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REVIEW

Mammalian Hibernation and Regulation of Lipid Metabolism: A Focus on Non-coding RNAs

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Abstract—Numerous species will confront severe environmental conditions by undergoing significant metabolic rate reduction. Mammalian hibernation is one such natural model of hypometabolism. Hibernators experience considerable physiological, metabolic, and molecular changes to survive the harsh challenges associated with winter. Whether as fuel source or as key signaling molecules, lipids are of primary importance for a successful bout of hibernation and their careful regulation throughout this process is essential. In recent years, a plethora of non-coding RNAs has emerged as potential regulators of targets implicated in lipid metabolism in diverse models. In this review, we introduce the general characteristics associated with mammalian hibernation, present the importance of lipid metabolism prior to and during hibernation, as well as discuss the potential relevance of non-coding RNAs such as miRNAs and lncRNAs during this process.

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Key words: hibernation, hypometabolism, lipid synthesis, fatty acid degradation, microRNAs, long non-coding RNAs

Several animals when confronted with environmental challenges such as cold temperatures or food restriction will enter a hypometabolic state in which they will remain until favorable conditions return. Natural strategies of hypometabolism are numerous and include, but are not limited to, aestivation, diapause, daily torpor, and mammalian hibernation. Hibernators can sustain cold ambient conditions for prolonged periods of time, and the changes associated with the process of hibernation are well characterized. Besides reduced metabolic rate, mammalian hibernation is also associated with a reduction in heart rate, blood flow, and oxygen consumption [1]. Significant metabolic changes are observed including a switch from a carbohydrate-based metabolism to one that leverages stored lipids [2]. At the biochemical and molecular levels, a plethora of modifications have been documented in hibernating mammals including reversible protein phosphorylation, differential expression of selected transcripts and proteins, as well as modulation of non-coding RNAs [3, 4]. This review discusses the current knowledge associated with mammalian hibernation with a particular focus on the potential role of non-coding RNAs involved in the regulation of lipid metabolism during this hypometabolic state.

Abbreviations: lncRNAs, long non-coding RNAs; miRNAs, microRNAs.

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MAMMALIAN HIBERNATION: A "COOL" PROCESS?

Natural models of hypometabolism. Metabolic rate depression is essential for survival of numerous species confronted with extreme environmental conditions and notably underlies aestivation, diapause, and hibernation. A series of concerted physiological, biochemical, and molecular levels are observed during these hypometabolic states. Such processes are usually associated with basal metabolic rate reduction to levels between 5 and 40% of those experienced by resting animals [5]. Aestivation, for example, is a state of aerobic torpor leveraged by species that are usually confronted with arid conditions. Well-characterized aestivating vertebrates notably include amphibians such as the spadefoot toad *Scaphiopus couchii* and mollusks such as the land snail *Otala lactea* [6]. An important element for long-term survival of species that aestivate is the accumulation, conservation, and usage of fuel reserves. Aerobic oxidation of lipid reserves is employed by species such as *S. couchii* as energy source during aestivation [7]. Hypometabolism is also observed

in species that undergo diapause such as cold-hardy insects. Diapause is undertaken by species as a developmental response to changing seasons and environmental conditions. This genetically programmed phenomenon allows species to face seasonally recurring environmental stresses as well as to initiate and regulate growth and development in favorable environmental conditions [8]. Although not its exclusive role, diapause often positively influences cold hardiness and overwintering survival in insects. Diapause-associated changes, including synthesis of cryoprotectants and changes in membrane lipid composition, ultimately help with protection against cold stress [9, 10]. Not unlike diapausing insects, mammalian hibernators also have to confront cold temperatures for extended periods of time. Several groups of mammals have been reported to hibernate including marsupials, rodents, bats, and primates [11]. A plethora of changes are undertaken to enter, maintain, and exit the hypometabolic state associated with hibernation. A strong reliance on lipid catabolism as the primary fuel source as well as differential expression of selected, torpor-responsive, transcripts is notably observed [12, 13]. As a well-characterized model of hypometabolism and a particular research interest of our laboratory, the focus of the review will now be directed towards mammalian hibernation.

