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Article

Hepatic rRNA Transcription Regulates High-Fat-Diet-Induced Obesity

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SUMMARY

Ribosome biosynthesis is a major intracellular energy-consuming process. We previously identified a nucleolar factor, nucleomethylin (NML), which regulates intracellular energy consumption by limiting rRNA transcription. Here, we show that, in livers of obese mice, the recruitment of NML to rRNA gene loci is increased to repress rRNA transcription. To clarify the relationship between obesity and rRNA transcription, we generated NML-null (NML-KO) mice. NML-KO mice show elevated rRNA level, reduced ATP concentration, and reduced lipid accumulation in the liver. Furthermore, in high-fat-diet (HFD)-fed NML-KO mice, hepatic rRNA levels are not decreased. Both weight gain and fat accumulation in HFD-fed NML-KO mice are significantly lower than those in HFD-fed wild-type mice. These findings indicate that rRNA transcriptional activation promotes hepatic energy consumption, which alters hepatic lipid metabolism. Namely, hepatic rRNA transcriptional repression by HFD feeding is essential for energy storage.

INTRODUCTION

Energy homeostasis requires the coordinated regulation of energy intake, storage, and expenditure. ATP, which is produced as an energy source, is consumed by most anabolic reactions (e.g., protein synthesis and fat synthesis), active transport of molecules and ions, nerve impulses, and muscle contraction. Ribosome biosynthesis in the nucleolus among them is the most energy-consuming process within proliferating eukaryotic cells, and it adapts to changes in the intracellular energy status (Grummt and Grummt, 1976; Moss et al., 2007). Mammalian cells quickly adjust the rate of ribosome synthesis on the basis of the availability of nutrients and growth-promoting mitogens. In addition, cells that exit the division cycle into a quiescent state greatly limit the ribosome production and overall protein synthesis. Ribosome biogenesis involves rRNA transcription, rRNA processing, and the assembly of maturated rRNA and ribosomal proteins. The rate-limiting step of ribosome biosynthesis is rRNA transcription in the nucleolus. Therefore, the control of rRNA transcription in the nucleolus is thought to regulate intracellular energy consumption.

rRNA genes are present in multiple copies (approximately 400 rRNA genes per mammalian cell). However, all of the rRNA genes in the human diploid genome are not transcriptionally active. rRNA synthesis is modulated by varying the transcription rate per gene or by varying the number of actively transcribed rRNA genes (Grummt, 2010; Grummt and Pikaard, 2003). The basal transcription factors, transcription initiation factor IA (TIF-IA), selectivity factor 1 (SL1), and upstream binding factor (UBF) are essential for transcription by RNA polymerase I (Pol I) and appear to be modulated by different signaling pathways in response to changes in environmental conditions. For example, the extracellular signal-regulated kinase, mammalian target of rapamycin, and c-Jun N-terminal kinase pathways regulate Pol I transcription via the activities of UBF, SL1, and TIF-IA (Grummt, 2010). In addition, recent findings point toward the existence of additional regulatory pathways such as epigenetic regulation of rRNA transcription. Santoro et al. (2002) revealed that the chromatin-remodeling complex nucleolar chromatin-remodeling complex (NoRC), which consists of the transcription-termination-factor-1-interacting protein 5 and the ATPase sucrose nonfermenting protein 2 homolog, recruits histone deacetylases, histone methyltransferases, and DNA methyltransferases to inactive rRNA gene repeats (Mayer et al., 2006; Santoro et al., 2002). Furthermore, lysine-specific demethylase 2A (KDM2A), KDM2B, KDM4C, and PHF8 are members of the JmjC family of demethylases that have been epigenetically implicated in rRNA transcription. KDM2A and KDM2B repress rRNA transcription (Frescas et al., 2007; Tanaka et al., 2010). In contrast, KDM4C and PHF8 activate rRNA transcription (Feng et al.,

