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Cohesin and chromatin organisation

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Cohesin defines the topology of chromosomes in mitosis and meiosis by holding sister chromatids together; more recently a role for cohesin in chromatin organisation and gene expression in interphase has emerged.

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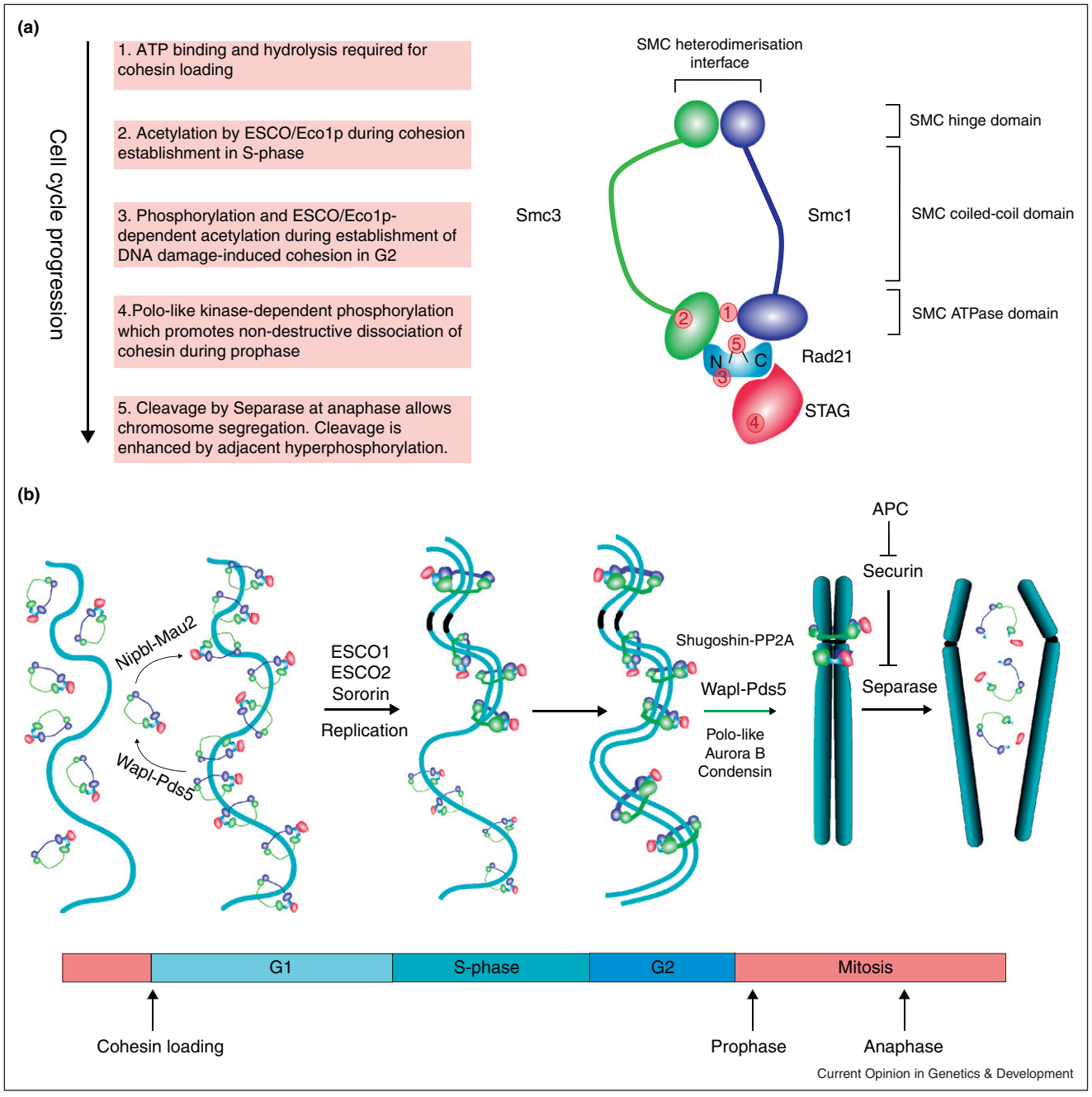
Overview

