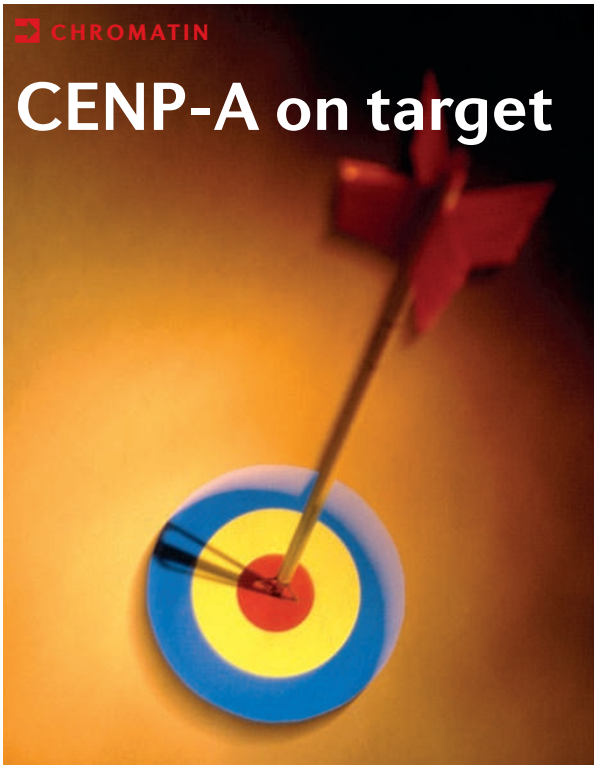
CHROMATIN

CENP-A on target



> “...HJURP is proposed to be an essential centromere-specific chromatin assembly factor...”

Centromeric chromatin is specified by the histone H3 variant CENP-A (centromere protein A). But how CENP-A is specifically targeted to and assembled at centromeres — and how centromeres are epigenetically inherited — is poorly understood. Three studies now provide insight into two factors, a CENP-A-specific histone chaperone and an ATP-dependent remodelling factor, that function in centromeric chromatin assembly and maintenance.

Foltz *et al.* and Dunleavy *et al.* purified prenucleosomal, soluble CENP-A fractions using independent approaches and identified HJURP (Holliday junction recognition protein) as a uniquely associated binding partner that is absent from other H3 variant fractions. Foltz *et al.* further showed that recognition of HJURP by CENP-A is mediated by the centromere-targeting domain of CENP-A, which is known to be required for its assembly at centromeres.

It had previously been shown that CENP-A incorporation into centromeric chromatin occurs from late telophase until early G1 phase. Both groups showed that HJURP localization to centromeres coincides with this short time window, which would make it an excellent candidate for mediating the deposition of CENP-A at centromeres.

To test whether this is the case, both teams transfected cells with HJURP small interfering RNAs (siRNAs). This resulted in reduced levels of endogenous CENP-A at centromeres. Indeed, cells that exhibited defects in chromosome segregation had reduced CENP-A levels. Overexpression of CENP-A in siRNA-treated cells did not increase the levels of centromeric CENP-A, which suggests that although the presence of HJURP might affect the stability of CENP-A, as would be expected from a histone chaperone, it also has a direct role in the loading of CENP-A at centromeric chromatin.

Next, both teams investigated whether HJURP also functions in the targeting and deposition of newly synthesized CENP-A at centromeres. Indeed it does, as loading of new CENP-A into centromeric chromatin was severely diminished in HJURP siRNA-treated cells and CENP-A was instead incorporated all over chromatin when overexpressed. So, HJURP is proposed to be an essential centromere-specific chromatin assembly factor, although other factors are also likely to have roles.

One such factor, the ATP-dependent remodelling and spacing factor (RSF), was analysed by Perpelescu *et al.* The authors found that RSF, which comprises the RSF1 and SNF2H subunits, associates with CENP-A-containing mononucleosomes, and that RSF transiently binds centromeric chromatin in mid-G1 phase. siRNA-mediated depletion of RSF1 and/or SNF2H delays normal mitotic progression, which is thought to be caused by a decrease in the stability of centromeric CENP-A. The authors envisage a two-step model for CENP-A assembly and maintenance with a role for RSF in the second step: CENP-A is initially recruited to centromeric chromatin in early G1 phase and is subsequently assembled through an RSF-mediated mechanism into stable centromeric chromatin in mid G1 phase. HJURP is presumably involved in the recruitment step.

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ORIGINAL RESEARCH PAPERS Foltz, D. R. *et al.* Centromere-specific assembly of CENP-A nucleosomes is mediated by HJURP. *Cell* **137**, 472–484 (2009) | Dunleavy, E. M. *et al.* HJURP is a cell-cycle-dependent maintenance and deposition factor of CENP-A at centromeres. *Cell* **137**, 485–497 (2009) | Perpelescu, M. *et al.* Active establishment of centromeric CENP-A chromatin by RSF complex. *J. Cell Biol.* **185**, 397–407 (2009)