

Hepatic transcriptional responses to fasting and feeding

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Mammals undergo regular cycles of fasting and feeding that engage dynamic transcriptional responses in metabolic tissues. Here we review advances in our understanding of the gene regulatory networks that contribute to hepatic responses to fasting and feeding. The advent of sequencing and -omics techniques have begun to facilitate a holistic understanding of the transcriptional landscape and its plasticity. We highlight transcription factors, their cofactors, and the pathways that they impact. We also discuss physiological factors that impinge on these responses, including circadian rhythms and sex differences. Finally, we review how dietary modifications modulate hepatic gene expression programs.

In mammals, the transitions between fasting and fed states are accompanied by complex changes in hepatic gene expression. The liver is a central hub for coordination of fasting–feeding transitions given its roles in maintaining blood glucose levels, processing dietary nutrients, and regulating whole-body energy metabolism (for review, see Trefts et al. 2017). During fasting the liver is the target of hormones such as glucagon, which shift it into an energy production mode (Sutherland and Cori 1951). In response, the liver takes up free fatty acids (FFAs) released into the circulation by adipose lipolysis to provide energy for itself and to generate ketones for use by other tissues (Fine and Williams 1960). It also breaks down glycogen and amino acids to generate glucose for the brain (for review, see Berg et al. 2002). In the postprandial state, signaled by insulin and the influx of dietary carbohydrates, liver suppresses the production of glucose and switches to using it as its main fuel (for review, see Rui 2014). Excess glucose is converted into glycogen and fatty acids. Newly synthesized and dietary fatty acids are esterified to generate triglycerides, which are packaged and exported to the circulation (for review, see Alves-Bezerra and Cohen 2017). Transcriptional regulation is fundamental to the execution of each these physiological responses. Regulation of transcription involves

the coordinated action of a bevy of transcription factors, coregulators, and chromatin modifying enzymes, all acting downstream from hormonal signaling pathways. Elucidating the complex metabolic changes associated with fasting and feeding and their transcriptional underpinnings is crucial for understanding both normal physiology and metabolic pathologies such as insulin resistance. Given the extent of transcriptional pathways affected, feeding status can be a critical variable in the design of experiments involving animals and humans.

Lipid metabolism

PPAR α , fatty acid oxidation, and ketogenesis

The nuclear receptor peroxisome proliferator-activated receptor α (PPAR α) sits atop a crucial node coordinating changes in hepatic lipid metabolism during fasting. Seminal studies by Gonzalez and colleagues showed that PPAR α -knockout mice are compromised in fatty acid oxidation and ketogenesis (Kersten et al. 1999; Leone et al. 1999). PPAR α governs the expression of a battery of genes that coordinates fatty acid uptake and oxidation, ketogenesis, and lipid droplet dynamics during fasting. Regulation of acyl-coA oxidase 1 (ACOX1) by PPAR α facilitates peroxisomal long chain fatty acid (LCFA) oxidation. PPAR α induces mitochondrial LCFA oxidation through up-regulation of carnitine palmitoyltransferase 1a and 2 (CPT1A and CPT2, which transport LCFA into the mitochondria), malonyl-CoA decarboxylase (which degrades the CPT1 inhibitor malonyl-CoA), and other β oxidation enzymes. PPAR α also induces ketogenesis pathway enzymes, including 3-hydroxy-3-methylglutaryl-CoA lyase (HMGCL), acetyl-CoA acetyltransferase 1 (ACAT1), and 3-hydroxy-3-methylglutaryl-CoA synthase 2 (HMGCS2) (Lee et al. 2004; Cheon et al. 2005). PPAR α regulates phospholipid remodeling as well by influencing expression of choline kinase isotypes a and b (CHKA and CHKB), as well as the acyl-transferases glycerol-3-phosphate

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acyltransferase 3 (GPAT3) and monoacylglycerol O-acyltransferase 1 (MOGAT1) (Régnier et al. 2018). Additionally, PPAR α induces expression of fibroblast growth factor 21 (FGF21), a liver hormone that promotes β oxidation and ketogenesis (Potthoff et al. 2009). FGF21 contributes to the up-regulation of proliferator-activated receptor γ coactivator protein-1 α (PGC-1 α), which serves as a transcriptional coactivator of genes in LCFA oxidation and ketogenesis (Rhee et al. 2003).

Importantly, fatty acids and their derivatives are activating ligands for PPAR α and thereby help to control their own metabolism (Keller et al. 1993; Forman et al. 1997; Kliewer et al. 1997). During fasting, PPAR α has been hypothesized to be activated by the influx of FFA from adipose lipolysis (Kersten et al. 1999; Montagner et al. 2016). However, Sanderson et al. (2010) suggested that PPAR δ rather than PPAR α is activated by FFA from adipose lipolysis during fasting. Chakravarthy et al. (2005) suggested that PPAR α could be activated by hepatic lipid products of fatty acid synthase (FASN). Other studies indicate that PPAR α may be activated by lipolysis of locally stored triglycerides (Ong et al. 2011). Glucagon, sirtuin 1 (SIRT1), glucocorticoid receptor (GR), and PPAR γ coactivator 1 α (PGC-1 α) are known to promote PPAR α activity during fasting (Fig. 1B; Vega et al. 2000; Longuet et al. 2008; Purushotham et al. 2009; Goldstein et al. 2017). Suppression of the mechanistic target of rapamycin kinase (mTOR) signaling in fasting was found to be necessary for PPAR α ketogenic activity (Sengupta et al. 2010). Additional evidence suggests that SRY-box transcription factor 17 (SOX17) and cyclin-dependent kinase inhibitor 1 α (p21) might also play roles in activation of PPAR α (Rommelaere et al. 2014; Lopez-Guadamillas et al. 2016).

Transcription factors in feeding-induced lipogenesis

In the fed state, the liver receives dietary carbohydrates from the portal vein, and the excess glucose is converted into fatty acids through de novo lipogenesis. Fatty acids are then esterified to make phospholipids, triglyceride, and cholesterol esters. Sterol regulatory element binding protein 1c (SREBP-1c) binds to sterol regulatory elements (SREs) in the regulatory regions of its target genes (Guan et al. 1997). SREBP-1c is induced in the fed state and plays a central role in coordinating lipid synthesis. Immature endoplasmic reticulum (ER) membrane-bound SREBP-1c protein is processed in the Golgi, and the mature transcription factor subsequently travels to the nucleus, where it activates its target genes (Brown and Goldstein 1999). SREBP-1c induces the transcription of multiple genes in fatty acid biosynthesis. It drives expression of ATP citrate lyase (ACLY) to make acetyl-CoA, and acetyl-CoA carboxylase α (ACC1) and FASN to convert acetyl-CoA into palmitate. Regulation of elongation of very long chain fatty acids protein 6 (ELOVL6) and stearoyl-CoA desaturase (SCD-1) by SREBP-1c facilitates the elongation and desaturation of fatty acids, respectively (Shimano et al. 1999; Matsuzaka et al. 2002). Regulation of fatty acid desaturases 1 and 2 (FADS1 and FADS2) by SREBP-1c further influences polyunsaturated fatty acid

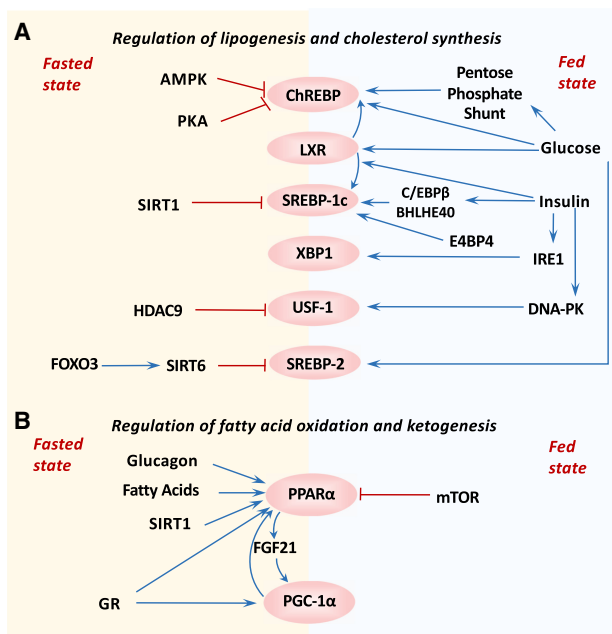


Figure 1. Transcription factors that regulate lipid metabolism in fasted and fed states. (A) Transcription factors such as ChREBP, LXR, SREBP1c, XBP, USF-1, and SREBP2 are activated by various factors in response to feeding signals such as glucose and insulin. These transcription factors induce the expression of genes that promote lipogenesis and cholesterol biosynthesis. Some of these transcription factors are also known to be actively inhibited during fasting. (B) Transcription factors such as PPAR α and PGC-1 α are activated by glucagon, SIRT1, and glucocorticoid receptor during fasting. These transcription factors induce the expression of genes that promote fatty acid oxidation and ketogenesis during fasting. Ketone bodies can be used as energy source for many other tissues.

(PUFA) generation. SREBP-1c also regulates the expression of genes encoding proteins linked to triglyceride synthesis, including patatin-like phospholipase domain containing 3 (PNPLA3), mitochondrial glycerol-3-phosphate acyltransferase (GPAM), malic enzyme (ME), and glucose-6-phosphate dehydrogenase (G6PD) (Huang et al. 2010). Studies have shown that ~50% of the hepatic lipogenic response to feeding is abolished in SREBP-1c-knockout mice (Liang et al. 2002).