Cohesin belongs to an ancient family of protein complexes that are dedicated to chromosome biology. Aptly named 'SMC' proteins for 'structural maintenance of chromosomes' cohesin, condensin and Smc5/6 complexes maintain the integrity of genetic information by enabling post-replicative DNA repair, shaping chromosomes in preparation for cell division, and holding sister chromatids together to ensure that daughter cells receive a full complement of chromosomes. Cohesin is essential for DNA repair and chromosome segregation [1,2]. Heterozygous cohesin mutations are the cause of multi-systems developmental disorder such as Cornelia de Lange syndrome [3–5], and cohesin mutations have also been reported in cancer [6•,7••,8]. However, it has been difficult to disentangle cell cycle-related cohesin functions in DNA repair and chromosome segregation from a potential role in interphase. Here we discuss recent progress towards understanding the role of cohesin in chromatin organisation and gene regulation. In particular, cohesin is recruited to specific sites on mammalian chromosome arms by mechanisms that include binding to the insulator protein CTCF [9•,10•,11•], tissue-specific transcription factors [12•] or the mediator complex [13••], which bridges tissue-specific transcription factors with RNA polymerase. Once positioned, cohesin facilitates long-range chromosomal interactions between its binding sites [13••,14•,15•,16•,17,18]. Finally, cohesin is required for correct gene expression in non-dividing cells in *Drosophila* [19•,20,21•] and in mammalian cells, as illustrated by the impact of cohesin deletion on T lymphocyte differentiation [16•].

The cohesin complex

Cohesin is a multi-subunit complex formed of a heterodimer of SMC proteins, SMC1 and SMC3, and two non-SMC proteins Rad21 (also known as Scc1) and STAG (also known as Scc3). The SMC proteins each consist of a large coiled-coil domain flanked by a hinge domain that mediates SMC dimer formation and ATPase 'head' that contacts Rad21 to form a topologically closed tripartite structure — commonly referred to as the cohesin ring. STAG interacts with Rad21 and is essential for the functional integrity of the complex (Figure 1). In mammalian cells cohesin is loaded onto chromosomes at the end of mitosis by a separate complex consisting of Nipbl (also known as Nipped-B or Scc2) and Mau-2 (also known as Scc4) [22–26]. Although there are dissenting views, cohesin is thought to associate with chromosomes by 'topological embrace' [1] or, more prosaically, by trapping chromosomes inside its ring-like structure. The stability of cohesin binding is regulated by additional proteins in a cell cycle-dependent manner. In the G1 phase of the cell cycle, cohesin is in a dynamic equilibrium of association and dissociation with a half-life of approximately 25 minutes [27]. This turnover requires the cohesin-interacting proteins Wapl and Pds5, which unload cohesin from chromatin. During S-phase this equilibrium shifts towards chromatin-association, and the half-life of cohesin binding increases considerably [27]. Stable cohesin binding requires the acetylation of Smc3 by the acetyltransferases Esco1 and Esco2 (also known as Eco1 and Eco2) and helps to establish cohesion between sister chromatids as they are formed in S-phase [28–31]. Mechanistically, Smc3 acetylation allows the Sororin protein to counteract the chromatin-dissociation activity of Wapl and Pds5 throughout S-phase and G2 [32•]. Once established, sister chromatid cohesion assists the repair of any DNA double strand breaks that occur during DNA replication: additional cohesin is loaded to the break sites and genome-wide [33–35]. Just like the establishment of S-phase cohesion, cohesin association with DNA double strand breaks requires Esco, but current evidence suggests that distinct modifications mark cohesin complexes that mediate sister chromatid cohesion in S-phase and cohesin complexes that facilitate post-replicative DNA repair [36,37•]. At the beginning of mitosis, vertebrate Sororin is phosphorylated, which allows Wapl and Pds5 to evict the majority of cohesin from chromosome arms. This coincides with the increased binding of

Figure 1



Structure and regulation of the cohesin complex. **(a)** Cohesin structure and topology. Smc1 and Smc3 heterodimerise via their hinge domains and their ATPase heads associate with the kleisin subunit Rad21 to form a tripartite ring structure. The STAG subunit interacts with Rad21. Key sites in the complex are numbered (1–5), and their involvement in cohesin's functions during the cell cycle is summarised on the left. **(b)** The cohesin cycle: dynamics and regulatory factors. The association of cohesin with chromatin is closely linked to cell cycle progression (stages indicated at the bottom) and is regulated by multiple factors (listed above and below the transition arrows). In G1, cohesin binds to chromatin in a dynamic equilibrium of association and dissociation. During S-phase sister chromatid cohesion is established, and cohesive complexes (represented in bold) become more stably bound to chromosomes. Cohesion is maintained genome-wide throughout G2 when it assists DNA double-strand break repair. During prophase, cohesin is unloaded from chromosome arms, the chromosomes condense, and cohesion is only maintained at the cetromeres until it is cleaved at anaphase, which allows chromosome segregation to take place.