Physiological changes associated with mammalian hibernation. The changes associated with mammalian hibernation are numerous and well documented. A period of hyperphagia that leads to body fat increase is frequently experienced in animals prior to the hibernating season as significant triglyceride synthesis and storage is undertaken in white adipose tissue [12]. These are essential, as lipid metabolism is an essential fuel source for hibernating species. A typical hibernating season consists in a series of multiple torpor bouts that can last up to several weeks and that are separated by brief arousal periods [14]. The duration of the torpor periods differs between species and is influenced by ambient temperatures [15]. Small mammalian hibernators, such as the thirteen-lined ground squirrel *Ictidomys tridecemlineatus* or the little brown bat *Myotis lucifugus*, can reduce vital functions significantly during torpor. Core body temperature is reduced to levels nearing the freezing point while heart rate can fall to 10 beats/min from the 350-400 beats/min measured in euthermic animals [11]. Another fascinating physiological feat observed in hibernating mammals includes a considerable reduction in breathing rate [16]. From a metabolic standpoint, mammalian hibernators can suppress their metabolism by up to 99% during torpor when compared with the basal metabolic rate measured in euthermic animals [11]. It is estimated that hibernators can save up to 90% of the energy they would otherwise require if they were to remain active during the cold season [17].

Molecular switches underlying metabolic depression in torpid animals. Numerous biochemical and molecular changes underlie metabolic rate depression during mammalian hibernation. Energy-consuming cellular processes including transmembrane ion transport and transcription are significantly suppressed in torpid animals [18, 19]. Interestingly, the rapid and reversible physiological changes associated with the torpor-arousal cycles experienced by hibernators must be supported by an equally dynamic system at the molecular level. Reversible protein phosphorylation has emerged over time as a crucial post-translational mechanism involved in regulating key molecular players involved in metabolic rate depression. Phosphorylation-mediated pyruvate dehydrogenase activity inhibition, leading to carbohydrate catabolism suppression, is well documented in different models of hypometabolism [20, 21]. Na^+,K^+-ATPase activity is another example of an enzyme with an activity that is strongly influenced by phosphorylation in mammalian hibernation [18]. Despite the importance of reversible protein phosphorylation for metabolic rate suppression, additional posttranslational mechanisms including sumoylation and ubiquitination are modulated to various degrees in hypometabolism [22, 23]. Protein synthesis, an important ATP-consuming process, is significantly inhibited during hibernation. A study performed in brain of torpid and euthermic ground squirrels showed that the translational rate during hibernation could be as low as 0.04% when compared with the one measured in euthermic squirrels [24]. An *in vivo* study of protein synthesis in hibernating Syrian hamsters *Mesocricetus auratus* demonstrated significant reduction of this process in several organs [25]. Posttranslational modifications of initiation and elongation factors of protein synthesis, such as eIF2α and eEF2, underlie in part the changes observed in translational rate during torpor [24]. Significant alterations in the activity of the mTOR signaling cascade, a key pathway linked to protein synthesis, have been reported in hibernating skeletal muscle of ground squirrels and could also account for the reduced translational rates observed in torpor [26]. More recently, studies have highlighted the potential importance of the small non-coding RNAs microRNAs (miRNAs) in regulating expression of selected transcripts in different models of hypometabolism providing yet another mean of translational control for hibernating mammals [4]. A particular emphasis will be placed in the final section of this review on the role that miRNAs can play during hibernation.

LIPID METABOLISM AND HIBERNATION

Lipid synthesis and degradation: fueling hibernation. Mammalian hibernators cycle on an annual basis between active and hibernating periods. Energy requirements associated with these two states differ significantly. Active hibernators spend a significant portion of their time eating and accumulating fat stores, primarily as triglycerides,

that contribute to a considerable gain in body mass [12]. The hibernating golden-mantled ground squirrels *Callospermophilus lateralis* can spend up to 57% of their active hours feeding prior to hibernation [27]. Elevated activities of enzymes involved in triglycerides synthesis, such as diacylglycerol acyltransferase, have been reported in white adipose tissue of summer active golden-mantled ground squirrels and of summer active yellow-bellied marmots *Marmota flaviventris* [28, 29]. These studies further demonstrated that enzymes involved in fatty acid synthesis possess higher activities in selected tissues of summer active animals when compared with torpid animals. In addition, recent work performed in tissues of hibernating golden-mantled ground squirrels showed significant overexpression in torpor of the phosphorylated and inactive form of acetyl-CoA carboxylase, an enzyme that catalyzes an essential step in fatty acid synthesis [30]. While in torpor, hibernators address their energy demands primarily via β-oxidation of fatty acids sourced from white adipose tissue [12]. Acyl-CoA dehydrogenase, the enzyme catalyzing the initial step in β-oxidation, exhibits marked induction in its activity in brown adipose tissue and white adipose tissue of the hibernating jerboa *Jaculus orientalis* [31]. Increased fatty acid plasma concentration has also been reported in selected hibernating models such as *M. flaviventris*, suggesting increased lipolysis in torpid animals [32, 33]. In addition to being an important fuel source for hibernators, it is also important to emphasize the role of fatty acids, and in particular polyunsaturated fatty acids, in preserving the fluidity of membrane phospholipids at low body temperatures [34]. Several studies have demonstrated that hibernating mammals or cold-water fish, for example, notably displayed a higher proportion of polyunsaturated fatty acids in their body fats than species in warmer climates [35, 36].

