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Autoregulation of the Rsc4 Tandem Bromodomain by Gcn5 Acetylation

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SUMMARY

An important issue for chromatin remodeling complexes is how their bromodomains recognize particular acetylated lysine residues in histones. The Rsc4 subunit of the yeast remodeler RSC contains an essential tandem bromodomain (TBD) that binds acetylated K14 of histone H3 (H3K14ac). We report a series of crystal structures that reveal a compact TBD that binds H3K14ac in the second bromodomain and, remarkably, binds acetylated K25 of Rsc4 itself in the first bromodomain. Endogenous Rsc4 is acetylated only at K25, and Gcn5 is identified as necessary and sufficient for Rsc4 K25 acetylation in vivo and in vitro. Rsc4 K25 acetylation inhibits binding to H3K14ac, and mutation of Rsc4 K25 results in altered growth rates. These data suggest an autoregulatory mechanism in which Gcn5 performs both the activating (H3K14ac) and inhibitory (Rsc4 K25ac) modifications, perhaps to provide temporal regulation. Additional regulatory mechanisms are indicated as H3S10 phosphorylation inhibits Rsc4 binding to H3K14ac peptides.

INTRODUCTION

Chromatin serves a central role in regulating the access of transcription factors to chromosomal loci. The primary repeating unit of chromatin, the nucleosome, helps organize DNA topology by wrapping DNA, a property that can occlude binding sites for regulatory factors and thereby contribute to transcriptional silencing (Kornberg and Lorch, 1999). However, the nucleosome is a dynamic participant in transcriptional activation, because nucleosome remodelers function to reposition nucleosomes to expose the underlying DNA. Furthermore, a large array of covalent modifications occur on the histone components and can serve as binding epitopes for protein domains specialized for their recognition. The principle of histone marking by covalent modification and recognition by specific domains has been termed "the histone code" (Fischle et al., 2003; Strahl and Allis, 2000). These binding domains reside on both chromatin regulators and transcriptional regulators. Thus, most factors are targeted to particular locations in the genome by one of two mechanisms: through interactions with site-specific DNA binding proteins or by using specialized domains to interact with modified histones. The most common posttranslational modification of histones is the acetylation of lysine residues by histone acetyltransferase (HAT) enzymes, which occurs primarily on the flexible N-terminal histone "tails" that emanate from the globular nucleosome core (Kouzarides, 2000). One of the best-studied HAT enzymes is yeast Gcn5, which acetylates lysine 14 of histone H3 (H3K14ac), a modification correlated with transcriptional activation (Brownell et al., 1996; Howe et al., 2001; Lo et al., 2000; Syntichaki et al., 2000; Trievel et al., 1999). Acetylated lysines are typically bound by ~110 amino acid residue structures called bromodomains that also recognize several of the residues flanking the acetyl-lysine, thereby providing acetyl-lysine recognition within a sequence context (Hudson et al., 2000; Mujtaba et al., 2002; Owen et al., 2000). There is considerable interest in determining which bromodomains bind particular histone acetyl-lysines and whether these interactions mediate targeting or some other aspect of regulation.

Complexes that rely on bromodomains for their full function include chromatin remodelers, which use the energy of ATP hydrolysis to move and/or eject nucleosomes to uncover the underlying DNA (Cairns, 2005). Indeed, how remodelers are targeted and regulated is a central question in chromatin biology. Important initial work demonstrated that bromodomains present on the yeast remodeler SWI/SNF are important for the retention of the remodeler on acetylated chromatin templates, consistent with a role for bromodomains in targeting (Hassan et al., 2002, 2006). The paralog of ySWI/SNF is the 15 subunit remodels