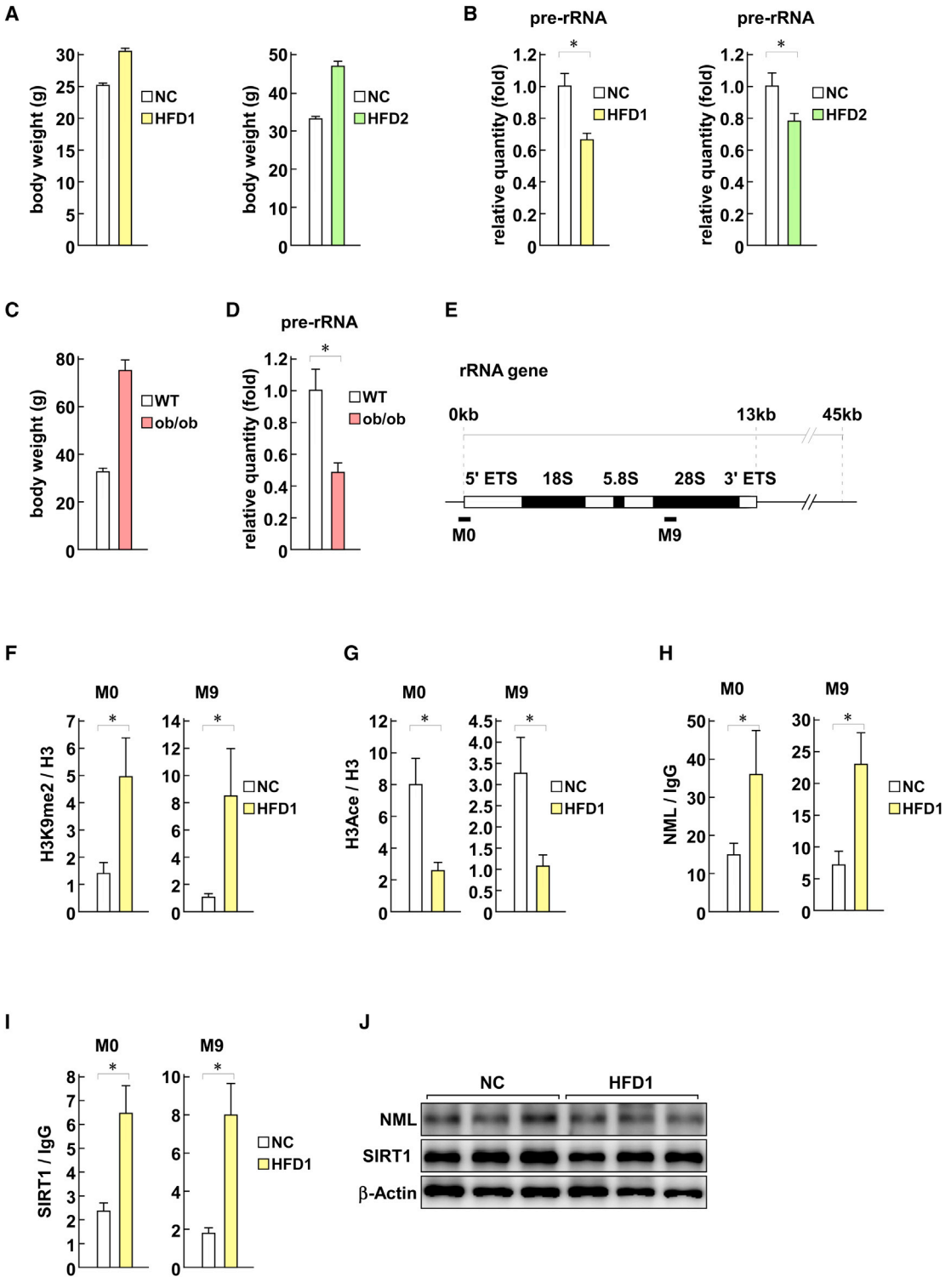

Figure 1. Hepatic Pre-rRNA Transcription Is Repressed in Obese Mice Fed on High-Fat Diet

(A) Body weight of WT (C57BL6) fed on normal chow diet (NC), high-fat diet 1 (HFD1) for 8 weeks, and HFD2 for 24 weeks.

(B) Pre-rRNA levels in livers of WT mice fed on NC, HFD1 for 8 weeks, and HFD2 for 24 weeks by quantitative RT-PCR (qRT-PCR). Pre-rRNA levels were normalized to cyclophilin.

(C) Body weight of WT and obesity model mice (ob/ob mice) fed on NC at the age of 24 weeks.

(D) Pre-rRNA levels in livers of WT and ob/ob mice fed on NC at the age of 24 weeks by qRT-PCR. Pre-rRNA levels were normalized to cyclophilin.

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