Insulin secretion in response to a carbohydrate-rich diet promotes both the transcription of *Srebf1* (the gene encoding SREBP-1c) and processing of immature SREBP-1c protein (Horton et al. 1998). Although it is clear from knockout studies that SREBP-1c is a major mediator of insulin's lipogenic actions (Foretz et al. 1999; Matsuda et al. 2001), the underlying mechanisms by which insulin controls SREBP-1c activity are incompletely understood. Yamamoto et al. (2010) and Matsumoto et al. (2003) provided evidence that inhibition of protein kinase C β and C λ (PKC β and PKC λ) reduces insulin-dependent SREBP-1c activation. Analysis of the *Srebf1* promoter has identified several transcription factors that contribute its insulin responsiveness, including liver x receptors (LXRs), CCAAT enhancer binding protein β (C/EBP β),

and basic helix-loop-helix family member e40 (BHLHE40) (Fig. 1A; Chen et al. 2004; Tian et al. 2016; Berthier et al. 2018). SREBP-1c also induces its own promoter (Ameiya-Kudo et al. 2000).

Multiple studies have shown that feeding increases SREBP-1c processing, and this effect appears to be in part mTORC1-dependent and facilitated by protein kinase B (also known as AKT) phosphorylation (Yellaturu et al. 2009; Owen et al. 2012). Studies have further suggested that SREBP-1c activity may be regulated by phosphorylation and acetylation. Phosphorylation by protein kinase A (PKA) was reported to attenuate SREBP-1c binding at lipogenic promoters (Lu and Shyy 2006). SREBP-1c may be acetylated under high-insulin and high-glucose conditions by histone acetyltransferase p300 (Ponugoti et al. 2010). E4 promoter-binding protein 4 (E4BP4), a transcription factor that is up-regulated during feeding by SREBP-1c, physically interacts with mature SREBP-1c and protects it from degradation by promoting its acetylation (Fig. 1A; Tong et al. 2016). Conversely, the fasting-responsive factor SIRT1 deacetylates SREBP-1c, leading to its degradation (Ponugoti et al. 2010).

Insulin-induced gene proteins (INSIG-1 and INSIG-2) capture SREBP cleavage-activating protein (SCAP) and prevent it from escorting SREBP-1c to the Golgi for cleavage. Regulation of *Insig1* and *Insig2* thereby provides another layer of control for the feeding response of SREBP-1c. Insulin reduces *Insig2a* expression in the fed liver, allowing SREBP-1c to be processed (Yabe et al. 2003). Additionally, dietary PUFAs have been shown to inhibit refeeding-induced SREBP-1c activation by suppressing processing (Yahagi et al. 1999). Xu et al. (2001) also showed that PUFAs can increase *Sreb1c* mRNA decay. More recently, Kim et al. (2017a) showed that inhibiting ACC1 decreased PUFA biosynthesis, which led to increases in *Sreb1c* mRNA expression. Other studies indicate that ER phospholipid composition is a determinant of SREBP-1c activity. In feeding and in obesity, increased levels of polyunsaturated phosphatidylcholine generated by the remodeling enzyme lysophosphatidylcholine acyltransferase 3 (LPCAT3) promote SREBP-1c processing (Rong et al. 2017). Further studies are needed to reveal the complex relationship between the effects of free PUFAs and polyunsaturated phospholipids on SREBP-1c activity.

LXR α is a nuclear receptor activated by oxysterols (Janowski et al. 1999). Although LXR α is required for maximal transcription of *Sreb1* (Repa et al. 2000), whether or not LXR α itself conveys a feeding signal is less clear. Anthonisen et al. (2010) suggested that glucose feeding can activate LXR α via O-linked β -N-acetylglucosamine (O-GlcNAc) modification (Fig. 1A). However, in contrast to *Sreb1*, most other LXR α targets genes in liver are not induced appreciably by feeding (e.g., *Abcg5/8* and *Abca1*). Furthermore, *Sreb1* expression is still induced by feeding in LXR α / β double-knockout mice, even though basal levels are reduced (Beaven et al. 2013). Interestingly, *Lpcat3* expression is also controlled by LXR α in the liver. Induction of LPCAT3-dependent ER phospholipid remodeling thus provides a mechanism whereby LXR can stimulate SREBP-1c processing as well as transcription (Rong et al. 2017).

Upstream transcription factor 1 (USF-1) is another factor important in the lipogenic response. USF-1 is necessary for the full activation of *Fasn* by feeding and insulin. USF-1 binds to the *Fasn* promoter constitutively, but its activity is modulated by post-translational modifications. USF-1 bound to the *Fasn* promoter is phosphorylated by DNA-dependent protein kinase (DNA-PK) during feeding, thereby inducing transcription (Fig. 1A; Wong et al. 2009). Studies suggest that USF-1 acts synergistically with SREBP-1c on *Fasn* and *Gpam* (Jerkins et al. 1995; Griffin et al. 2007). In contrast, USF-1 has been reported to be deacetylated by histone deacetylase 9 (HDAC9) during fasting, which prevents the recruitment of activating factors (Wong et al. 2009).

Carbohydrate-responsive element-binding protein (ChREBP) is a transcription factor that induces hepatic lipogenesis in response to glucose signals. ChREBP heterodimerizes with Max-like protein X (MLX) and binds to carbohydrate response elements (ChoREs) in its target genes (Stoeckman et al. 2004). Known lipogenic targets for ChREBP include *Acly*, *Fasn*, *Acc1*, and *Scd1* (Iizuka et al. 2004). ChREBP has been shown to physically interact with hepatocyte nuclear factor 4 α (HNF4 α) on the *Fasn* promoter, facilitating its binding during feeding (Adamson et al. 2006). Hepatic ChREBP deficiency reduces lipogenic gene expression along with SREBP-1c expression, suggesting that both ChREBP and SREBP-1c must be activated by glucose and insulin, respectively, to enable the full lipogenic response to feeding (Linden et al. 2018).

Similar to SREBP-1c, ChREBP can induce its own gene expression in a feed-forward loop (for review, see Iizuka 2013). The *Chrebpa* gene is also an LXR target, and LXR α is necessary for induction of ChREBP α expression and activity (Fan et al. 2017). Additionally, post-transcriptional modifications, especially phosphorylation by PKA and 5'-AMP-activated protein kinase (AMPK) during fasting, have been shown to decrease ChREBP DNA binding (Fig. 1A; Kawaguchi et al. 2001, 2002). In the setting of high glucose availability, xylulose-5-phosphate (Xu5P), an intermediate of the pentose-phosphate shunt, leads to the dephosphorylation of ChREBP through Xu5P-activated protein phosphatase (PP2a) (Kabashima et al. 2003). ChREBP is also O-GlcNAcylated under high glucose conditions, thus stabilizing the protein (Guinez et al. 2011; Sakiyama et al. 2010).

Cholesterol biosynthesis controlled by SREBP-2 is also up-regulated in the fed state. Forkhead box protein O3 (FOXO3) was reported to cause down-regulation of the SREBP-2 pathway during fasting by recruiting SIRT6 to the promoter of *Sreb2* (the gene encoding SREBP-2) (Fig. 1A; Tao et al. 2013). Using liver-specific glucose transporter 2 (GLUT2) knockout mice, Seyer et al. (2013) showed that the up-regulation of cholesterol biosynthesis genes in the fed condition was influenced by hepatic glucose uptake. Interestingly, a recent paper by Lu et al. (2020) indicates that feeding also induces cholesterol synthesis by stabilizing the SREBP-2 target 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR), which catalyzes the rate-limiting enzyme in cholesterol synthesis. They showed that feeding-activated mTORC phosphorylates ubiquitin

C-terminal hydrolase 20 (USP20), which in turn is recruited to the HMGCR complex to prevent its degradation.

There is conflicting evidence as to the role of inositol-requiring, endoplasmic reticulum-to-nucleus signaling protein 1a (IRE1a) and X-box-binding protein-1 (XBP1) signaling in fasting and refeeding. Zhang et al. (2018a) showed that hepatic growth differentiation factor 15 (GDF15), which promotes hepatic β oxidation and ketogenesis, is activated by IRE1a-XBP1 during fasting. However, Pfaffenbach et al. (2010) reported that mTORC1 activates IRE1a-XBP1 in the postprandial period in the context of lipogenesis.

Glucose metabolism

Transcriptional regulators of glucose metabolism during fasting

CREB Cyclic AMP (cAMP) response element-binding protein (CREB) plays a dominant role in driving hepatic glucose production during fasting. CREB controls the expression of enzymes catalyzing key steps for hepatic glucose production such as glucose 6-phosphatase (G6Pase; encoded by *G6pc*), which is necessary for both glycogenolysis and gluconeogenesis, and phosphoenolpyruvate carboxykinase (PEPCK; encoded by *Pck1*), which is needed for gluconeogenesis from tricarboxylic acid (TCA) cycle intermediates (Quinn and Granner 1990; Liu et al. 1991). Inhibition of CREB reduces fasting hepatic glucose production (Herzig et al. 2001). The CREB homolog CREB-H is also induced during fasting and binds to CREB-regulated transcription coactivator 2 (CRTC2; also known as TORC-2) to promote the expression of gluconeogenic genes (Lee et al. 2010). In addition to its direct targets, CREB induces the expression of other transcription factors that promote gluconeogenesis (such as yin yang 1 [YY1] and NUR77) and ketogenesis (such as transcription factor EB [TFEB]) (Pei et al. 2006; Lu et al. 2013; Seok et al. 2014). CREB is activated during acute fasting through phosphorylation and dephosphorylation events. A cascade involving glucagon receptor-cAMP-PKA leads to the formation of an active CREB-CREB binding protein (CBP)-CRTC2 complex (Fig. 2B; for review, see Altarejos and Montminy 2011). In contrast, in long-term fasting, SIRT1 deacetylates and AMPK phosphorylates CRTC2. These modifications reduce CREB activity and facilitate a switch to FOXO1/PGC-1 α -driven gluconeogenesis (Koo et al. 2005; Liu et al. 2008). In feeding, insulin signaling causes phosphorylation of CBP and CRTC2 via PKC λ / ι and salt-inducible kinase 2 (SIK2), respectively, triggering the dissociation of the CREB-CBP-CRTC2 complex and cessation of CREB activity (Dentin et al. 2007; He et al. 2009). Additionally, during refeeding after fasting, ER stress activates activating transcription factor 6 (ATF6) as part of the unfolded protein response pathway. ATF6 binds to CRTC2 and sequesters it from CREB, thereby inhibiting gluconeogenic gene expression (Wang et al. 2009).