Regulatory roles of lipids during hibernation. Besides being an important source of energy and essential molecules underlying membrane fluidity at low temperatures, lipids can also influence a myriad of torpor-related processes via diverse signaling and regulatory functions. For example, fatty acids can act as ligands and activate the nuclear receptors peroxisome proliferator-activated receptors (PPARs) [37]. These transcription factors regulate lipid metabolism via differential expression of numerous target genes. Target genes such as pyruvate dehydrogenase kinase isozyme-4 and apolipoprotein A-I can impact lipid metabolism as well as ketone body formation, respectively, and are differentially expressed in hibernation [38, 39]. PPAR protein levels are also modulated in several models of hypometabolism including PPARγ in the hibernating bat *M. lucifugus*, ground squirrel *I. tridecemlineatus*, and jerboa *J. orientalis* [40-42]. PPARα is differentially expressed in hibernating *J. orientalis* and has been put forward as a key controller of torpor [43, 44]. In addition to PPARs, additional nuclear receptors such as the retinoid-related orphan receptor alpha (RORα) and the liver X receptors (LXRs) can regulate expression of genes involved in lipid metabolism and also warrant closer attention for their potential role during torpor. LXRs target genes including the apolipoprotein E and the ATP-binding cassette transporter AI (ABCA1) can affect cholesterol homeostasis [45]. Plasma and tissue cholesterol levels vary significantly during hibernation, and LXR activity is thought to underlie this balance [46, 47]. RORα, a nuclear receptor that can influence circadian rhythms and metabolism through the expression of its target genes, regulate key molecular players involved in mammalian hibernation [48]. Interestingly, cholesterol sulfate, a RORα ligand, is altered in hibernating ground squirrels as they undergo a hibernation cycle [49]. Whether as an integral part of the energy source associated with torpor, as an important component of biological membranes at low temperatures, or as signaling molecules with far-reaching translational impacts, lipids are undoubtedly essential to several facets of mammalian hibernation. Accordingly, molecules that can impact the synthesis, degradation, or signaling processes associated with lipids are of significant interest.

FAMILIES OF NON-CODING RNAs

Cold-associated miRNAs. MiRNAs are examples of molecules with such ubiquitous implications. MiRNAs are short, approximately 21 nucleotides in length, non-coding transcripts that can bind to target mRNAs and repress their translation. MiRNA biogenesis has been extensively described elsewhere and will not be the scope of this review [50]. It is estimated that expression of more than 60% of all protein-coding genes can be regulated by miRNAs, which highlights the far-reaching capabilities of these molecules in modulating different cellular processes [51, 52]. A growing body of evidence has positioned miRNAs as molecules involved in the regulation of hypometabolic models including diapause in the flesh fly *Sarcophaga bullata* [53], aestivation in the sea cucumber *Apostichopus japonicus* [54], and cold hardiness in insects [55, 56]. The freeze-tolerant wood frog *Rana sylvatica* displayed elevated miR-21 levels and reduced miR-16 levels in skeletal muscle during freezing [57]. Subsequent work in liver of frozen *R. sylvatica* reported elevated levels of miR-26a, miR-126, and miR-217, three miRNAs that can regulate PTEN expression and thus potentially contribute to anti-apoptotic functions via Akt activation during freezing [58]. Differential expression of miRNAs, including miR-1a-1 and miR-34a, was also presented in frozen hepatopancreas and foot muscle of the freeze-tolerant land snail *Littorina littorea* [59]. Several studies have reported modulated miRNAs during mammalian hibernation. Pioneering work on this topic demonstrated differentially expressed miRNAs in several tissues of the hibernating *I. tridecemlineatus* [60]. Subsequent reports

