \(\) \(\) \(\) \(\) \(\) | =          | \(\)    | =                | (44)      |
|              | HFD      | Global knockout | =          | ND      | ND               | (39)      |
|              | High-fat diet | Liver-specific knockout | \(\) \(\) \(\) \(\) \(\) | =          | \(\)    | =                | (43)      |
| MondoA       | Standard diet | Global knockout | =          | ND      | ND               | =                  | (36)      |
|              | Liver-specific knockout | \(\) \(\) \(\) \(\) \(\) | =          | ND      | ND               | (44)      |
|              | Muscle-specific knockout | \(\) \(\) \(\) \(\) \(\) | =          | ND      | ND               | (44)      |
|              | Muscle-specific knockdown | =          | ND      | ND               | (44)      |
| MondoA/ChREBP | High-fat diet | MondoA/ChREBP signaling | \(\) \(\) \(\) \(\) \(\) | \(\) \(\) \(\) \(\) \(\) | =                  | (45)      |

*“=“ means not changed. ND, not determined. The upward and downward arrows indicate an increase and decrease in the level, respectively.*
play key roles in mediating metabolic adaptations (21, 77). Overexpression of a constitutively active ChREBP isoform (caChREBP) in adipose tissues leads to an increase in expression of key enzymes involved in de novo lipogenesis (37). Conversely, adipocytes lacking ChREBP display impaired sucrose-induced lipogenesis (36). In WAT, Glut4-mediated glucose uptake induces ChREBP expression and activates the de novo lipogenic pathway. In Glut4 knockout mice, ChREBP expression in adipose tissues decreases by 50%. It is noteworthy that Glut4-mediated changes in glucose flux have a stronger effect on the transcriptional expression of ChREBPβ than ChREBPα in WAT (16). ChREBP activity in adipocytes depends on ACLY, one of its transcriptional targets. In the absence of ACLY, the expression of both ChREBP and its target genes is significantly suppressed. Consequently, ACLY and ChREBP form a positive feedback loop in adipocytes to foster dietary carbohydrates uptake, fatty acid synthesis and storage of lipids (78). Moreover, specific ablation of Rictor, the essential subunit of the mechanistic target of rapamycin complex 2 (mTORC2) in mature adipocytes reduces ChREBPβ expression and downregulates de novo lipogenesis in WAT and brown adipose tissue (BAT) (79). In mature brown adipocytes, AKT2, which can be phosphorylated by mTORC2, is required for lipogenesis driven by ChREBP activation (21, 80).

To date, the role of ChREBP in regulating thermogenic adipocyte function has been indicated in a growing body of literatures (Figure 4). Reduced brown fat mass and hypothermia in response to excess energy intake are observed in ChREBP-deficient mice (32). ChREBPβ and UCP1 expression levels positively correlate in human BAT, suggesting that ChREBPβ expression might indicate brown adipocyte activity (21). Under chronic cold exposure, specific impairment of ChREBP-driven lipogenesis in BAT promotes beige adipocyte development, which is probably a compensatory response (21). Moreover, studies in adipocytes exposed to high glucose show that ChREBP is a critical mediator in triiodothyronine-induced upregulation of UCP1 expression in brown adipocytes (81). However, there is no significant binding of ChREBP protein to the UCP1 promoter, indicating that ChREBP regulates UCP1 transcription indirectly (82), which awaits further study. In mice fed a chronic high sucrose diet, expression of UCP1 in BAT is significantly increased compared with controls, which is probably due to the activated ChREBP-FGF21 axis (83). Moreover, overexpression of constitutively active ChREBP in adipocytes induces PPARγ activity and upregulates its thermogenesis-related target genes including UCP1 that promotes browning of WAT, while depletion of endogenous ChREBP in adipocytes has reciprocal effects (84). Furthermore, adenoviral overexpression of ChREBP in mice increases mRNA level of white adipose tissue UCP1 with increased plasma FGF21 level (46). After ChREBPβ is identified, it is important to consider the functional difference between the two isoforms of ChREBP. Of note, overexpression of ChREBPβ in brown adipocytes leads to impaired BAT thermogenesis and WAT browning, reflecting the role of ChREBPβ as a feedback regulator upon cold exposure (82). Moreover, given the expression of ChREBP in metabolic organs and macrophages, global gain-of-function or loss-of-function mouse models of ChREBP may not be ideal for analyzing the role of ChREBP in adipose tissues. Additional studies will be needed to develop a full picture of the specific role and mechanism of the two isoforms of ChREBP in adipocyte thermogenesis.

**MondoA: Inter-Organ Metabolic Crosstalk**

MondoA is expressed predominantly in skeletal muscle which makes up ~40% of body weight and is responsible for ~80% of glucose uptake (62, 85). Therefore, as a transcriptional factor
required for maintaining body homeostasis, MondoA plays a crucial part in inter-organ metabolic crosstalk.