FOXO1 A member of the FOXO family of transcription factors, FOXO1 regulates hepatic gluconeogenesis in both

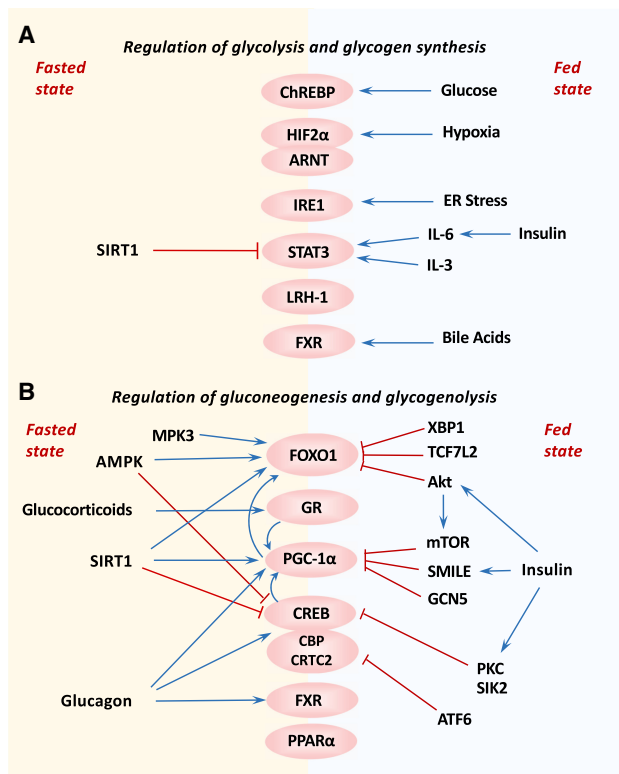


Figure 2. Transcription factors that regulate glucose metabolism in fasted and fed states. (A) Transcription factors such as ChREBP, HIF2 α -ARNT, IRE1, STAT3, LRH-1, and FXR are activated by various factors in response to feeding such as glucose and insulin. These factors induce the transcription of genes that promote glycolysis and glycogen synthesis. In response to an increase in available glucose and insulin, energy metabolism switches to using glucose as fuel and replenishes glycogen stores. (B) Transcription factors such as FOXO1, GR, PGC-1 α , CREB, PPAR α , and FXR are activated by glucagon, AMPK, SIRT1, and glucocorticoids during fasting. These transcription factors induce the expression of genes that promote gluconeogenesis and glycogenolysis. This switch is crucial in maintaining blood glucose levels during fasting. There is evidence for cross talk between these transcription factors, one inducing the expression of another. Some of these transcription factors are also known to be actively inhibited by insulin signaling in response to feeding.

fasting and feeding. FOXO1 binds to insulin response elements in the promoters of genes involved in gluconeogenesis (Haeusler et al. 2010). During fasting, mitogen-activated protein kinase (MAPK) phosphatase 3 (MPK3) dephosphorylates FOXO1, increasing its nuclear localization and activation (Fig. 2B; Wu et al. 2010). In the fed state, insulin suppresses gluconeogenesis by inhibiting FOXO1. Insulin signaling leads to AKT-dependent phosphorylation of FOXO1, which drives its cytosolic localization and proteasome-mediated degradation (Nakae et al. 1999). Interestingly, the absence of hepatic insulin signaling is sufficient to induce inappropriate gluconeogenesis that can be ameliorated by FOXO1 knockout (Dong et al. 2008). FOXO1 is regulated negatively by acetylation, such as by p300/CBP (Matsuzaki et al. 2005). In response

to fasting, FOXO1 is deacetylated and thus activated by zinc finger and BTB domain-containing 7c (ZBTB7C) and SIRT1, as well as by histone deacetylases (HDACs) that are phosphorylated by AMPK (Frescas et al. 2005; Mihaylova et al. 2011; Choi et al. 2019).

Similar to CREB, FOXO1 regulates rate-limiting steps in gluconeogenesis (Zhang et al. 2006). The importance of FOXO1 in hepatic glucose homeostasis has been extensively documented by constitutive-active mutant and knockout studies. Liver-specific FOXO1 knockout reduces hepatic gluconeogenesis and glycogenolysis, leading to a 30% decrease in fasting blood glucose (Matsumoto et al. 2007). Constitutively active FOXO1 prevents the inhibitory effect of insulin on gluconeogenic genes (Puigserver et al. 2003). There may be some redundancy between FOXO1 and other FOXO family members in regulating gluconeogenesis (Kim et al. 2011).

Interactions with other proteins can affect FOXO1 activity. PGC-1 α and β -catenin bind to FOXO1 and increase its transcriptional activity, while transcription factor 7-like 2 (TCF7L2) competes with FOXO1 on the promoters of gluconeogenic genes, thereby inhibiting their transcription (Puigserver et al. 2003; Liu et al. 2011; Oh et al. 2012). The nuclear receptor Nr0b2 (also known as SHP), which is a FOXO1 target, inhibits gluconeogenic FOXO1 activity in a negative feedback loop (Wei et al. 2011). Interestingly, the promoter context determines how FOXO1 interacts with HNF4 α . In fasting, FOXO1 cooperates with HNF4 α on *G6Pase* but antagonizes HNF4 α on the glucokinase (*Gck*) promoter (Hirota et al. 2008).

PGC-1 α PGC-1 α is a transcriptional coactivator induced by glucagon and glucocorticoid signaling that facilitates gluconeogenesis (Yoon et al. 2001). CREB induces the gene encoding PGC-1 α in the setting of long-term fasting to sustain gluconeogenesis (Fig. 2B; Herzig et al. 2001). FGF21 promotes the expression of PGC-1 α as well (Pothoff et al. 2009), but PGC-1 α in return negatively regulates the expression of FGF21 (Estall et al. 2009b). PGC-1 α is also regulated by post-transcriptional modifications. The gluconeogenic functions of PGC-1 α are inhibited in the fed state as a result of phosphorylation by S6 kinase, an effector of mTOR and AKT signaling downstream insulin (Li et al. 2007; Lustig et al. 2011). Moreover, lysine acetyltransferase 2A (KAT2A; also known as GCN5) acetylates and inhibits PGC-1 α in the fed state, while SIRT1 deacetylates PGC-1 α during fasting, thereby increasing its activity (Rodgers et al. 2005; Lerin et al. 2006).

During fasting, PGC-1 α interacts with several hepatic transcription factors, including FOXO1 and the nuclear receptors HNF4 α , PPAR α , and GR (Yoon et al. 2001; Puigserver et al. 2003). Livers of PGC-1 α knockout mice show decreased gluconeogenesis along with decreased fatty acid oxidation and increased hepatic steatosis (Burgess et al. 2006; Estall et al. 2009a). Conversely, PGC-1 α overexpression increases hepatic glucose output and fatty acid oxidation (Liang et al. 2009; Morris et al. 2012). Recently, PGC-1 α was reported to impact insulin signaling during fasting by altering the ratio of insulin receptor substrates 1 and 2 (IRS1 and IRS2) (Besse-Patin et al. 2019). While PGC-1 α

deficiency increases insulin sensitivity, PGC-1 α overexpression causes insulin resistance (Koo et al. 2004; Leone et al. 2005; Liang et al. 2009). Additionally, insulin signaling inhibits gluconeogenic PGC-1 α activity by inducing the expression of SHP-interacting leucine zipper protein (SMILE). SMILE directly competes with PGC-1 α and consequently inhibits HNF4 α (Lee et al. 2016).

Other transcriptional regulators in glucose metabolism during fasting GR is activated by binding to stress-related glucocorticoid hormone ligands during fasting (McCallum et al. 1983; Opherker et al. 2004). GR induces the expression of gluconeogenic genes such as *Pck1* (Cassuto et al. 2005). Hepatocyte-specific GR knockout mice have a survival rate of ~50% in the first 2 d of life due to hypoglycemia. If they survive to adulthood, the knockout mice exhibit fasting hypoglycemia (Opherker et al. 2004). Nuclear transcription factor Y (NF-Y) and nuclear factor kb subunit 2 (NF- κ B2) have also been suggested respond to glucagon in fasting and induce gluconeogenesis (Zhang et al. 2019). NF-Y was shown to promote the expression of gluconeogenic genes through interacting with CREB (Zhang et al. 2018c). The bile acid receptor FXR, induced by PKA and FOXA1, has also been reported to promote gluconeogenic genes (Ploton et al. 2018; for review, see Massafra and van Mil 2018).

In addition to its role in fasting-induced fatty acid oxidation, PPAR α also affects the expression of genes linked to gluconeogenesis, glycerol metabolism, and glycogen synthesis (for review, see Kersten 2014). Loss of PPAR α causes severe hypoglycemia in fasted mice and reduces hepatic glycogen levels in refeed mice. Loss of PPAR α also prevents hepatic glycogen breakdown during short-term fasting (Bandsma et al. 2004).

Transcriptional regulators of glucose metabolism in the fed state Consistent with its regulation by dietary glucose, ChREBP induces genes linked to glycolysis. ChREBP is necessary for the glucose-dependent induction of pyruvate kinase (PKLR), which catalyzes the last step of glycolysis (Fig. 2A; Rufo et al. 2001). Loss of ChREBP in mice decreases glycolysis at the pyruvate kinase and glucose-6-phosphatase steps and consequently increases liver glycogen content (Iizuka et al. 2004). ChREBP β expression is up-regulated by carbohydrate feeding, while ChREBP α expression is down-regulated (Stamatikos et al. 2016).