on miRNA expression in different hibernating species were presented in recent years and have contributed markedly in positioning these molecules as important molecular players in torpor. The little brown bat *M. lucifugus* notably exhibits elevated levels of eight miRNA species in hibernating pectoral muscle tissue [61]. Interestingly, transcript targets of these miRNAs were shown to code for muscle-specific proteins, including FoxO3a and SMAD7, suggesting a potential relevance for bat muscle preservation during torpor. A follow-up study evaluating miRNA expression in euthermic and hibernating brain of *M. lucifugus* also demonstrated eight overexpressed miRNAs with probable impact on axon guidance and focal adhesion processes in torpor [62]. Genomic analysis performed in the Arctic ground squirrel *Spermophilus parryii* revealed numerous miRNAs such as miR-451 and miR-486 that were differentially expressed at different stages of hibernation when compared with control animals [63]. While the exact role of these miRNAs remains to be determined in torpid *S. parryii*, such molecules likely impact diverse processes including cell growth. Levels of miR-106b, a miRNA that can influence HIF-1α expression, were also shown to be reduced in skeletal muscle of torpid *M. lucifugus* and *I. tridecemlineatus* [64]. A microarray-based approach that assessed miRNA levels in the brain of euthermic and hibernating *I. tridecemlineatus* revealed down-regulation of miRNAs that were part of the miR-182 and miR-200 families of miRNAs [65]. Members of these families, including miR-200a, miR-200b, and miR-200c, as well as miR-182, were all involved in regulating the expression of ubiquitin-like modifiers, which underlie cellular response to various stresses. As evidenced by these studies, a growing list of differentially expressed miRNAs in different animal species that can confront and survive cold temperatures is being built. This family of cold-associated miRNAs, loosely referred to as "CryomiRs" [4], is likely to expand in the near future.

MicroRNAs and impact on lipid metabolism. MiRNAs that can modulate key metabolic cascades of hibernation such as those associated with lipid metabolism are foreseen to join the list of "CryomiRs". Examples abound, in non-hypometabolic models, of interactions between miRNAs and target transcripts that code for proteins involved in lipid metabolism. For example, miR-33b can target key enzymes involved in fatty acid oxidation such as carnitine palmitoyltransferase 1A and the alpha subunit of AMP kinase (AMPKα) in human hepatic cell lines [66]. AMPKα phosphorylation is also influenced by miR-144 and miR-451 notably via translational regulation of key mediators in this pathway such as MO25α and acetyl-CoA carboxylase [67]. Table 1 presents miRNAs that can target AMPK as well as upstream regulators of this cascade. Interestingly, AMPK and acetyl-CoA carboxylase protein and activity levels are modulated to different extents in hibernating ground squirrels [30, 70], which raises the question of whether or not these miRNAs participate in such control. It is of particular interest to note that miR-144 is strongly expressed in liver tissue of torpid *S. parryii* [63]. MiR-195, a miRNA that targets fatty acid synthase (FAS) in human osteosarcoma cells, is elevated in hibernating liver tissue of *I. tridecemlineatus* [71]. The same study demonstrated that protein levels of FAS, an enzyme involved in fatty acid synthesis, were down-regulated under the same conditions, suggesting a potential importance for the miR-195–FAS axis in hibernating ground squirrels. As mentioned above, PPARγ is a key transcription factor modulated in selected models of hibernation and that can regulate the expression of a plethora of target genes involved in lipid metabolism. Numerous miRNAs can regulate the expression of PPARγ and of genes under its control. An overview of the potential miRNA-mediated regulatory nodes associated with PPARγ and its target genes is presented in Fig. 1. MiR-27 and miR-130 for instance can regulate PPARγ expression in mice and human adipocytes, respectively [78-80]. MiR-126 also plays an important role in PPARγ-mediated gene expression via regulation of two PPARγ-associated genes, phosphatidylinositol 3-kinase (PI3K) and insulin receptor substrate-1 (IRS1) [86, 90]. PPARα, also differentially expressed in selected hibernators, is targeted by miR-22 in mouse cardiomyocytes [96]. Expression of the nuclear receptor liver X receptor α (LXRα) is regulated by miRNAs such as miR-1, miR-206, and miR-613 in human and mouse models [97-99]. MiRNAs that can target LXRα and its target genes are presented in Fig. 2. Interestingly and despite the relative lack of expression data on these molecules in hibernating models, the sterol regulatory element-binding proteins (SREBPs) transcription factors are crucial regulators of lipid homeostasis [111]. Multiple evidences of miRNAs that can regulate the expression of SREBPs and their target genes have been put forward. These interactions are summarized in Table 2. MiR-185 and miR-342 have notably been shown to inhibit both SREBP1 and SREBP2 expression, leading to negative regulation of their target genes in human

