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COMMENTARY

Role of SIRT7 in hepatic lipid metabolism

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Sirtuins are evolutionarily conserved enzymes that regulate a wide variety of biological processes, such as aging, genomic stability, tumorigenesis, and metabolism [1]. To date, seven sirtuins have been identified in mammals (SIRT1–SIRT7), which share a highly conserved NAD^+-binding and catalytic core domain, but have distinct flanking N- and C-terminal domains. The divergent N- and C-termini of sirtuins are responsible for the different functions and subcellular localizations of these enzymes. Although sirtuins were originally described as NAD^+-dependent histone deacetylases, these enzymes are now known to act not only on histones, but also on numerous transcription factors and enzymes. SIRT1 controls the acetylation of proliferator-activated receptor-γ co-activator 1α (PGC1α), p53, and forkhead box O, among other targets, whereas SIRT3 is a major deacetylase in mitochondria [2, 3]. In addition, a few sirtuins have either weak or undetectable deacetylase activity. For example, SIRT4 is reported to act as an ADP-ribosyltransferase [4], and SIRT5 has both demalonylase and desuccinylase activities [5]. SIRT6 has been shown to deacetylate acetylated lysine 9 of histone H3 (H3K9Ac) and was also recently reported to preferentially hydrolyze long-chain fatty acyl groups on acylated protein targets [6].

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SIRT7 mRNA is ubiquitously expressed in all tissues examined to date, with the exception of skeletal muscle [7]. Human (NP_057622.1), mouse (NP_694696.2), and rat (NP_001100543.1) SIRT7 proteins consist of 400, 402, and 402 amino acids, respectively. Human SIRT7 contains a conserved NAD^+-binding and catalytic core domain (amino acids 90–331) as well as flanking N-terminal (amino acids 1–89) and C-terminal (332–400) regions (Fig. 1a). The histidine residue at position 187 (H187) (corresponding to mouse H188) is highly conserved among sirtuins and is reported to be important for binding with NAD^+ [8]. The N-terminal region of SIRT7 contains a nuclear localization signal (NLS) (LQGRSRRREGLKRRQE, amino acids 61–76), and the C-terminal region contains a nucleolar localization signal (NoLS) (KRTKRKKVT, amino acids 392–400) [9]. SIRT7 is enriched in the nucleolus, but is also present in the nucleoplasm (Fig. 1b).

In contrast to SIRT1 to SIRT6, the enzymatic activity and physiological functions of SIRT7 were poorly defined until recently. SIRT7 was first reported to promote ribosomal RNA transcription by interacting with RNA polymerase I (Pol I) and the transcription factor UBF [7, 10]. PAF53, a subunit of Pol I that is required for rDNA transcription, was recently identified as a target of SIRT7 [11]. SIRT7 was also shown to function as NAD^+-dependent deacetylase with high selectivity for acetylated lysine 18 of histone H3 (H3K18Ac) [12]. This deacetylase activity plays a role in the gene-specific transcriptional repression of a select subset of H3K18Ac-containing promoters, such as *RPS20* and *NME1* [12]. H3K18Ac-specific deacetylation by SIRT7 is important for maintaining the phenotype and stabilizing the tumorigenicity of human cancer cells [12]. Our group also demonstrated that Myb-binding protein 1a (Mybbp1a) binds to SIRT7, thereby inhibiting the deacetylation of H3K18 [13].

a

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          10         20         30         40         50
MAAGGLSRSE RKAAERVRRL REEQQRERLR QVSRILRKAA AERSAEEGRL
          60         70         80         90        100
LAESADLVTE LQGRSRRREG LKRRQEEVCD DPEELRGKVR ELASAVRNAK
         110        120        130        140        150
YLVVYTGAGI STAASIPDYR GPNGVWTLLQ KGRSVSAADL SEAEPTLTHM
         160        170        180        190        200
SITRLHEQKL VQHVVSQNCD GLHLRSGLPR TAISELHGNM YIEVCTSCVP
         210        220        230        240        250
NREYVRVFDV TERTALHRHQ TGRTCHKCGT QLRDTIVHFG ERGTLGQPLN
         260        270        280        290        300
WEAATEAASR ADTILCLGSS LKVLKKYPRL WCMTKPPSRR PKLYIVNLQW
         310        320        330        340        350
TPKDDWAALK LHGKCDDVMR LLMAELGLEI PAYSRWQDPI FSLATPLRAG
         360        370        380        390        400
EEGSHSRKSL CRSREEAPPG DRGAPLSSAP ILGGWFGRGC TKRTKRKKVT
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b