A number mechanisms inhibit gluconeogenesis in the fed state. XBP1 can bind to FOXO1 and direct it to degradation (Fig. 2B; Zhou et al. 2011). During feeding, interleukins 6 and 13 (IL6 and IL13) activate signal transducer and activator of transcription 3 (STAT3) (Fig. 2A; Inoue et al. 2006; Stanya et al. 2013), which represses gluconeogenic genes such as *Pck1* and *G6pase* (Ramadoss et al. 2009). In the fasted state, SIRT1 deacetylates STAT3, thus inactivating it to negate its repression of gluconeogenesis (Nie et al. 2009). Additionally, hypoxia-inducible factor 2 α (HIF2 α) is activated by hypoxia in postprandial liver, where it attenuates glucagon signaling and gluconeogenesis together with its partner aryl hydrocarbon receptor nuclear translocator (ARNT) (Ramakrishnan et al. 2016; Scott et al. 2017).

Nr5a2 (also known as LRH-1) plays a role in postprandial glycolysis and glycogen synthesis by stimulating *Gck* expression (Oosterveer et al. 2012). The postprandial uptake of bile acids activates FXR to support glycogen synthesis, while during fasting, FXR induced by PKA and FOXA1 promotes gluconeogenic genes (Fig. 2A,B; Ploton et al. 2018; for review, see Massafra and van Mil 2018).

Other fasting/feeding responsive pathways

Several metabolic and nonmetabolic processes other than glucose and lipid metabolism are affected by fasting and feeding responses in the liver. We highlight some of these, emphasizing how their regulation may contribute to the adaptation to the nutritional state.

Amino acid metabolism

Amino acid catabolism appears to play an important role in providing fuel for gluconeogenesis during fasting. Ammonia resulting from amino acid catabolism is detoxified through the urea cycle in periportal hepatocytes and through glutamine synthesis pericentrally (Brosnan and Brosnan 2009). Enzymes involved in both processes including carbamoyl phosphate synthetase-1 (*Cps1*), argininosuccinate lyase (*Asl*), ornithine-aminotransferase (*Oat*), and proline dehydrogenase (*Prodh*) are up-regulated in fasting (Sokolović et al. 2008). However, the up-regulation of amino acid catabolism enzymes has been shown to be limited to the first 24 h of fasting and to enzymes involved in the degradation of branched-chain keto-acids, such as acetyl-coenzyme A dehydrogenase (*Acaddm*) and hydratase/3-hydroxyacyl-coenzyme (*Ehhadh*). This finding indicates that fasting-induced amino acid degradation happens primarily outside of liver and that the liver's role is to detoxify the resulting ammonia. In contrast, protein biosynthesis is rapidly induced during refeeding via mTOR (Mosoni et al. 1996; Kimball et al. 2000).

Hepatic C/EBP α expression is induced by glucagon in fasting. It regulates the expression of *Cps1* and several other urea cycle enzymes (Kimura et al. 1998). By regulating these targets, it has been suggested to promote expression of gluconeogenic genes such as *Pck1* (Louet et al. 2010). Furthermore, the tumor suppressor p53 is stabilized by prolonged fasting through an AMK-dependent mechanism. p53 along with Kruppel-like factor 15 (KLF15) facilitates amino acid catabolism, thus promoting gluconeogenesis (Teshigawara et al. 2005; Gray et al. 2007; Prokesch et al. 2017).

Bile acid metabolism

Bile acids are inherently tied to the fasting and feeding cycle. Bile acids are synthesized in liver from cholesterol and stored in the gallbladder. They are secreted into the lumen of small intestine to allow solubilization and absorption of dietary fats and fat-soluble vitamins. Bile acids reabsorbed in the gut are transported to liver, where they activate

FXR. In the fed state, FXR down-regulates bile acid synthesis enzymes via SHP, FGF15, and MAF BZIP transcription factor G (MAFG), in a negative feedback loop (Kong et al. 2012; de Aguiar Vallim et al. 2015). Agonist and knockout studies have revealed that FXR also plays a role in keeping postabsorptive pathways in check, including inhibiting SREBP-1c-driven fatty acid and triglyceride synthesis and promoting triglyceride lipolysis by inhibiting apolipoprotein C3 (APOCIII) and angiopoietin-like 3 (ANGPTL3) (Claudel et al. 2003; Watanabe et al. 2004; Duran-Sandoval et al. 2005).

Iron metabolism

The fasting and feeding processes alter iron metabolism in the liver and plasma. Fasting-induced PGC-1 α directly induces the expression of 5'-aminolevulinatase synthase 1 (ALAS1; the rate-limiting enzyme of hepatic heme biosynthesis) and HEPCIDIN (which inhibits the iron transporter ferroportin), thereby limiting iron efflux (Handschin et al. 2005; Vecchi et al. 2014). These two strategies increase iron retention in liver during prolonged fasting. SREBP-1c activated in the refed state was shown to induce heme oxygenase 1 (HMOX1), the rate-limiting enzyme in heme catabolism. This regulation is postulated to protect cells from oxidative stress (Kallin et al. 2007).

Stress responses

ER and mitochondria are sites of high metabolic activity during fasting and feeding cycles. In the 24-h fasted liver, the capacity for ATP synthesis is increased. There is increased TCA cycle activity and oxidative phosphorylation from amino acid and fatty acid oxidation (Sokolović et al. 2008). Increased oxidative phosphorylation may lead to oxidative stress owing to the accumulation of reactive oxygen species (ROS). Dietary restriction and high-fat feeding, both of which increase fatty acid oxidation, increase the expression of oxidative stress defense genes such as glutathione-S transferases and those involved in glutathione synthesis (Renaud et al. 2014). ER stress pathways are also up-regulated in 24-h fasted liver (Sokolović et al. 2008). ATF4 activated by ER stress induces the expression of FGF21 (Örd et al. 2018), which acts to reduce ER stress (Maruyama et al. 2018). The DNA repair enzyme 8-oxoguanine DNA glycosylase (Ogg1) protects mitochondrial DNA from damage from metabolic reactions. Ogg1 has been shown to facilitate the channeling of glucose into the glycolytic pathway, TCA cycle, and mitochondrial electron transport chain specifically in the fed liver (Scheffler et al. 2018).

Autophagy

Autophagy is a critical adaptation to low nutrient states. In fasting and starvation, autophagy is activated by multiple pathways. FOXOs, activated by AMPK in fasting and starvation, directly induce critical parts of the autophagy machinery (van der Vos et al. 2012). In addition, FOXO3 and FOXO1 can activate autophagy by inhibiting mTOR

and interacting with autophagy-related 7 (ATG7), a key regulator of the autophagosome (Zhao et al. 2010). Additional mechanisms for regulation of autophagy are discussed below in the epigenetics section.

High-throughput sequencing and -omics studies

Next-generation sequencing has become an essential tool for probing the transcriptome. RNA sequencing (RNA-seq) has been very effective at identifying new genes, revealing pathways that respond to specific stimuli, and characterizing global transcriptomic profiles in various contexts. As transcriptomic methods have continued to evolve, studies have combined RNA-seq with other methods in the -omics toolkit, such as DNase I hypersensitive site sequencing (DNase-seq) and assay for transposase-accessible chromatin using sequencing (ATAC-seq), both of which profile accessible chromatin regions, chromatin immunoprecipitation followed by sequencing (ChIP-seq), which defines sites of transcription factor binding or histone modification, metabolomics, and proteomics. From a bird's eye view, studies comparing the fasted and fed states, or different time points within in a fasting regimen, have found hundreds to thousands of differentially expressed genes, or up to 10% of the hepatic transcriptome (Robertson et al. 2011). The extent of these change underscores the complexity of the physiological response.

Pathway analysis

Pathway analysis tools aid in describing patterns in large data sets and highlighting unexpected associations. Not surprisingly, the top changing pathways in fasting versus fed liver involve lipid, carbohydrate, and amino acid metabolism (Sokolović et al. 2008). Mitochondrial LCFA uptake, fatty acid β oxidation, ketogenesis, and PPAR α signaling are among the most prominent responses, peaking at 24 h of fasting (Morgan et al. 2005; Sokolović et al. 2008; Zhang et al. 2011). Conversely, fatty acid and sterol biosynthesis pathways are down-regulated in fasting liver samples, reflecting suppression of SREBP-1c and SREBP-2 activity (Morgan et al. 2005; Hakvoort et al. 2011; Zhang et al. 2011). Gluconeogenesis is up-regulated in fasting, relying on enhanced TCA and malate-aspartate cycling enzymes and increased expression of *Pck1* (Sokolović et al. 2008). Liver glycogen is depleted by 12 h of fasting in mice (Geisler et al. 2016) and 17 h in rats (Morgan et al. 2005). Accordingly, at 12–24 h, glycolysis and glycogenolysis genes are down-regulated. Amino acid degradation and urea cycle enzymes are enriched in the up-regulated genes in the 24-h fasted liver, consistent with amino acid oxidation (Sokolović et al. 2008; Zhang et al. 2011). These changes continue at 72 h of fasting, even though other fasting-related transcriptomic changes are largely resolved. Hellerstein et al. (1997) observed persistence of gluconeogenic flux into glycogen and glycogen turnover in humans even during prolonged fasting. Liver glycogen was shown to accumulate in mouse liver after 72 h of fasting, suggesting that amino acid oxidation is the

predominant source of fuel for glucose and glycogen synthesis during prolonged fasting. TCA cycle, electron transport chain, and oxidative phosphorylation pathways are induced in the 24-h fasted liver (Sokolović et al. 2008; Zhang et al. 2011). As these processes can cause oxidative stress, it is not surprising that pathways for unfolded protein response/ER stress are up-regulated concurrently. Last, fasting is also associated with a down-regulation of immune and inflammation-related pathways (Zhang et al. 2011).