In the context of chronic energy overload, MondoA is activated by glucose and fructose, which leads to the upregulation of TXNIP and ARRDC4, and concomitantly the impairment of glucose uptake in the skeletal muscle via suppression of insulin action (44, 45, 55). Additionally, the chronic activation of MondoA in skeletal muscle results in lipotoxicity, namely deleterious effects of ectopic triglyceride accumulation (44, 45, 55, 86). Therefore, MondoA activation results in myocellular insulin resistance and lipid accumulation (44), serving as an intriguing supplement to the well-known insulin resistance based on triglyceride accumulation (87). These defects, along with hyperglycemia and hyperlipidemia, contribute to obesity-induced type 2 diabetes (T2D) (88).

In obesity, pancreatic β cells adaptively produce more insulin to maintain blood glucose level, resulting in an amplified burden on β cells. Intriguingly, MondoA serves as a significant glucose-responsive transcription factor in β cells (89). Under high glucose conditions, MondoA shuttles to the nucleus to induce its targets TXNIP and ARRDC4 in β cells. TXNIP is a major factor promoting β cell apoptosis (89–93). Hence, impaired β cells might lead to progressive dysfunction of pancreas and even loss of its ability to produce and secrete insulin (94, 95).

All facts mentioned above will lead to an inter-organ vicious cycle of nutrient disposal and metabolism. The ideal solution is to limit energy intake while increasing the aerobic oxidation of fat in skeletal muscle by exercising (88). Therefore, to get out of this cycle of nutrient disposal and metabolism. The ideal solution is to limit energy intake while increasing the aerobic oxidation of fat in skeletal muscle by exercising (88). Therefore, to get out of this cycle of nutrient disposal and metabolism. The ideal solution is to limit energy intake while increasing the aerobic oxidation of fat in skeletal muscle by exercising (88). Therefore, to get out of the vicious cycle and regain the virtuous cycle, it is worthwhile to treat MondoA in skeletal muscle as a therapeutic target for obesity and insulin resistance.

**MONDO FAMILY AS A TARGET FOR METABOLIC DISORDERS**

In view of the central role of Mondo family in regulating energy homeostasis, the possibility to target MondoA or ChREBP in metabolic disorders has been explored.

As MondoA downregulates insulin sensitivity and promotes lipid storage in skeletal muscle (44, 45), it could be a promising therapeutic target for insulin resistance and lipotoxicity. For diet-induced obesity, muscle triglyceride accumulation and insulin resistance are partially relieved in muscle-specific MondoA knockout mice (44). MondoA deletion increases muscle glucose uptake and glycolytic capacity, resulting in enhanced sprint capacity (43). Moreover, SBI-477, a potent inhibitor of MondoA, alleviates muscle triglyceride levels and hepatic steatosis, thereby improving glucose tolerance in mice on a high-fat diet (45). However, the significant role of MondoA in skeletal muscle development has been recently revealed in mice (62). Therefore, in the development of MondoA as a novel therapeutic target, the timing for treatment is critical and the risk of interfering with normal myogenesis needs to be avoided.

Reducing ChREBP activity is considered as a promising target in the treatment of obesity according to studies utilizing ob/ob and ChREBP double knockout mice (33). Of note, ChREBP plays an important role in promoting white adipocyte browning (81). Therefore, ChREBP in brown and beige adipocytes can be regarded as a treatment option for obesity. In consideration of the well-established role of brown and beige adipocytes in counteracting obesity, we await further research in this respect.

**SUMMARY**

Mondo family transcription factors are critical for metabolic homeostasis, as they sense multiple nutrient molecules and regulate metabolic enzyme genes transcriptionally. MondoA limits glucose uptake and glycolysis mostly in skeletal muscle and immune cells, while ChREBP promotes de novo lipogenesis in liver and adipose tissue. In pathological states of nutrient overload, MondoA could interfere with insulin signaling, while adipose ChREBP is linked to systemic insulin sensitivity and its role extends from white to brown and beige adipose tissues. The role of ChREBP in browning of white adipocytes is especially worth further exploration. Targeting MondoA and ChREBP to counteract obesity and related diseases is an appealing strategy that requires further investigations. As the manipulation of Mondo family in different organs and tissues could yield distinct systemic metabolic consequences, future studies should be conducted using more specific and rigorous models in order to clarify the beneficial or deleterious effects of Mondo family in different contexts. Meanwhile, before the therapeutic approaches could be developed, it is noteworthy that MondoA and ChREBP could be involved in normal myogenesis and adipogenesis. Moreover, under certain circumstances, the target genes and metabolic pathways of MondoA and ChREBP are overlapping. In this regard, in the knockout phenotype of one of the two transcription factors, whether the other acts in a compensatory way requires special attention. Furthermore, increasing studies reveal the involvement of Mondo family in critical signaling pathways, which awaits mechanistic investigations to expand our understanding of the action and regulation of these transcription factors.

**AUTHOR CONTRIBUTIONS**

XT designed and revised the manuscript. HK, YL, SW, and YZ wrote the manuscript, made the figures and the table. All authors contributed to the article and approved the submitted version.

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