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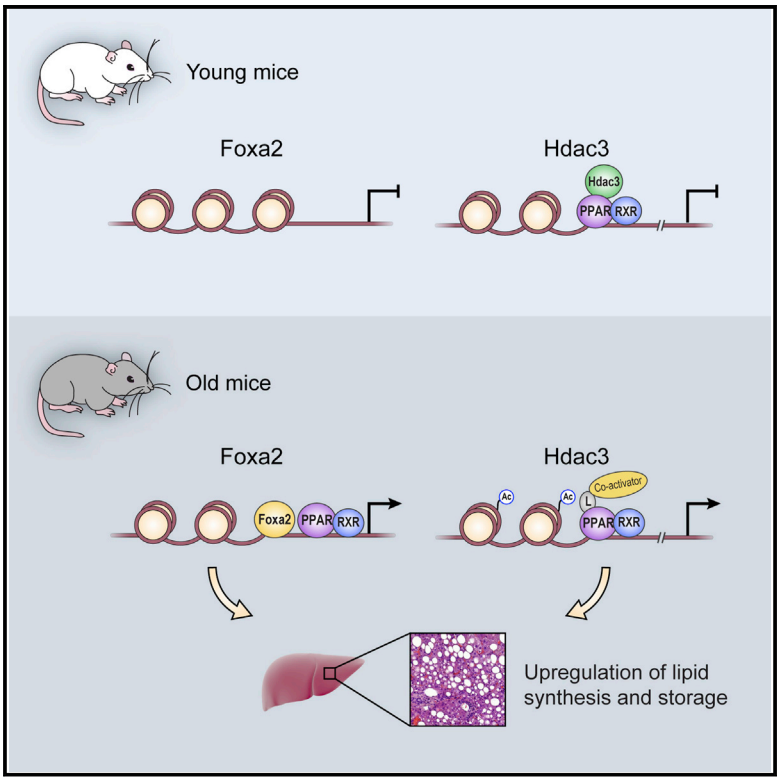
Changes in Nucleosome Occupancy Associated with Metabolic Alterations in Aged Mammalian Liver

Graphical Abstract



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In Brief

Bochkis et al. use genome-wide profiling in the livers of young and old mice to observe age-dependent changes in PPARα targets as well as nucleosome occupancy linked to Foxa2 and Hdac3 binding sites. A reciprocal binding pattern of Foxa2 and Hdac3 at PPARα targets contributes to gene-expression changes that lead to steatosis in the aging liver.

Highlights

An in vivo genome-wide nucleosome map in the aging liver is described

Foxa2 binds regions of decreased nucleosome occupancy at PPARα targets in old livers

Hdac3 and Srf are implicated in age-dependent metabolic dysfunction

Reciprocal binding of Foxa2 and Hdac3 at PPARα targets contributes to steatosis

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Changes in Nucleosome Occupancy Associated with Metabolic Alterations in Aged Mammalian Liver

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SUMMARY

Aging is accompanied by physiological impairments, which, in insulin-responsive tissues, including the liver, predispose individuals to metabolic disease. However, the molecular mechanisms underlying these changes remain largely unknown. Here, we analyze genome-wide profiles of RNA and chromatin organization in the liver of young (3 months) and old (21 months) mice. Transcriptional changes suggest that derepression of the nuclear receptors PPARα, PPARγ, and LXRα in aged mouse liver leads to activation of targets regulating lipid synthesis and storage, whereas age-dependent changes in nucleosome occupancy are associated with binding sites for both known regulators (forkhead factors and nuclear receptors) and candidates associated with nuclear lamina (Hdac3 and Srf) implicated to govern metabolic function of aging liver. Winged-helix transcription factor Foxa2 and nuclear receptor corepressor Hdac3 exhibit a reciprocal binding pattern at PPARα targets contributing to gene expression changes that lead to steatosis in aged liver.

INTRODUCTION

Aging is associated with increased prevalence of metabolic disease and cancer, reduced capacity for tissue regeneration, and physical decline (Rodriguez et al., 2007; Willis-Martinez et al., 2010). In particular, triglyceride accumulation is the common metabolic phenotype of aging liver and of metabolic syndrome, an age-related disorder that increases the risk of developing diabetes and cardiovascular disease. While mechanisms of age-dependent defects in tissue regeneration have been studied extensively (Jin et al., 2010; Jin et al., 2009), causes of age-onset metabolic impairments remain largely unknown.

Previous studies suggest a role for chromatin and nuclear organization in aging-associated lipid dystrophies. First, changes in chromatin organization mediate age-dependent impairments in several tissues (Chambers et al., 2007; Jin et al., 2010). Furthermore, mutations in lamin A/C (*LMNA*), a nuclear envelope protein, cause progeria, a premature aging syndrome, and lamin-dependent defects have been connected to physiological human aging (Scaffidi and Misteli, 2006). *LMNA* is also mutated in partial lipodystrophy (Shackleton et al., 2000), a condition associated with insulin-resistant diabetes and hepatic steatosis. Clinical features of lipodystrophy due to mutations in *LMNA* closely resemble those in individuals with mutations in *PPARG*, a nuclear receptor involved in pathogenesis of fatty liver (Gavrilova et al., 2003). Progeria attributed to defects in DNA repair (Schumacher et al., 2009) is modeled in mice by deletion of *Ercc1*, an enzyme crucial to nucleotide excision repair (Niedernhofer et al., 2006). *Ercc1* mutants exhibit upregulation of targets of the hepatic nuclear receptors (PPARα and PPARγ) and hepatic steatosis. Finally, liver-specific loss of *Foxa2*, a pioneer transcription factor regulating nucleosome dynamics, leads to premature aging, increased hepatic lipogenesis, and age-onset obesity (Bochkis et al., 2013). While the progeroid models described above propose a role for epigenetic conformation in modulating age-dependent metabolic impairments, this hypothesis has not yet been tested in a model of physiological aging.

To study the relation between chromatin organization and age-dependent metabolic impairments in the liver, we examined gene expression and genome-wide nucleosome occupancy in livers isolated from young (3 months) and old (21 months) mice (Figure 1A). Age-dependent induction of expression in lipid synthesis and storage genes, similar to metabolic changes seen in progeroid syndromes, is consistent with derepression of the nuclear receptors PPARα, PPARγ, and LXRα. Analysis of transcription factor binding sites that are overrepresented in regions where nucleosome occupancy changes with age identified established regulators of age-dependent metabolic dysfunction and lamina-associated candidates. Winged-helix transcription factor Foxa2 that regulates nucleosome dynamics binds regions of decreased nucleosome occupancy at PPARα targets in old livers. Conversely, binding of nuclear receptor corepressor Hdac3, detected from motifs found in regions of increased nucleosome occupancy, exhibits a reciprocal pattern. Together, altered Foxa2 and Hdac3 occupancy at PPARα targets contributes to gene expression changes that lead to steatosis in aged liver.