Since feeding is used as the comparison state to fasting in most profiling studies, the reverse of what is reported in the fasted is generally observed for fed and refeed conditions. When comparing refeed with fasted mice, fatty acid oxidation pathways dependent on PPAR α and gluconeogenesis through PEPCK are down-regulated, while fatty acid biosynthesis is up-regulated (Chi et al. 2020). Compared with the ad libitum-fed state, refeed samples show increased enrichment of pathways for the biosynthesis of macromolecules. Zhang et al. (2011) observed that the majority of fasting-induced changes are in fact reversed by refeeding. Cholesterol biosynthesis is up-regulated in the fed state compared with fasting and is further up-regulated in refeed state. Notably, genes that do not change in the fasting and refeeding response are enriched for housekeeping functions, including nucleic acid metabolism, RNA processing, and cell organization pathways (Zhang et al. (2011).

Multiomics and network analysis

Combining -omics technologies allows for integrative analysis. Such analyses may incorporate different profiling techniques (lipidomics, DNase-seq, and ChIP-seq) and computational methods and/or correlate changes in different tissues (adipose, muscle, and liver). For example, studies that integrated transcriptomic analyses across multiple organs during fasting found that the previously accepted sequence of using carbohydrate, then lipids, and finally proteins as the source of fuel was not well supported by their data. In fact, pathways for utilization of these fuels were activated in parallel across different organs (Sokolović et al. 2008; Hakvoort et al. 2011; Schupp et al. 2013). The fatty acid oxidation pathway and genes involved in ketone body synthesis were up-regulated in a number of metabolic organs during fasting, such as the liver, kidney, intestine, and muscle to preserve glucose for brain (Hakvoort et al. 2011; Robertson et al. 2011). Accordingly, the transcriptome of the brain changes minimally in fasting. Network and text mining analyses have further shown that a number of transcription factors are shared in the fasting and feeding process between metabolically active organs, including PPAR α , HNF4A, GR, SREBP-1/2, p53, FOXO, early growth response protein 1 (EGR1), AP-1 (c-FOS/c-JUN), Myc proto-oncogene protein (c-MYC), transcription factor Sp1 (SP1), YY1, and protein C-ets-1 (ETS1) (Hakvoort et al. 2011; Schupp et al. 2013).

Combining metabolomics and metabolic flux studies with transcriptional analysis has provided insight into the coordination of metabolic responses. Robertson

et al. (2011) showed that changes in the serum and urine metabolome in response to fasting are small in magnitude but broad in scope. The same study found that a reduction in serum glucose coincides with down-regulation of the hepatic glycolytic genes *Gck* and *Pklr*. Serum glucose levels partially recover between 12 and 16 h of fasting as *Pck1* expression rises. *Pck1* expression, thus gluconeogenesis, is up-regulated when glycogen stores are depleted (Geisler et al. 2016). As serum FFAs derived from adipose lipolysis increase, the expression of genes for acyl-CoA synthesis, genes facilitating fatty acid import into mitochondria, and genes involved in fatty acid oxidation increases in parallel (Robertson et al. 2011). Since β oxidation and the TCA cycle require NAD^+ , the expression of genes to produce NAD^+ is up-regulated: uncoupling protein 2 (*UCP2*), which is a *PPAR α* target, and 3-hydroxybutyrate dehydrogenase 1 (*BDH1*), which converts acetoacetate to the ketone β -hydroxybutyrate (β -OH butyrate) (Geisler et al. 2016).

In contrast to fasting, responses to refeeding are quick and robust. Within 1–2 h of refeeding, *G6pc* and *Pck1* are down-regulated along with increases in liver glycogen. Serum β -OH butyrate levels are decreased as well as expression of *PPAR α* , *CPT1*, and *HMGCS2* (Geisler et al. 2016). Moreover, combining transcriptomics and lipidomics, Régnier et al. (2018) observed an increased abundance of many phospholipid species in response to fasting in a *PPAR α* -dependent fashion, along with differential expression of genes involved in phospholipid homeostasis such as *Chka*, *Chkb*, *Agpat9*, and *Mogat1*. Using metabolic flux and quantitative modelling, Hui et al. (2017) suggested that glycolysis and TCA cycle are uncoupled during fasting and that circulating lactate becomes the major substrate for TCA cycle for most tissues. These findings highlight how integrating the transcriptome and metabolome can provide a more complete picture of physiological responses.

Network analysis and motif enrichment analysis can provide insight into specific transcriptional regulators associated with global changes in the transcriptome (Zhang et al. 2011; Lopez-Guadamillas et al. 2016; Kinouchi et al. 2018). Using transcription factor footprint depth and motif flanking accessibility analyses of DNase-seq and histone 3 lysine 27 acetylation (H3K27Ac) ChIP-seq data, Goldstein et al. (2017) identified two roles for GR during fasting. For gluconeogenic genes, GR rapidly enhanced CREB activity. However, with respect to ketogenesis-related genes, GR action increased the expression of *PPAR α* gradually, leading to slower ramp up of ketogenic genes (Goldstein et al. 2017). Additionally, using self-organizing maps to compare multiple conditions collectively, Rennert et al. (2018) revealed that 24-h fasting initiated in the morning stimulated glucose consumption and gluconeogenesis, while fasting initiated in the evening was associated with comparatively less gluconeogenesis and more fatty acid and cholesterol synthesis. Sano et al. (2016) used mathematical modeling and transcriptomics to determine that genes up-regulated by insulin respond faster than those down-regulated, but need a higher dose of insulin to respond.

Epigenetics and transcription factor relationships

Chromatin structure, chromatin remodelers, and histone modifiers all have regulatory roles in the fasting and feeding response. Fasting and feeding dynamically change the genomic accessibility landscape, opening up thousands of new enhancers, rearranging transcription factor binding, and altering cofactor interactions (Goldstein et al. 2017). Several histone and DNA modifiers have been found to influence the response to fasting and feeding, including the well-characterized SWI/SNF chromatin remodeling complexes. A subunit of this complex, SWI/SNF complex 60-kDa subunit (*BAF60a*) responds to glucagon to activate fatty acid oxidation genes in fasting by interacting with *PGC-1 α* and engaging in cross talk with *PPAR α* (Li et al. 2008). Conversely, in the fed state a different subunit, *BAF60c*, forms a *lipoBAF* complex that interacts with *USF-1* specifically on lipogenic genes and thus promotes their expression (Wang et al. 2013).

The deacetylase *SIRT1*, which largely targets transcription factors, is involved in the induction of gluconeogenesis and β oxidation genes in fasting. *SIRT1* is activated in response to an increase in the NAD^+/NADH ratio during fasting (Bitterman et al. 2002). CREB induces *SIRT1* expression in fasting (Noriega et al. 2011), and the cAMP/PKA pathway has also been implicated in activating *SIRT1* through phosphorylation (Gerhart-Hines et al. 2011). PKA signaling has been reported to induce an interaction between *SIRT1*, *PPAR α* , and lysine-specific demethylase 6B (*KDM6B*; also known as *JMJD3*) (Seok et al. 2018), leading to the activation of β oxidation genes. In the fed state, *SIRT1* expression and activity are repressed by *ChREBP* and glycosylation, respectively (Noriega et al. 2011; Chattopadhyay et al. 2020). In contrast, *SIRT1* overexpression reduces hepatic steatosis and improves glucose tolerance in obese mice (Li et al. 2011). *PPAR α* signaling and fatty acid β oxidation are also impaired in hepatocyte *SIRT1* knockout mice (Purushotham et al. 2009). *SIRT1* deacetylates *PGC-1 α* during fasting (thereby increasing its coactivator activity) (Rodgers et al. 2005) and up-regulates *FGF21* in a *PPAR α* -dependent and *PGC-1 α* -dependent manner. Other studies have shown that *SIRT1* affects gluconeogenesis in long-term fasting. *SIRT1* deacetylates *TORC2* and *FOXO1*, thereby reducing CREB activity and facilitating a switch to *FOXO1/PGC-1 α* -driven gluconeogenesis (Frescas et al. 2005; Liu et al. 2008). *SIRT1* has been shown to induce gluconeogenesis by repressing antigluconeogenic *STAT3* (Nie et al. 2009). At the same time, studies suggest that *SIRT1* helps to keep *FOXO1*-driven gluconeogenesis in check by providing negative feedback through *SHP* (Wei et al. 2011).

GCN5/KAT2A, an epigenetic modifier, can wear different hats based on nutritional status. It can function as a histone acetyltransferase (*HAT*) in fasting when PKA phosphorylates *GCN5* in a *CBP/p300*-interacting transactivator 2 (*CITED2*)-dependent manner (Sakai et al. 2016). *GCN5* is recruited to and acetylates histone *H3* at gluconeogenic gene promoters, thus driving fasting gluconeogenesis. However, in the fed state, *GCN5* can function

as an acetyltransferase for PGC-1 α . Insulin inhibits the interaction between GCN5 and CITED2 (Sakai et al. 2012). GCN5 directly acetylates PGC-1 α (countering PGC-1 α deacetylation by SIRT1), repressing its transcriptional activity (Lerin et al. 2006).

Other epigenetic factors have also been identified as modulators of glucose and lipid metabolism in fasting. For instance, tet methylcytosine dioxygenase 3 (TET3), a DNA demethylation enzyme, is recruited to the *Hnf4a* promoter by FOXA2 during fasting (Li et al. 2020a). It demethylates the promoter, leading to increased expression of *Hnf4a* and its gluconeogenic target genes. Additionally, glucocorticoids induce the histone-lysine N-methyltransferase SETDB2 to regulate *Insig2* transcription during fasting, negatively regulating SREBP-driven lipid synthesis (Roqueta-Rivera et al. 2016). These examples highlight how DNA and histone modifications contribute to executing responses to nutritional demands.

