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Integrative genomics approach for a systems level understanding of the regulatory networks underlying fat cell differentiation

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Abstract

Adipose tissue plays an important role in maintaining energy homeostasis while deregulation of adipocyte differentiation leads to metabolic syndromes like obesity and insulin resistant type-2 diabetes. This signifies the importance of understanding the transcriptional mechanisms / gene regulatory networks underlying fat cell differentiation (i.e. adipogenesis). The knowledge about the molecular involvement of TFs and their co- regulators especially co-repressors for generating adipogenic networks is far from being complete. We used integrative genomics approach to identify the novel TFs enhancing fat cell differentiation and the mechanism of co-repressor action, in terms of their genomic employment, their target gene specificity, impact on the local chromatin state, their protein interaction partners and how and to which extent they influence gene transcription during adipogenesis.

We first generated an ORF clone library for 750 TFs to perform high-throughput screening in white adipocytes using inducible lentiviral vectors. The candidate TFs showing significant increase in fat accumulation were further validated for their effects on adipogenic TFs (e.g., PPARγ and C/EBPα). In parallel, the genome-wide DNA-binding profiling of co- repressors SMRT and NCoR during adipogenesis revealed that they are predominantly located in active chromatin regions and recruitment is primarily mediated by KAISO and C/EBPβ. After SMRT clearance, the C/EBPβ overlapping sites are occupied by pro- adipogenic TFs, revealing its enhancer masking role in pre-adipocytes. Using a microfluidics approach, we found that KAISO binds only to the methylated TCTCGCGAGA motif and as similar to SMRT, accelerates cell cycle and fat accumulation upon knockdown, identifying KAISO as a novel repressor of adipogenesis. Finally, we identified SMRT as an adipogenic gatekeeper as it directly fine-tunes transcription of pro- and anti-adipogenic genes. This ultimately led to a mechanistic model of SMRT's involvement in terminal adipogenesis.