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Mini-review

The dark side of cohesin: The carcinogenic point of view

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ABSTRACT

Genome instability is a hallmark of cancer cells and how it arises is still not completely understood. Correct chromosome segregation is a pre-requisite for preserving genome integrity. Cohesin helps to ensure faithful chromosome segregation during cell cycle, however, much evidence regarding its functions have come to light over the last few years and suggests that cohesin plays multiple roles in the maintenance of genome stability. Here we review our rapidly increasing knowledge on the involvement of cohesin pathway in genome stability and cancer.

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1. Introduction

1.1. Cohesin and correct chromosome segregation

Accurate chromosome segregation is indispensable for genome stability maintenance. It requires that sister chromatids are tightly associated until metaphase/anaphase transition and then properly separated. Cohesin plays a pivotal role in this process by helping the establishment of sister chromatid cohesion. The cohesin complex, conserved from yeast to humans, is constituted by four proteins, namely SMC1A, SMC3, RAD21/SCC1 and STAG/SCC3/SA (Fig. 1). SMC proteins are composed of two coiled coil domains separated by a globular hinge domain. The hinge domains of SMC1A and SMC3 interact with each other to create a heterodimer, while their head domains interact with RAD21, creating a closed ring-like structure [1]. Finally, the RAD21 subunit associates with SA. In vertebrates there are two isoforms, SA1 and SA2, but their functional roles are still unclear [2,3]. The finding that cohesin forms a ring has led to the proposal that it associates with chromosomes by trapping DNA [4]. However, several alternative models have been proposed [5–8] but how cohesin mediates sister chromatids cohesion still remains poorly understood.

Cohesin is found in high densities at centromeric regions, while only with a frequency of 10 kbp in yeast and up to 100 kbp in the higher organisms along the chromosome arms [9,10]. The deposition of cohesin onto chromatin, which requires the activity of the auxiliary factor NIPBL, occurs in G1 in yeast or at the end of telophase of the previous cell cycle in mammalian cells. During the S-phase the interaction of cohesin with sister chromatids is stabilized by Eco1/Ctf7 activity that acetylates the SMC3 subunit [11–13]. Additional factors are necessary to establish cohesion, ensuring the proper sister chromatids pairing. PDS5 interacts with cohesin for its establishment and maintenance [14]. In vertebrates, two isoforms have been identified, PDS5A and PDS5B. Their function

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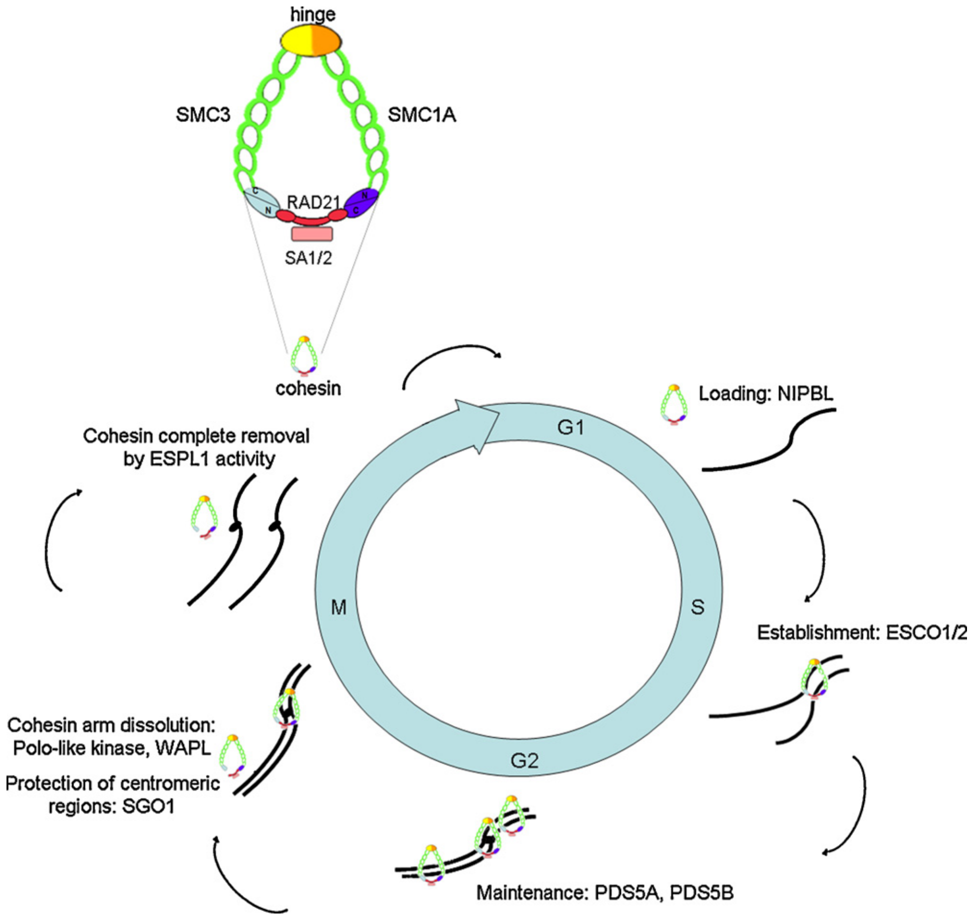