Noncoding RNAs are an exciting new class of regulators that brings another layer of fine-tuning to transcriptional and translational responses in fasting/feeding. MicroRNAs have been noted to be involved in the dynamic transition from fasted to fed state (Maniyadath et al. 2019). MicroRNAs abundant in the fed state, such as let-7i, miR-221, and miR-222, target fasting-induced SIRT1, PGC-1 α , and their target genes *Cpt1*, medium chain-specific acyl-CoA dehydrogenase (*Acadm*), *Sirt3*, and transcription factor a, mitochondrial (*Tfam*). In the absence of these fed-state microRNAs, gluconeogenesis is disinhibited and cells are unable to switch from catabolism to anabolism, as evidenced by activated AMPK and reduced phosphorylation of AKT (Maniyadath et al. 2019). Batista et al. (2019) found that >150 noncoding RNAs respond to insulin or fasting and refeeding. Among these, long noncoding RNA (lncRNA) Gm15441 was shown to regulate fatty acid oxidation in hepatocytes (Batista et al. 2019). Zhang et al. (2018b) showed that lncRNA H19 is induced by fasting and regulates hepatic glucose output by altering the promoter methylation and expression of *Hnf4a*. Another recent study found that 5-methylcytosine is enriched on enhancer RNAs with fasting (Aguilo et al. 2016). Additional research is needed to determine how this RNA modification fine-tunes transcriptional regulation.

Transcription factor interactions

Multimics methods have highlighted cooperation and antagonism between transcription factors during fasting and feeding. For example, Everett et al. (2013) used transcriptomics and ChIP-seq to reveal that although CREB is constitutively bound to its target genes, it engages in cooperative interactions with other factors such as C/EBP β , GR, PPAR α , and FOXA2 during fasting. In addition, TORC2, p300, ATF5, and NF-Y are all activated by fasting and promote gluconeogenic gene expression by enhancing CREB activity (Koo et al. 2005; Shimizu et al. 2009; He et al. 2012; Zhang et al. 2018c). Glucagon stimulates gluconeogenesis by dephosphorylating TORC2, which then travels to the nucleus and complexes with CREB (Koo

et al. 2005). TORC2 also associates with p300 upon glucagon signaling, and this enhances its activity (Liu et al. 2008). Interestingly, Liu et al. (2008) observed that SIRT1 deacetylates TORC2 in the late stages of fasting, thereby down-regulating it.

Transcription factor interactions also impact regulation of hepatic glucose metabolism in the fed state. Insulin phosphorylates CBP, destroying the CREB–CBP complex (He et al. 2009). However, the closely related coactivator p300 lacks a similar phosphorylation site and therefore does not get inactivated by insulin. p300 continues to bind to CREB on the *Ppargc1* gene (encoding PGC-1 α) to maintain basal hepatic glucose production for glycogen synthesis even in the postprandial state (He et al. 2012, 2013). FXR also influences glucose metabolism in the fed state by interacting with ChREBP. FXR binds to the same site as the ChREBP–HNF-4 α complex on the *Pklr* promoter and triggers the release of ChREBP, leading to repression in the fed state (Caron et al. 2013). FXR knockout mice show an increased *Pklr* response to refeeding along with reduced plasma glucose and hepatic glycogen levels (Duran-Sandoval et al. 2005).

The activity of transcription factors important in postprandial lipid metabolism is also modulated by cooperative interactions. For instance, HNF-4 α physically interacts with ChREBP on the *Fasn* promoter to fully up-regulate its expression in response to glucose feeding (Adamson et al. 2006). Furthermore, SREBP-1c was shown to cooperate with NY-F and LXR at the promoters of lipogenic genes such as *Fasn* and *Acc1* to induce their expression in response to insulin (Joseph et al. 2002; Talukdar and Hillgartner 2006; Bennett et al. 2008). Recently B-cell lymphoma 6 protein (BCL6) was shown to colocalize with and represses PPAR α activity at genes involved in lipid catabolism in the fed state (Sommars et al. 2019).

Transcriptional regulation of autophagy during fasting also involves transcription factor interactions and epigenetic modifiers. Fasting-induced FGF21 phosphorylates JMJD3, increasing its nuclear transport and interaction with PPAR α (Byun et al. 2020). This interaction induces a number of PPAR α autophagy target genes, including *Tfeb*, *Atg7*, and *Pnpla2* (also known as Atgl). In addition, the CREB–TORC2 complex promotes expression of genes involved in autophagy and lipophagy under nutrient-deprived conditions (Seok et al. 2014). In contrast, during feeding, FXR disrupts the CREB–TORC2 complex and competes with PPAR α to *trans*-repress these genes (Lee et al. 2014; Seok et al. 2014). In later stages of feeding, FGF19 induces SHP, which recruits the lysine-specific histone demethylase 1A (KDM1A; also known as LSD1) to CREB-bound autophagy genes and promotes the disassociation of TORC2, leading to inhibition of autophagy (Byun et al. 2017).

Insulin signaling and insulin resistance

Insulin signaling and the mechanisms by which it is altered in insulin resistance have been the focus of intense study. Insulin is secreted by glucose-sensing pancreatic β

cells in the postprandial state. In the liver, insulin induces lipogenesis and lipoprotein synthesis, allowing conversion of dietary carbohydrates to triglycerides and their export to adipose tissue for storage. Insulin also suppresses gluconeogenesis and glycogenolysis and promotes glycogen synthesis. Insulin-induced hepatic lipogenesis is dependent on cell-autonomous signaling. Insulin reaches the liver through the periportal vein and binds to the insulin receptor (IR) on hepatocytes. IRS1 and IRS2 are direct targets of insulin receptor, and their expression is dynamically regulated in fasting/feeding (Ide et al. 2004). Upon insulin binding, they recruit phosphoinositide 3-kinase (PI3K), which generates phosphatidylinositol (3,4,5)-trisphosphate (PIP3). PIP3 promotes recruitment of pyruvate dehydrogenase kinase 1 (PDK1), which activates AKT by phosphorylation (for review, see Titchenell et al. 2017). Activation of mTOR and suppression of FOXO1 by AKT are necessary for insulin induction of lipogenesis through SREBP-1c (Titchenell et al. 2016). Insulin also suppresses expression of INSIG1 and INSIG2, which inhibits SREBP-1c processing and activation (Boden et al. 2013).

Studies point to hepatic and extrahepatic insulin effects on liver glucose output in the postprandial state. Liver IR knockout (LIRKO) mice show hyperglycemia, confirming that FOXO1 is derepressed without hepatic insulin signaling (Michael et al. 2000). However, in the absence of both AKT and FOXO1, hepatic glucose production remains responsive to insulin, indicating that additional modes of regulation exist (Lu et al. 2012). Insulin has widespread effects on the hepatic transcriptome. Batista et al. (2019) profiled the transcriptomic effects of insulin in the absence of changing glucose levels. They reported that hepatic insulin alters not only glucose and lipid metabolic pathways, mitochondrial function, and autophagy but also nonmetabolic pathways such as Toll-like receptors (TLRs) and Notch signaling. Using proteomics, Capuani et al. (2015) showed that loss of IR induces oxidative stress pathways, suggesting that insulin signaling in liver is protective against oxidative stress. Insulin has also been shown to repress the expression of adiponectin receptors (AdipoR1 and AdipoR2), reducing sensitivity to adiponectin, which mediates fatty acid oxidation through AMPK and PPAR α (Tsuchida et al. 2004).

Diet-induced obesity can lead to selective hepatic insulin resistance, in which suppression of glucose production in the postprandial state is impaired, but insulin-stimulated lipogenesis and very low-density protein (VLDL) secretion remain intact. Diet-induced obesity and insulin resistance alter the expression of number of genes involved in fasting and feeding. IRS1 and IRS2 expression is altered in insulin resistance. Kubota et al. (2016) described that in obese mice, insulin signaling is impaired in the periportal zone, the primary site for gluconeogenesis, as *Irs2* expression is reduced there. At the same time, insulin signaling is enhanced in the primary site for lipogenesis (the perivenous zone) as the predominant *Irs1* in this zone remains unaffected. This phenomenon may shed light on how differential regulation of insulin signal-

ing can lead to selective insulin resistance. Additionally, PGC-1 α induced in fasting was shown to increase the IRS2 to IRS1 ratio in hepatocytes, increasing the sensitivity for insulin-induced suppression of glucose production (Besse-Patin et al. 2019). This phenomenon may help explain how continuous feeding could reduce the IRS2 to IRS1 ratio and impair glucose suppression. Further supporting this point, FGF21 secreted in fasting has been suggested to sensitize insulin signaling at the beginning of feeding (Markan et al. 2014).

Effect of time on fasting and feeding response

Circadian rhythm

Light input to the suprachiasmatic nucleus (SCN) of the hypothalamus creates oscillations in circadian clock proteins to set the body's daily sleep-wake cycle. The sleep-wake cycle establishes an intrinsic fasting-feeding rhythm. In peripheral tissues such as the liver, up to 12% of the total transcriptome has been shown to vary with the circadian cycle, with many of these transcripts encoding metabolic proteins (Panda et al. 2002; Storch et al. 2002; Li et al. 2020b). The circadian cycle is driven by the actions of a complex consisting of the proteins clock circadian regulator (CLOCK) and brain and muscle ARNT-like 1 (BMAL1). This complex promotes transcription of the *Per* and *Cry* families of genes. The period circadian regulator (PER) and cryptochrome (CRY) proteins subsequently form a heterodimeric complex that represses the transcription of *Clock* and *Bmal1*, creating the characteristic back-and-forth 24-h rhythm of the circadian cycle (Fig. 3). In mice, which are nocturnal, BMAL1 and CLOCK protein expression increases during the light phase, while PER and CRY increase during the dark. However, in humans, this cycle is reversed, with BMAL1 and CLOCK increasing during the night and PER and CRY increasing during the day.

