

1                    **The expanding territories of condensin II**

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9    **Key words**

10   Condensin / senescence / chromosome condensation

1 The 3D structure of the eukaryotic genome and its spatial regulation within nuclei are  
2 governed by a range of architectural proteins. One class of such factors is the  
3 condensins, highly conserved multi-subunit protein complexes. Most eukaryotic  
4 species have two condensins, condensin I and II, and both condensins are essential  
5 for mitotic chromosome assembly and segregation, yet with distinct functions.  
6 However, increasing evidence indicates that condensins play diverse biological roles  
7 beyond mitosis and meiosis.<sup>1</sup> Condensin II in particular has been implicated in the  
8 spatial organization of chromosomes during interphase, where condensin II  
9 facilitates chromosome territory formation.<sup>2</sup> Yokoyama et al. now provide evidence  
10 for a new function of condensin II in the modulation of senescence and its associated  
11 alterations in chromatin structure (Figure 1).<sup>3</sup>

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13 Yokoyama et al. showed first that hCAP-H2, the regulatory subunit of condensin II,  
14 exists at least in two isoforms, a full-length (FL) and a shorter ( $\Delta$ N) isoform, the latter  
15 lacking the first 50 amino acids. Although the relative expression of these two  
16 isoforms at the basal level appears to be cell type dependent, their expression levels  
17 and localization are differentially regulated during the cell cycle: the FL isoform is  
18 both expressed and associated with chromosomes primarily at mitosis, while the  $\Delta$ N  
19 isoform, which is mostly localized at the nuclear matrix, accumulates in the  
20 quiescence and senescence states. Of note, some tumor cell lines only express  
21 hCAP-H2 FL, including HeLa cells, from which condensin II was originally identified.<sup>1</sup>

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23 It has been shown that the activities of condensin are dynamically and tightly  
24 regulated at both the post-transcriptional and post-translational levels.<sup>1</sup> For example,  
25 hCAP-H2 is a substrate of a number of mitotic kinases. Indeed, FL, but not  $\Delta$ N,

1 hCAP-H2 appears to be phosphorylated during mitosis.<sup>3</sup> However, it is not entirely  
2 clear how condensin II is regulated during interphase. In *Drosophila*, condensin II  
3 activity is controlled through SCF<sup>Slimb</sup> E3 ubiquitin ligase-mediated degradation of  
4 Cap-H2, although a similar mechanism has not been found in mammalian cells.<sup>1</sup>  
5 Yokoyama et al. provide additional mechanistic insight: they identified within the  
6 *NCAPH2* transcript, a small upstream open reading frame (uORF), which facilitates a  
7 re-initiation of translation from the second in-frame AUG to produce the  $\Delta$ N isoform,  
8 thus contributing to the reciprocal regulation of these isoforms at the post-  
9 transcriptional level. Perhaps these mechanisms collectively provide complexity in  
10 Cap-H2 regulation, allowing for the fine-tuned regulation of condensin II activities.

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12 Yokoyama et al. went on to show that overexpression of either isoform is sufficient to  
13 induce senescence-associated heterochromatic foci (SAHFs) in human diploid cells,  
14 and, conversely, that endogenous hCAP-H2 is required for SAHF formation during  
15 oncogene-induced senescence (OIS). Notably, individual SAHFs are composed of  
16 single chromosomes, thus SAHF formation could be viewed as a process of  
17 chromosome territory modulation.<sup>4</sup> This is consistent with the critical role for  
18 condensin II in organizing the genome into chromosome territories during interphase  
19 in part through its ability to induce the axial compaction of chromosomes and to  
20 suppress inter-chromosome interaction and the clusterization of peri-centric  
21 heterochromatin in *Drosophila* and mammalian cells.<sup>2,5</sup>

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23 Another striking chromatin structure alteration during senescence is senescence-  
24 associated distension of satellites (SADS).<sup>6</sup> Unlike SAHF, which has been best  
25 appreciated in OIS, SADS was suggested to occur more consistently in senescent

1 cells regardless of the type of cell or trigger.<sup>6</sup> Interestingly, ectopic expression of  
2 hCAP-H2 appears to induce senescence that exhibits SAHFs, but not SADS,  
3 highlighting the distinct nature of these two major senescence-associated chromatin  
4 alterations.

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6 Interestingly it was recently shown that condensin II, together with other architectural  
7 proteins, is enriched at the borders of topologically associating domains (TADs), a  
8 chromatin unit in which frequent chromatin local-interactions were detected through  
9 a genome-wide chromosome conformation analysis (Hi-C).<sup>1</sup> Another recent Hi-C  
10 study, using a SAHF-forming OIS model, revealed a global reduction in local  
11 chromatin interactions within TADs with increased longer interactions across TAD  
12 borders<sup>7</sup>, supporting a model whereby SAHFs are formed through the spatial  
13 repositioning of the genome.<sup>4</sup> Since TAD borders, where hCAP-H2 is enriched, are  
14 devoid of local chromatin interactions, it is tempting to speculate that the extra  
15 deposition of hCAP-H2 on chromatin facilitates SAHF formation through a global  
16 reorganization of local chromatin interactions. What remains to be elucidated  
17 includes: common and distinct functions between these isoforms at the endogenous  
18 level and how modulation of hCAP-H2 affects genomic structure and gene regulation  
19 as well as cell proliferation or tumorigenesis in the context of senescence. Although  
20 the  $\Delta N$  isoform appears to be able to associate with other subunits of condensin II,<sup>3</sup>  
21 it is unclear whether it functions in the condensin II complex and/or different forms of  
22 protein multimers. The link between condensin II and SAHF, a model for dynamic  
23 interphase chromatin re-organization, might provide an additional platform for  
24 condensin studies.

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1 **References**

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12 **Figure 1. Two isoforms of hCAP-H2, the regulatory subunit of condensin II.** The  
13 SMC2 and SMC4 subunits are members of the structural maintenance of  
14 chromosomes (SMC) family of chromosomal ATPases and are shared with  
15 condensin I. hCAP-D3 (D3) and hCAP-G2 (G2) are subunits unique to condensin II.  
16 uORF facilitates the re-initiation of translation from a downstream in-frame AUG  
17 ( $\Delta N$ ). The full-length (FL) isoform is mainly expressed at mitosis, whereas the  $\Delta N$   
18 appears to be expressed both in mitosis and interphase and is upregulated in both  
19 quiescence and senescence conditions. When overexpressed, both isoforms induce  
20 SAHF in IMR90 cells, where they are localized in the area surrounding SAHF. The  
21 mRNA diagram not to scale.

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