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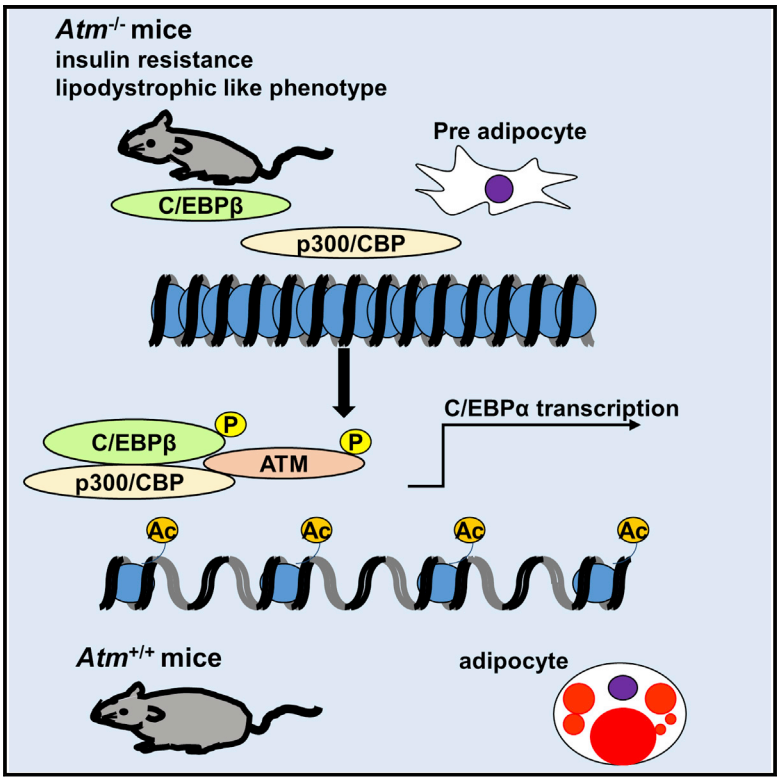
Cell Reports

ATM Regulates Adipocyte Differentiation and Contributes to Glucose Homeostasis

Graphical Abstract



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In Brief

Ataxia telangiectasia (A-T) patients develop diabetes mellitus. ATM, linked to A-T, is known to be involved in the DNA damage checkpoint. Takagi et al. reveal that ATM regulates adipocyte differentiation and attenuates differentiation of adipocytes in A-T patients, contributing to glucose metabolism in vivo.

Highlights

- ATM, linked to ataxia telangiectasia, regulates adipocyte differentiation
- The adipocyte differentiation defect in A-T contributes to type 2 diabetes
- Transcriptional activation of C/EBPα and PPARγ depends on ATM
- Binding of ATM to C/EBPβ and p300 induces transcriptional regulation of C/EBPα

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ATM Regulates Adipocyte Differentiation and Contributes to Glucose Homeostasis

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SUMMARY

Ataxia-telangiectasia (A-T) patients occasionally develop diabetes mellitus. However, only limited attempts have been made to gain insight into the molecular mechanism of diabetes mellitus development in A-T patients. We found that *Atm*$^{-/-}$ mice were insulin resistant and possessed less subcutaneous adipose tissue as well as a lower level of serum adiponectin than *Atm*$^{+/+}$ mice. Furthermore, in vitro studies revealed impaired adipocyte differentiation in *Atm*$^{-/-}$ cells caused by the lack of induction of C/EBPα and PPARγ, crucial transcription factors involved in adipocyte differentiation. Interestingly, ATM was activated by stimuli that induced differentiation, and the binding of ATM to C/EBPβ and p300 was involved in the transcriptional regulation of C/EBPα and adipocyte differentiation. Thus, our study sheds light on the poorly understood role of ATM in the pathogenesis of glucose intolerance in A-T patients and provides insight into the role of ATM in glucose metabolism.

INTRODUCTION

Ataxia-telangiectasia (A-T) is often accompanied by glucose intolerance and insulin resistance (Bar et al., 1978; Blevins and Gebhart, 1996; McFarlin et al., 1972; Morio et al., 2009; Schalch et al., 1970), and our previous study revealed that 17% of A-T patients developed type 2 diabetes mellitus (Morio et al., 2009). A-T patients also exhibit poor weight gain, a progressive decrease in their BMI, and progressive dystrophy (Schubert et al., 2005). In addition to A-T patients, A-T carriers, who comprise an estimated 0.05%–0.1% of the normal population, suffer an increased risk of ischemic heart disease (Su and Swift, 2000) and diabetes (Morrell et al., 1986). As in A-T patients, glucose intolerance has been reported in *Atm*$^{-/-}$, *Atm*$^{+/-}$*ApoE*$^{-/-}$, and *Atm*$^{-/-}$*ApoE*$^{-/-}$ mice (Miles et al., 2007; Schneider et al., 2006); the *Atm*$^{+/-}$*ApoE*$^{-/-}$ mouse model generates a state of insulin resistance similar to that observed in type 2 diabetes. In addition, Miles et al. reported impaired insulin secretion in aged *Atm*$^{-/-}$ mice (Miles et al., 2007). However, the mechanism by which an ATM deficiency affects the development of type 2 diabetes remains unknown.

ATM, the gene responsible for A-T, plays a central role in the DNA damage response. Previous reports have suggested that ATM is activated in response to insulin stimulation and phosphorylates the Cap-dependent translation inhibitor 4E-BP1 (Yang and Kastan, 2000). A recent large-scale proteomic ATM substrate analysis identified several proteins involved in the insulin-signaling pathway, such as AKT and FOXO1 (Matsuoka et al., 2007). Together, these observations strongly support the hypothesis that ATM is involved in the insulin-signaling pathway and modulates glucose homeostasis.

Insulin resistance is a frequent complication of obesity; however, lipoatrophic diabetes is paradoxical because it is