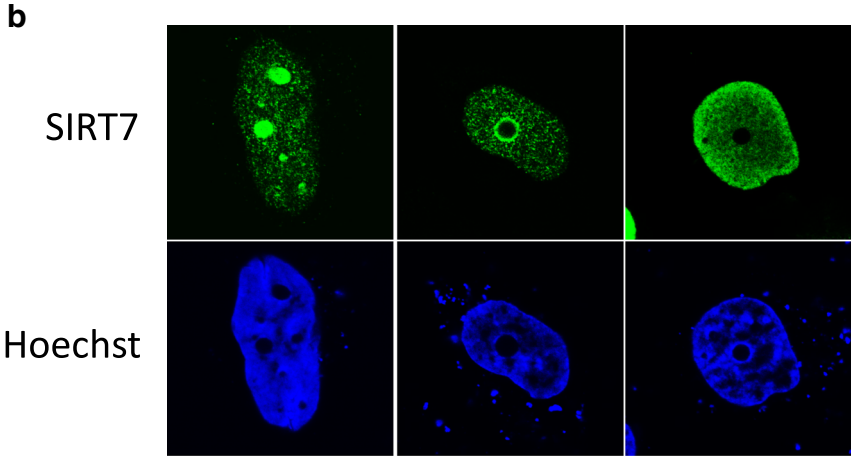

Fig. 1 **a** Amino acid sequence of human SIRT7 (UniProtKB/Swiss-Prot: Q9NRC8). The catalytic domain of SIRT7 is shown in *red*. The highly conserved histidine residue among sirtuins is highlighted in *yellow*. The N-terminal nuclear localization signal (LQGRSRRREGLKRRQE, amino acids 61–76) and C-terminal nucleolar localization signal (KRTKRKKVT, amino acids 392–400) are indicated by *broken boxes*. **b** Intracellular localization of FLAG-tagged SIRT7 in HeLa cells. SIRT7 signals (FLAG staining, *green*) were detected in the nucleoplasm and nucleoli

Despite the recent characterization of the binding properties of SIRT7, the metabolic function of SIRT7 has remained largely unknown. As SIRT1, SIRT3, and SIRT6 play critical roles in metabolism, and because the loss of these sirtuins in mice results in the hepatic accumulation of lipids [14–16], we examined whether the loss of SIRT7 affected lipid metabolism in mice. In striking contrast to *Sirt1*, *Sirt3*, and *Sirt6* knockout (KO) mice, *Sirt7* KO mice fed a high-fat diet (HFD) showed less accumulation of hepatic lipid than wild-type (WT) controls [17]. Hepatic triglyceride accumulation was also attenuated in liver-specific *Sirt7* KO mice fed an HFD.

The nuclear receptor TR4 regulates the expression of *Cd36*, cell death-inducing DFFA-like effector a (*Cidea*), cell death-inducing DFFA-like effector c (*Cidec*), monoacylglycerol *O*-acyltransferase 1 (*Mogat1*), and peroxisome proliferator activated receptor gamma (*Pparg*), and it is a key factor in the regulation of lipid homeostasis [18]. Among these proteins, CD36 plays a crucial role in fatty acid uptake [19], and CIDE-A and CIDE-C are involved in lipid storage, lipid droplet formation, and lipolysis [20]. In addition, MOGAT1 catalyzes the synthesis of diacylglycerol, the precursor of triglyceride (TG). Thus, the activation of hepatic TR4 increases fatty acid uptake and TG synthesis/storage in the liver. Notably, the hepatic level of TR4 protein is decreased in *Sirt7* KO mice as well as in several types of hepatic cells with *Sirt7* knockdown (KD) using siRNA [17]. In addition, the overexpression of WT-SIRT7, but not inactive SIRT7-H188Y mutant protein, restores TR4 expression in *Sirt7* KD AML-12 mouse hepatocyte cells, suggesting that the NAD^+-dependent enzymatic activity of SIRT7 is required for the regulation of TR4 expression [17]. Furthermore, the observed decrease of hepatic lipid accumulation and *Cd36* expression in *Sirt7*

KO mice is restored to control levels by infection with TR4-expressing adenovirus. Taken together, these results suggest that hepatic SIRT7 controls hepatic lipid accumulation and functions, at least partly, in a TR4-dependent manner.

Our group has also demonstrated that *TR4* mRNA levels are unchanged in the livers of *Sirt7* KO mice and in *Sirt7* KD AML-12 cells. Mechanistically, we found that SIRT7 binds to and prevents the DCAF1/DDB1/CUL4B E3 ubiquitin ligase complex from degrading TR4 [17]. Therefore, the decreased accumulation of hepatic lipids in *Sirt7* KO mice may be attributable to the decreased levels of TR4 due to the increased activity of the E3 ubiquitin ligase complex (Fig. 2). To our knowledge, this is the first example of the functional regulation of a ubiquitin ligase complex by the direct binding of a sirtuin. However, the exact molecular mechanism of how SIRT7 inhibits the function of the DCAF1/DDB1/CUL4B complex remains unclear.