In the liver, the CLOCK:BMAL1 complex functions as a pioneer factor, opening chromatin to allow binding of other transcription factors such as HNF6 (Menet et al. 2014). CLOCK:BMAL1 also regulates daily fluctuations in blood cholesterol through its activation of low-density lipoprotein (LDL) receptor transcription (Lee et al. 2012), and regulates hepatic glycogen content by activating transcription of glycogen synthase 2 (*Gys2*) (Doi et al. 2010). As feeding occurs, insulin suppresses BMAL1:CLOCK by causing AKT to phosphorylate BMAL1 at Ser42, leading to its nuclear exclusion (Dang et al. 2016). During fasting, glucagon causes recruitment of the CREB:CRTC2 complex to the *Bmal1* promoter to enhance its expression (Sun et al. 2015). Recent studies have shown, however, that this fasting-induced increase in expression is accompanied by a loss in BMAL1 phosphorylation and acetylation and a decrease in expression of its target genes (Kinouchi et al. 2018).

During feeding and acute fasting, PER2 promotes glycogenesis by binding E-boxes in the promoters of genes encoding the protein phosphatase 1 subunits PP1R3A and PP1R3B, which activate *Gys2* (Zani et al. 2013).

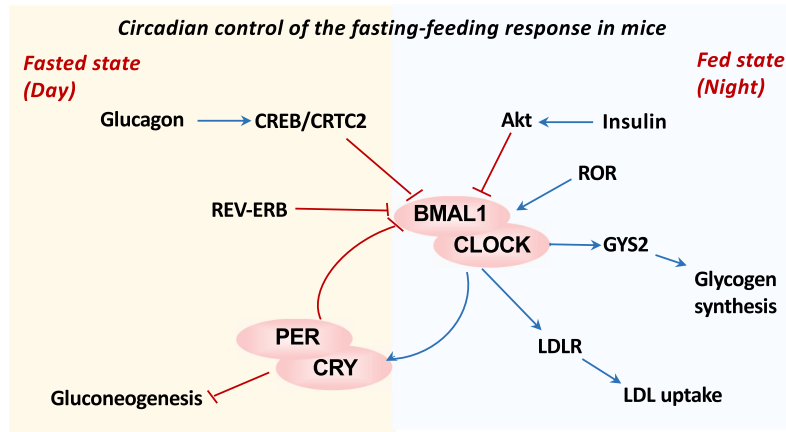


Figure 3. Interplay of circadian rhythm and hepatic gene regulation in mice. (Left) PER/CRY is the major effector of the circadian clock in the liver during the day, while mice are asleep. Effects of PER/CRY include inhibition of gluconeogenesis and suppression of BMAL1/CLOCK. BMAL1/CLOCK activity is also repressed by REV-ERB transcription factors and glucagon via CREB/CRTC2. (Right) At night, when mice are active and feeding, the BMAL1/CLOCK complex is the main circadian regulator of the liver transcriptome. Its effects include increasing LDL uptake and glycogenesis while also increasing levels of the PER/CRY complex. Among the factors that increase BMAL1/CLOCK expression is the daytime accumulation of ROR. As feeding occurs throughout the night, rising insulin levels cause AKT to suppress BMAL1/CLOCK activity.

Accordingly, whole-body loss of *Per2* lowers fasting hepatic glycogen and glycogen synthase levels (Carvas et al. 2012). Degradation of CRY1 by the DNA damage-binding protein 1-Cullin 4A (DDB1-CUL4A) E3 ligase enhances FOXO1-mediated gluconeogenesis in the liver (Tong et al. 2017). Small molecule activators of CRY have been shown to inhibit glucagon-mediated gluconeogenesis in primary hepatocytes (Hirota et al. 2012). In humans, polymorphisms causing increased CRY2 levels have been correlated with increased hepatic triglyceride content and fasting hyperglycemia (Machicao et al. 2016). *Cry1*^{-/-}*Cry2*^{-/-} mice show elevated blood glucose upon refeeding following an overnight fast and severely impaired glucose clearance (Lamia et al. 2011).

In the accessory circadian loop, the BMAL1:CLOCK transcriptional targets ROR and REV-ERB compete for the ROR/REV-ERB Response Element (RRE) in the BMAL1 promoter (Guillaumond et al. 2005). REV-ERB levels rise during the dark phase to repress *Bmal1* expression, while ROR levels rise during the light phase to increase expression (Takeda et al. 2012). REV-ERB controls diurnal recruitment of HDAC3 and the nuclear receptor corepressor complex to the *Bmal1* promoter to repress transcription (Yin and Lazar 2005; Feng et al. 2011). In the liver, REV-ERBa and REV-ERB β are required for circadian oscillations of core clock genes such as *Bmal1* and *Cry1*. Whole-body REV-ERBa/ β -deficient mice have disrupted daily wheel-running patterns, as well as elevated fasting glucose and triglycerides (Cho et al. 2012). ROR α and ROR γ both regulate circadian variations in *Insig2* expression to provide a check on SREBP-1c-mediated lipogenesis during feeding (Zhang et al. 2017). Liver-specific ROR α deletion in mice leads to hepatic steatosis, obesity, and insulin resistance on high-fat diet (HFD) (Kim et al. 2017b).

Outside of the canonical clock genes, a host of other transcription factors have been shown to exhibit circadian variations in expression and activity. Of the 49 nuclear receptors expressed in mice, 20 exhibit rhythmic circadian oscillations, including the PPAR family, retinoic acid receptor RAR α , retinoid X receptor RXR α , the estrogen receptors, and thyroid receptor α . Many of these receptors

peak shortly after the light–dark transition when mice begin to feed (Yang et al. 2006).

Time-restricted feeding and intermittent fasting

As circadian proteins exert control over metabolism, food intake conversely regulates circadian cycles. Mice fed a high-fat diet have altered diurnal feeding behavior, consuming more food in the day and less in the night, as well as altered locomotor activity (Kohsaka et al. 2007). Restricting the food availability of nocturnal mice to daytime hours inverts the circadian rhythm of peripheral tissues, such as the liver, while having no effect on the SCN (Damiola et al. 2000). Furthermore, subjecting wild-type mice to a 24-h fast results in loss of rhythmicity of >80% of liver transcripts that normally display circadian variation (Vollmers et al. 2009). Further evidence of the influence of food timing on metabolism comes from studies of time-restricted feeding (TRF), in which food is limited to a certain interval each day. TRF protects against the development of metabolic disease in a number of mouse models. This effect is believed to stem from the alignment of food intake with circadian timing in the body's peripheral tissues, particularly the liver, which allows for more efficient clearing and processing of ingested nutrients (Tahara and Shibata 2016).

Mice subject to a daily regimen of 8 h feeding/16 h fasting on a HFD take in the same number of total calories as their ad libitum-fed counterparts but do not develop metabolic syndrome (Hatori et al. 2012). A key mediator of this effect is the liver, where TRF rescues the blunted rhythmicity of circadian genes and the function of nutrient-responsive pathways like mTOR, CREB, and AMPK that are altered by HFD (Sherman et al. 2012). This protective effect has been shown to extend to mice subjected to high-fructose and high-fructose/high-fat dysmetabolic diets as well, as long as food availability was limited to <12 h a day. Feeding in TRF HFD mice is accompanied by a concomitant increase in GCK expression; however, in ad libitum HFD mice, GCK levels remain persistently elevated throughout the day. Thus,

modulation of the fasting–refeeding interval restores glucose homeostasis in HFD-fed mice. In the livers of TRF HFD-fed mice, PPAR γ displays mild oscillations in amplitude throughout the circadian cycle with a peak in during the active phase. In ad libitum HFD-fed mice, however, these oscillations dramatically increase in amplitude and instead peak in the day/inactive phase (Chaix et al. 2014).

TRF has also been shown to prevent the development of metabolic abnormalities in mice with clock gene mutations. Whole-body *Cry1*^{-/-}*Cry2*^{-/-} KO mice have a near complete loss of rhythmic gene expression in the liver, an effect partially rescued by TRF (Vollmers et al. 2009). In addition, genetically modified mice that lack a regular feeding rhythm consume the same number of calories as their ad libitum counterparts but resist weight gain and hyperleptinemia (Chaix et al. 2019). Recently, these findings have been extended to humans. In a study of 19 patients with metabolic syndrome on statins or antihypertensives, limiting food intake to a 10-h window each day over 12 wk led to reductions in body weight, visceral fat, blood pressure, total cholesterol, LDL, and HbA1c (Wilkinson et al. 2020).

Fasting and refeeding protocols

Although it is unsurprising that the hepatic transcriptome differs dramatically between ad libitum feeding and 24-h fasting conditions, substantial differences exist even between ad libitum-fed and 24-h refed livers, with expression differences in key pathways controlling lipid metabolism and small molecule biochemistry (Zhang et al. 2011). A study of both BALB/cJ and C57BL/6J mice fasted for 24 h and refed found that differential gene expression peaks at 6 h after refeeding with up-regulation of lipogenic pathways in comparison with amino acid and carbohydrate metabolism (Chi et al. 2020). Moreover, fasting–refeeding regimens are themselves highly heterogeneous. As stated in the “Pathway Analysis” section, a time course comparing the hepatic transcriptome after 0, 12, 24, and 72 h of fasting found that strong induction of the urea cycle was apparent at every time point. In contrast, pathways controlling amino acid, carbohydrate, and lipid metabolism peak at 24 h and return to baseline by 72 h, at which point, β oxidation and ketogenesis pathway expression increases (Sokolovic 2008). Another time course study in 48-h fasted mice revealed up-regulation of hepatic gluconeogenesis and ketogenesis at 3 h; additionally, these mice showed marked up-regulation of PPAR α targets, including *Pck1*, *G6pc*, and *Fgf21* (Schupp et al. 2013). Another recent study comparing 24-h fasted mice refed for either 12 or 21 h found that even after 12 h of refeeding, mice had continued dysregulation of liver lipid metabolism and autophagy; however, this effect was largely abrogated in the 21-h refed group (Rennert et al. 2018). A better understanding of the dynamics of fasting and refeeding in mice will allow experiments to be standardized across different laboratories and focused on desired pathways of study (i.e., ketogenesis, gluconeogenesis).