Table 1. MiRNA regulation of AMPK signaling. MiRNAs with reported transcript targets related to AMPK and upstream signaling

Target	miRNAs	References
AMPK	miR-33a/b, miR-144, miR-451	[66, 67]
CaMKK	miR-9	[68]
LKB1	miR-199a	[69]

Note: AMPK, AMP-activated protein kinase; CaMKK, Ca^{2+}/calmodulin-dependent protein kinase kinase; LKB1, serine/threonine kinase 11.

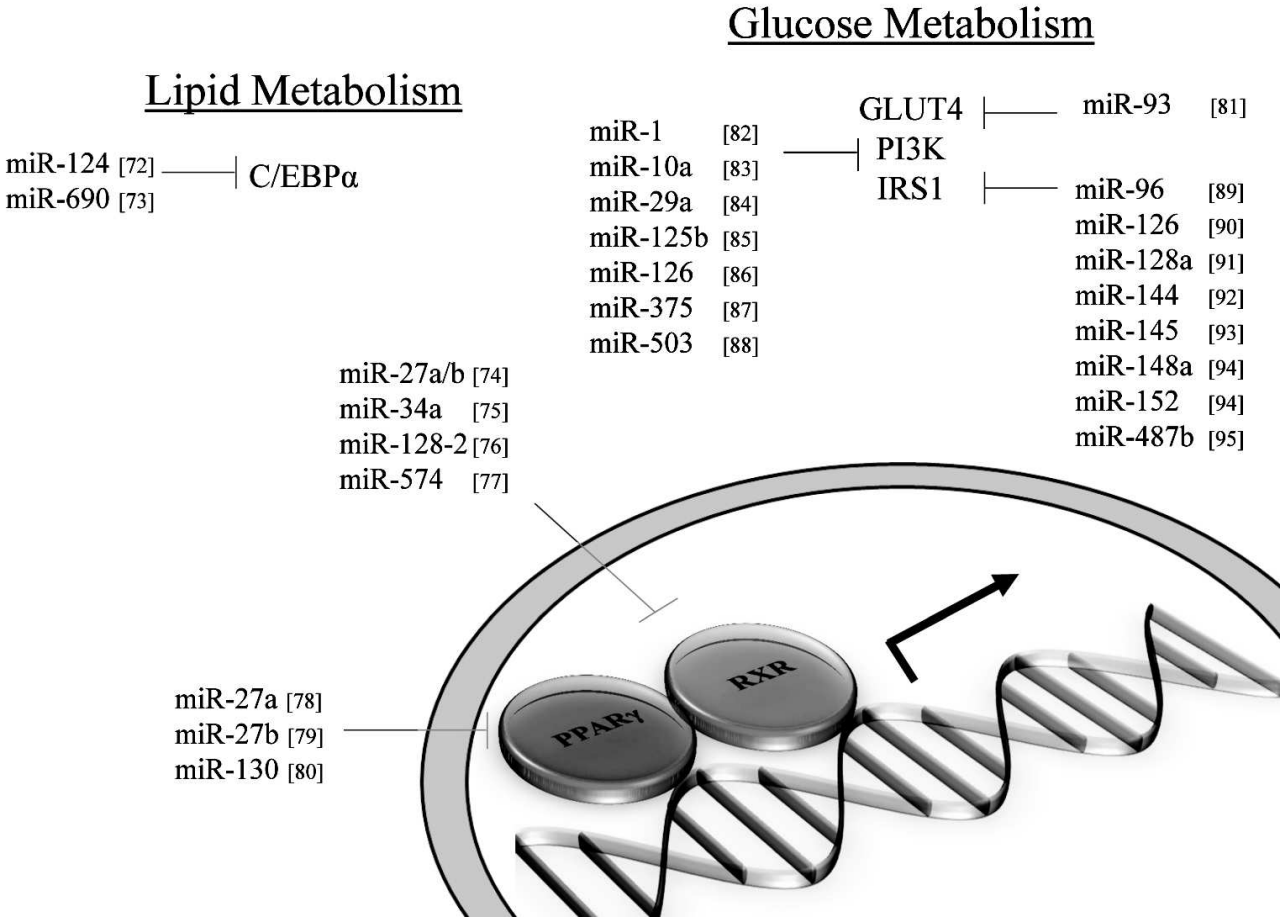

Fig. 1. PPARγ and related miRNAs. MiRNA-mediated regulation of PPARγ and selected target genes. Note: C/EBPα, CCAAT/enhancer-binding protein alpha; GLUT4, glucose transporter 4; IRS1, insulin receptor substrate-1; PI3K, phosphatidylinositol 3-kinase; PPARγ, peroxisome proliferator-activated receptor gamma; RXR, retinoid X receptor.

prostate cancer cells [112]. MiR-33 was shown to impact SREBP1 expression in a mouse model and that this regulation had potential implications in obesity [113]. Overall, several transcripts coding for proteins involved in lipid metabolism have been identified as miRNA targets. Validating and understanding the relevance of these miRNA-transcript interactions in natural models of hypometabolism will need to be undertaken next to have a clearer idea of the extent to which miRNAs play a role in such species.

Long non-coding RNAs: additional "CryomiRs"? The surface has barely been scratched when it comes to elucidating the impact of miRNAs in torpor, and yet another family of non-coding RNAs emerges as another layer of regulation; the long non-coding RNAs (lncRNAs). LncRNAs are non-coding transcripts that are longer than 200 nucleotides [119]. More than a thousand lncRNAs have been identified to date in mammals and other vertebrates and this number is increasing [120, 121]. Not surprisingly, the list of functions associated with this family of molecules is also expanding. Some of the better known functions associated with lncRNAs include epigenetic regulation of gene expression via recruitment of histone-modifying complexes. The lncRNA Xist can recruit key factors that can contribute to histone methy-

Table 2. SREBP-associated miRNAs. MiRNAs with reported transcript targets associated with SREBPs and target genes

Target	miRNAs	References
SREBP1	miR-33, miR-185, miR-342	[112, 113]
SREBP2	miR-185, miR-342	[112]
FAS	miR-107, miR-130a, miR-195, miR-320, miR-424	[114-118]
ACC	miR-144, miR-451	[67]

Note: SREBP, sterol regulatory element-binding protein; ACC, acetyl-CoA carboxylase; FAS, fatty acid synthase.