Two other research groups have also independently generated and characterized the hepatic phenotypes of *Sirt7* KO mice. Shin et al. reported that SIRT7 is induced by endoplasmic reticulum (ER) stress and is stabilized in the promoter regions of genes encoding ribosomal proteins through interaction with Myc, resulting in the silencing of ribosomal protein gene expression [21]. In their study, *Sirt7* KO mice fed a chow diet develop fatty liver because of reduced suppression of ER stress [21]. Notably, however, the expression of ER stress-related genes was not increased in livers of our *Sirt7* KO mice (unpublished data) or another line of *Sirt7*-deficient mice [22]. GA-binding protein (GABP) is a nuclear transcription factor that is important for mitochondrial biogenesis and function. The GABP complex is composed of two subunit proteins, GABPα and GABPβ1, which function in DNA binding and transcriptional activation, respectively. Ryu et al. found that SIRT7 deacetylates GABPβ1, facilitating its transcriptional activation through complex formation with GABPα. They also reported that aged (42 weeks old) *Sirt7* KO mice exhibit hepatic microvesicular steatosis because of mitochondrial dysfunction [22]. As we mainly examined young (11–17 weeks of age) *Sirt7* KO mice fed an HFD, it

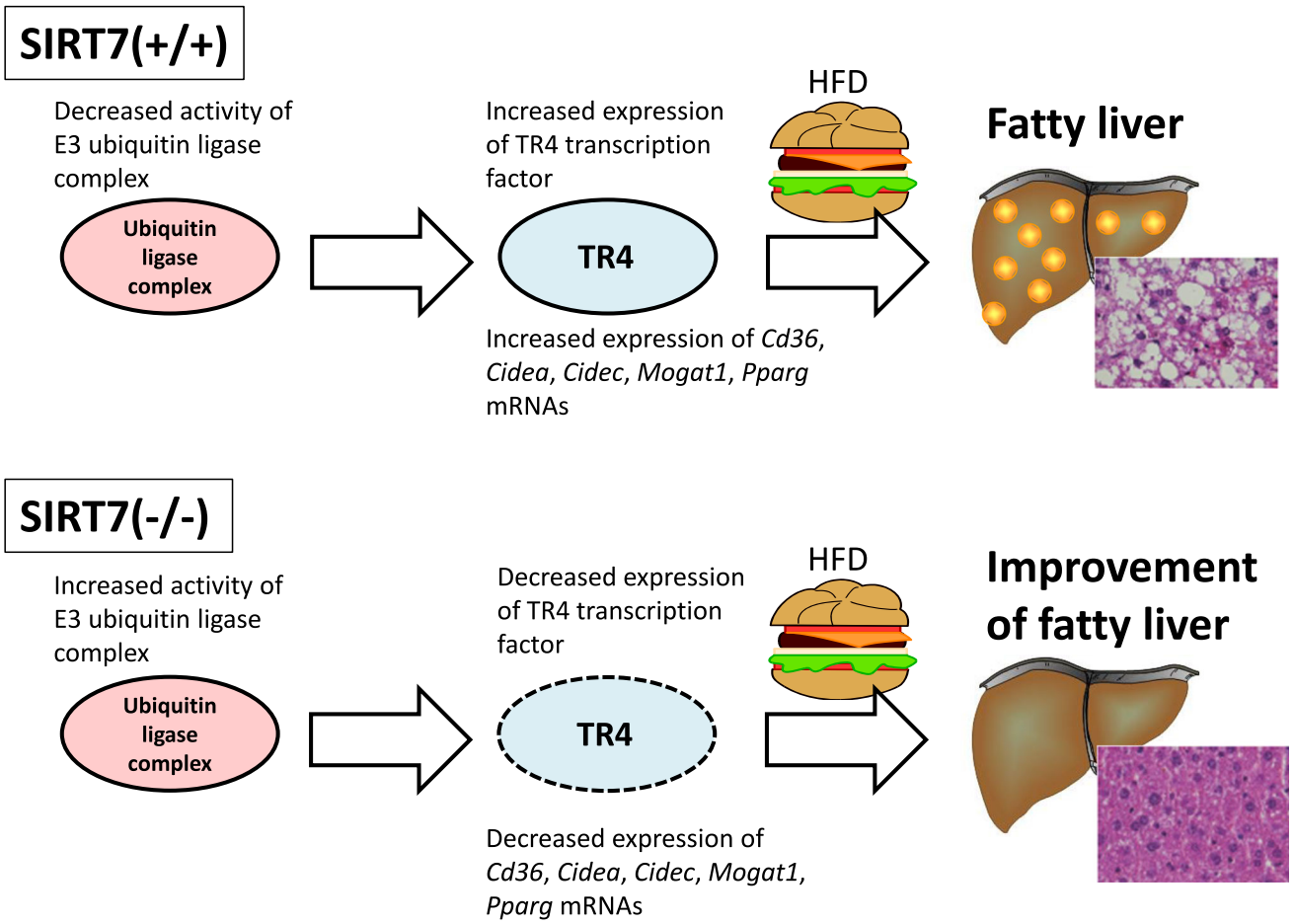

Fig. 2 Schematic representation of SIRT7-mediated regulation of TR4-dependent hepatic lipid metabolism

is necessary to investigate hepatic lipid accumulation in aged *Sirt7* KO mice. Although we have no adequate explanation (e.g., targeting construct, genetic background, or gut microbiota) for these different phenotypes at present, these studies demonstrate that SIRT7 has important roles in hepatic lipid metabolism. Further studies are necessary to improve our understanding of the function of SIRT7 in humans.

Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest.

Human rights statement and informed consent This article does not contain any studies with human or animal subjects performed by the any of the authors.

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