Fig. 1. Regulation of cohesin during cell cycle. Cohesin loading is mediated from NIPBL. It occurs in G1 in yeast or at the end of telophase of the previous cell cycle in mammalian cells. The presence of ESCO1 and ESCO2 factors permit cohesin establishment in the S phase, and PDS5A and PDS5B guarantee its maintenance. Cohesin dissolution begins at chromosome arms in prophase at first via phosphorylation by Polo-like kinase 1 and WAPL activity, whereas most pools of cohesin remain protected at centromeric regions by SGO1. Finally, cohesin is completely removed from chromatin by ESPL1-mediated proteolysis.

may be redundant, as reduction of one or the other does not cause defects in the cohesion [3,15].

The precise timing of sister chromatid separation is also determined by the coordinated activity of the spindle assembly checkpoint (also termed the mitotic or metaphase checkpoint) which involves many proteins including MAD2, BUB1B, BUB3 and Cdc20 (Fig. 2). A single lagging chromosome can activate the spindle checkpoint and inhibit the progression of cell cycle. Once chromosomes are correctly bi-oriented on the mitotic spindle, the Anaphase Promoting Complex/Cyclosome (APC/C, an E3 ubiquitin ligase) triggers the metaphase–anaphase transition. In vertebrates, cohesin dissolution occurs in two steps. First, cohesin is removed from chromosome arms following the phosphorylation of RAD21 and SA1/SA2 subunits by Polo-like kinase 1 (PLK1) [3], whereas cohesion is preserved around centromeres since it is protected by SGO1 [16]. Cohesin dissociation from chromatin also requires the regulation of the WAPL factor which interacts directly with RAD21 and SA1 and SA2 [17,18]. Second, the APC/C complex prompts the degradation of PTTG1 (Securin) during anaphase so that ESPL1 (Separase) can remove centromeric cohesin by cleaving RAD21 [19,20]. Nevertheless, the presence of cohesin has also been observed after mitosis, probably derived from pools remaining bound [21] or re-associated [22] to chromosomes, suggesting that it is necessary for additional biological roles. Beyond its known role, increasing experimental evidence suggests that cohesin plays a part also in the maintenance of genome stability. Here, we review recent findings on the non canonical role of cohesin with an emphasis on its involvement in genome integrity and tumorigenesis.

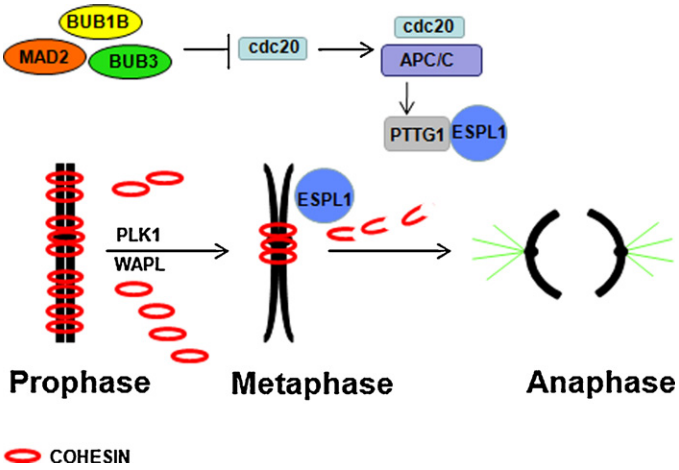

Fig. 2. Mitotic cohesin dissolution. During prophase, the combined action of PLK1 and WAPL cause the removal of cohesin from chromosome arms through the phosphorylation of cohesin. During the metaphase-to-anaphase transition when all chromosomes have bioriented, Cdc20, the activator of APC/C, is liberated from the mitotic checkpoint complex sequestration. The mitotic checkpoint complex is constituted from MAD2, BUB1B and BUB3. This allows APC/C-Cdc20 to recruit PTTG1 and to promote its proteolysis. Upon liberation from PTTG1, the activated ESPL1 cleaves RAD21, promoting sister chromatid separation.