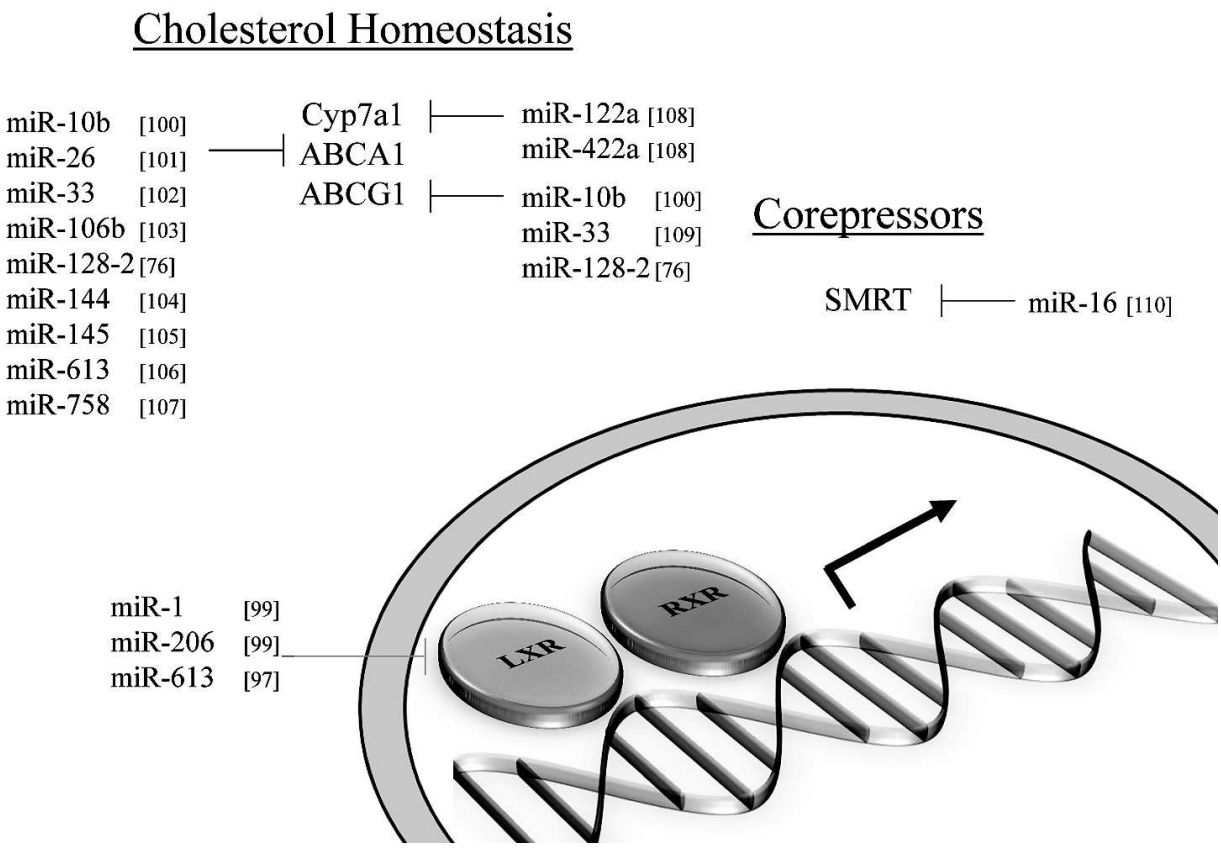

Fig. 2. Liver X receptors and related miRNAs. Regulation of LXR and target genes by miRNAs. Note: ABCA1, ATP-binding cassette transporter AI; ABCG1, ATP-binding cassette transporter GI; LXR, liver X receptor; RXR, retinoid X receptor; SMRT, silencing mediator of retinoic acid and thyroid hormone receptor.

lation and ubiquitination [122]. LncRNAs, including Evf-2, can also act as co-activators of proteins involved in transcriptional regulation [123]. LncRNAs can even affect the subcellular localization of proteins and influence their activity. For example, the lncRNA NRON can affect the cytoplasm-nucleus trafficking of the NFAT transcription factor [124]. With such diverse functions, it is not surprising that lncRNAs can impact different cellular processes including lipid metabolism. A recent study has highlighted a potential role for the lncRNAs colorectal neoplasia differentially expressed (CRNDE) transcripts in colorectal cancer cells [125]. Their findings suggested that such lncRNAs could influence gene expression of key molecules involved in glucose and lipid metabolism. Similarly, work performed in esophageal squamous cell carcinoma identified differentially expressed lncRNAs with the potential to regulate expression of genes implicated in lipid metabolism [126]. APOA1-AS and DYNLRB2-2 are other examples of lncRNAs that can influence the expression of targets involved in lipid homeostasis and metabolism [127, 128]. While the field is still in its infancy, it is reasonable to postulate that lncRNAs play an important part in regulating key molecules involved in lipid metabolism, and other cascades, during mammalian hibernation. Pioneering work in *M. lucifugus* has revealed decreased levels of the natural antisense long non-coding RNA HIF-1a, known as aHIF, in torpid *M. lucifugus* skeletal muscle tissue when compared with euthermic samples [64]. The authors proposed a likely correlation between aHIF levels and HIF-1a expression and suggested that the non-coding RNA might have a significant role in influencing transcriptional expression of HIF-1 target genes during torpor. While a clearer knowledge of lncRNA expression and function in mammalian hibernation remains to be performed to better assess the relevance of these molecules in this process, the characterized impact of lncRNAs in non-hibernating models suggest that they will play an important role.

OUTLOOK

Natural models of hypometabolism undergo a series of physiologic, biochemical, and molecular changes to successfully confront environmental challenges that arise. Several metabolic cascades are affected by this hypometa-

bolic state, and this review took a particular interest in discussing the dynamics of lipid metabolism in mammalian hibernators as well as highlighting the potential regulation by miRNAs of key molecular players involved in such pathways. Looking ahead, it is possible to foresee the need to better characterize the miRNA targets, lipid or non-lipid related, underlying mammalian hibernation. In addition, the identification and quantification of additional non-coding RNAs, such as lncRNAs, with potential implications in this process will be of uttermost importance. Ultimately, the far-reaching implications of non-coding RNAs in mammalian hibernation will be elucidated.

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