Effect of diet, exercise, and sex on fasting and feeding response

Diet

The contents of the diet play a modifying role in transcriptional responses to both fasting and feeding. Studies have compared diets rich in fat versus carbohydrates, glucose versus fructose, high versus low protein, and effects of calorie restriction. HFD has been found to increase hepatic de novo lipogenesis (e.g., expression of *Fas* and *Scd1*) to a lesser degree than carbohydrate feeding (Sánchez et al. 2009). Furthermore, cholesterol biosynthesis genes controlled by SREBP-2 are down-regulated by increased dietary cholesterol (Renaud et al. 2014). In contrast to fatty acid biosynthesis genes, mitochondrial and peroxisomal β oxidation genes (such as *Cpt1a* and *Acox1*, respectively) are induced in HFD-fed mice (Renaud et al. 2014). PPAR α , the master regulator of fatty acid oxidation, is induced by fat feeding, drawing a similarity to the extended fasted state, as both contexts use fat as a primary energy source (Sánchez et al. 2009). Consistent with this idea, AMPK activity is increased in livers fed with PUFAs or a high-fat diet (Suchankova et al. 2005; Castro et al. 2015). In contrast to fasting, a HFD also increases some aspects of the immune response, such as *Nfkb1* and its target genes tumor necrosis factor *Tnfa*, *Il1b*, prostaglandin-endoperoxide synthase 2 (*Ptgs2*), and nitric oxide synthase 2 *Nos2* (Lee et al. 2013).

Fatty acid synthesis genes are more robustly up-regulated by high-fructose diets compared with complex carbohydrate diets (Fiebig et al. 1998). Also, the dynamics of the fructose and glucose transcriptional responses are different. Glucose refeeding causes a more acute SREBP-1c induction (Matsuzaka et al. 2004). Furthermore, in the absence of insulin signaling, lipogenic genes such as *Fasn* are more induced by fructose than glucose feeding. Recent studies suggest that ChREBP may be playing an important role in this process. Fan et al. (2017) documented increased expression of the ChREBP target *Pklr* in fructose-fed mice compared with glucose-fed mice. They also reported that while LXRA facilitates the increase in ChREBP activity in glucose-fed mice, the ChREBP response to fructose feeding was independent of LXRA. Additionally, while excess dietary fructose can increase stress signaling via c-Jun N-terminal kinase (JNK) signaling, glucose feeding has been reported to promote hepatic inflammatory responses more than fructose feeding, as evidence by increased expression of TLR2 and inflammatory genes such as C-X-C motif chemokine ligand 2 (*Cxcl2*), *Cxcl10*, *Cxcl1*, *Nfkb1*, and *Nfkb2* (Wei et al. 2007; Oarada et al. 2015).

Dietary protein content is also a modifier of hepatic transcription. Unlike food restriction, where proportionality of nutrients is preserved, modified protein diets affect many aspects of whole-body homeostasis. Refeeding with high-protein diet after a prolonged fast can cause acute liver damage (Oarada et al. 2012). Conversely, feeding with low-protein diet affects growth through down-regulation of insulin-like growth factor I (*Igf1*) and induces

inflammatory genes such as *Il6* (Oarada et al. 2012). Dietary protein induces PPAR γ -dependent hepatic IGF-1 secretion and promotes mTOR phosphorylation and the interaction between PPAR γ and mTOR (Wan et al. 2017). Leucine deficiency was shown to up-regulate transcription of tribbles homolog 3 (*Trib3*), a factor known to inhibit insulin signaling by binding to AKT (Carraro et al. 2010). TRB3, encoded by *Trib3*, also interacts with ATF4, inhibiting it from inducing FGF21 (Örd et al. 2018).

Calorie restriction

Calorie restriction (CR) has been associated with health benefits and longevity. CR is a less extreme version of fasting that can be continued for extended periods, at least in laboratory settings. CR decreases the expression of lipogenic genes such as *Fasn* and *Elovl3* and genes involved in formation of lipid droplets such as perilipin-2 (*Plin2*) and fat storage-inducing transmembrane protein 1 (*Fitm1*) (Renaud et al. 2014). On the other hand, genes involved in lipid droplet breakdown and fatty acid oxidation are increased by CR. Drawing parallels to a fasting-like state, CR animals also respond to fasting with increased expression of PPAR α (Soltis et al. 2017). Decreased lipid formation and increased lipid breakdown lead to a decrease in fat mass (van Harten et al. 2013; Renaud et al. 2014; Xu et al. 2019). However, refeeding chow or a HFD up-regulates lipogenesis more robustly in CR compared with ad libitum-fed mice (Stelmanska et al. 2004). This is reminiscent of the observation that humans often gain more weight back than they have lost after stopping restrictive dieting. CR feeding also leads to increased expression of genes involved in oxidative stress response such glutathione synthesis genes and glutathione-S transferases (Renaud et al. 2014). Some benefits of CR have been proposed to be mediated by SIRT1. Although SIRT1 activity is increased by CR in many tissues, SIRT1 activity is actually decreased in liver by CR (Chen et al. 2008).

Exercise

Exercise can change the energy demands of the body and reprogram metabolism in many tissues. Exercise has been reported to blunt the up-regulation of lipogenesis in liver in response to carbohydrate feeding. However, exercise was less effective in reducing the lipogenic response in fructose feeding (Fiebig et al. 1998). Exercise is also known to increase insulin sensitivity in adipose and muscle but not in the liver (Cuthbertson et al. 2016). On the other hand, exercise can increase expression of genes involved in fatty acid oxidation and transport into mitochondria (Cho et al. 2014). Additionally, exercise has been suggested to decrease hepatic oxidative stress (Hu et al. 2013) and to decrease HFD-induced NF- κ B activation and proinflammatory cytokine production (Gehrke et al. 2019). These beneficial effects of exercise on lipid metabolism appear to be independent of the mTOR pathway (Tu et al. 2020) and potentially mediated by increased PPAR α -stimulated fat oxidation (Alex et al. 2015).

Sex differences

Premenopausal women are more resistant to diet-induced insulin resistance than men. Sex differences are also seen in responses to fasting and feeding. Bazhan et al. (2019) showed that changes in expression of genes involved in the fasting response, such as *Fgf21*, *Ppara*, and *Cpt1a*, were more pronounced in female mice than in males. In contrast, they reported that hepatic expression of *Fasn* was higher in male mice than in females, possibly due to male-specific hyperinsulinemia. Male mice also have higher insulin to glucagon ratios, leading to increased glucose metabolism (Gustavsson et al. 2010). According to this study, male mice exhibit increased hepatic glucose output and expression of gluconeogenic genes such as *G6Pase* and *Pck1* compared with females. Males also have higher glycogen synthesis, which is commonly observed with high gluconeogenic capacity.

Growth hormone secretion and signaling is also sexually dimorphic. While adult males secrete growth hormone in episodic bursts, females display a continuous pattern of growth hormone secretion (Jansson et al. 1985). Growth hormone may exert its impact on sex-specific hepatic metabolic gene expression through STAT5 and its male-biased transcriptional repressor BCL6. BCL6 binds preferentially to STAT5 target genes involved in lipid metabolism that have a female-biased expression (Zhang et al. 2012).

Limitations

Rodent models provide many benefits to metabolic researchers; however, it is important to be aware of their limitations. One cannot always extrapolate findings to a human clinical setting. Humans have both physiological and psychological differences from mice with respect to feeding and fasting behavior. While mice eat small portions frequently during the dark, humans eat few larger meals during the day (Ellacott et al. 2010). Humans may choose to eat or not eat for social reasons, which are not captured by most experimental designs in rodent models. Many clinical tests are run on overnight-fasted patients. Overnight fasting in mice is not an equivalent challenge because of their nocturnal feeding and higher rate of metabolism. While mice glucose levels are lower after an overnight fast, humans are able to maintain their basal glucose levels for >18 h (Ayala et al. 2010; Geisler et al. 2016). It is suggested that fasting mice 5–6 h during the day better resembles human overnight fasting when comparing glucose and insulin levels. Finally, whereas mice respond to prolonged fasting with enhanced insulin-stimulated glucose utilization, humans display an impairment of insulin-stimulated glucose utilization (Ayala et al. 2006). These and other differences need to be taken into account when making predictions of human physiology based on murine studies.

Conclusions

Changes in nutrients, hormones, and post-translational modifications regulate a broad hepatocyte transcriptional

network. During fasting, the liver switches to using lipids and amino acids as its primary energy source to make ketones and glucose, respectively. PPAR α , FOXO1, PGC-1 α , and CREB are among the key players enacting this shift. In the fed state, the liver takes up glucose and increases glycolysis and lipogenesis in response to carbohydrates via ChREBP and Srebp1c. The fasting/feeding response is also shaped by a network of additional transcriptional regulators. High-throughput -omics methods have just started investigating these complex relationships and their effects in a systematic way. Many other pathways, including those involving bile acids, iron metabolism, immune responses, circadian rhythms, and stress responses, are affected by nutritional status. Proper control of hepatic transcription by diet is crucial for physiology, and perturbation of these pathways are a hallmark of metabolic diseases. With the continued development of new methods and new genetic models, future research is likely to reveal additional connections and expand our understanding of this central physiologic response.

Competing interest statement

The authors declare no competing interests.

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