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Cohesin: It's Functions and Relevance to Cancer

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Abstract

Oncogene mutations, inactivation of tumor suppressor genes and chromosome instability are classic features of cancer. The sister chromatid cohesion complex, known as cohesin, is conserved among eukaryotes and is essential for efficient chromosome segregation. In this review, we focus on the key findings about cohesin biology and how cohesin misregulation can be deleterious.

Keywords: Cancer genetics; Cohesin; Chromosome segregation

Introduction

With TCGA running in its seventh successive year, researchers across the globe have witnessed unprecedented success in expanding the knowledge of the cancer genome and the epigenome. Established as a large collaboration between the National Cancer Institute (NCI) and the National Human Genome Research Institute (NHGRI), The Cancer Genome Atlas, serves to help understand the molecular basis of cancer through the application of genome analysis technologies. Mutations have been identified in a diverse array of cellular processes such as cell signaling, DNA-methylation, chromatin modification, transcription factors, tumor-suppressors, splicing, apoptosis and cell cycle regulation. Discovered for its ability to hold newly replicated sister chromatids in physical proximity, a process known as sister chromatid cohesion (SCC), the cohesin complex plays a central role in the cell cycle. In the following sections, we discuss its role in chromosome segregation, organizing chromatin architecture, regulation of transcription and maintenance of genome stability; functions if misregulated, can promote tumorigenesis and cell death.

Cohesin: Cohesion and chromosome segregation

Faithful segregation of chromosomes during mitosis and meiosis is mediated by the dynamic association and dissociation of the cohesin complex to and from the sister chromatids. The core cohesin complex (Figure 1A), conserved from yeast to humans (Table 1), consists of structural maintenance of chromosomes (SMC) proteins SMC1A and SMC3, RAD21 and STAG [1]. SMC proteins are characterized by a globular hinge domain flanked by two alpha-helical domains, which fold back on themselves at the hinge, forming a long antiparallel alpha-helical coiled coil arm that brings the N- and C-termini together. SMC1A and SMC3 dimerize at the hinge domains, forming a V-shaped structure through hydrophobic interactions. The kleisin family protein RAD21 physically connects their ATPase heads, thus forming a tripartite ring-like structure (Figure 1A) with an outer diameter of ~40 nm. The SCC3 subunit interacts with RAD21 and further stabilizes the cohesin ring. It is believed that the cohesin ring entraps replicated DNA helices inside one ring until their segregation thus the "embrace model". Another model of cohesin topography has also been proposed, namely "handcuff" model. It is suggested that each of DNA helices is embraced with one cohesin ring and cohesion is mediated by an interaction between these two cohesin rings [1].

As shown in Figure 1B, cohesin is loaded in the G1/S phase in yeast and in telophase in mammals, by a complex consisting of NIPBL and MAU2 [2-6]. Refer to Table 2 for a list of homologs across species. In G1 phase of the cell cycle, antagonizing activities of WAPL and PDS5 maintain a dynamic state of cohesin association and dissociation on chromosomes, with a turnover of approximately 25 mins [7]. Acetylation of Smc3 by ESCO1 and ESCO2, establishes stable cohesion between the newly replicated sister chromatids in the S-phase, followed by cohesion maintenance throughout the G2 phase [8-15]. Cohesin on the arms is removed during the metaphase to anaphase transition by phosphorylation of RAD21 and SA1/SA2 by PLK1 (Polo-like kinase 1), while centromeric cohesion is protected by SGO1/PP2A (Shugosin1/Protein phosphatase 2A) [14,16-19]. Once chromosomes are bi-oriented on mitotic spindles, Anaphase promoting complex/Cyclosome (APC/C) is activated and leads to ubiquitin mediated degradation of PTTG1 (Securin), releasing ESPL1 (Separase), which then cleaves RAD21, dissolving centromeric cohesion and thus separating the sisters [20-22]. A similar biphasic removal of cohesin occurs in meiosis, where RAD21 is replaced by REC8 [23]. Phosphorylation of Histone 2A by Bub1 kinase and Aurora B kinase has also been implicated in the targeted recruitment of SGO1/PP2A, protecting centromeric and pericentromeric cohesion until meiosis II [24,25].

Cohesin and genome instability

Over a hundred years ago, while studying chromosome and cell behaviour in sea urchin, German biologist Theodore Boveri suggested that cancer might be a manifestation of an underlying abnormal chromosome constitution [26]. Today, in the 21st century, genome instability is widely accepted as a hallmark of cancer cells [27]. The DNA sequence is continuously confronted by a variety of exogenous and endogenous stimuli that introduce single and double strand breaks. *In vivo* double strand breaks (DSBs) are common during replication and V(D)J recombination in B-lymphocytes and the cell has precociously evolved mechanisms to repair such DNA damage [28,29]. DNA damage repair is mediated via homologous recombination (HR) between sister chromatids in the S and G2 phases. On the contrary, non-homologous end joining (NHEJ), involving re-ligation of broken DNA, occurs throughout the cell cycle.

The cohesin complex was identified to play a role in DNA damage

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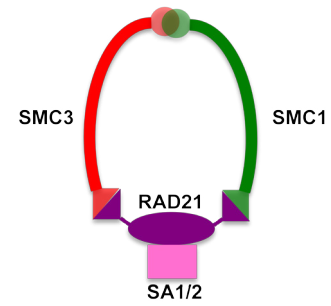

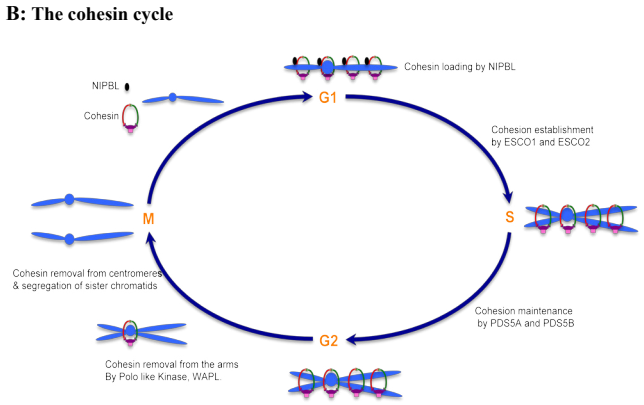

Figure 1: Cohesin and the cell cycle. (A). Cohesin is a ring-shaped complex. Cohesin is composed of four subunits. Smc1 and Smc3 fold back on themselves by anti-parallel coiled-coil interactions to yield molecules with a 'hinge' domain at one end and a globular ATPase 'head' at the other. Smc1 and Smc3 interact via the hinge domain, whereas the Smc heads are connected by the α-kleisin Scc1/Rad21. The fourth subunit is called Scc3/SA (either SA1 or SA2 in vertebrate somatic cells) and interacts with the central region of Scc1/Rad21. (B). Regulation of cohesin during cell cycle. Cohesin loading is mediated by NIPBL. It occurs in G1 in yeast or at the end of telophase of the previous cell cycle in mammalian cells. Cohesion is established by ESCO1 and ESCO2 mediated acetylation during S phase and is maintained in G2 by PDS5A and PDS5B. 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 Separase mediated proteolysis.

response when *Schizosaccharomyces pombe* mutants for Rad21 were found to be sensitive to γ-radiation and defective in DNA repair [30,31]. Studies in yeast and mammals have shown that sister chromatid cohesion (and not cohesin itself) is required for double stand break (DSB) repair [32]. Replication stress is followed an increase in SMC1A and SMC3 protein synthesis and *de novo* cohesion is established at the DSB site upon laser induced DNA damage in human cells, (Figure 2E), [33-35]. Moreover cohesin is required for intra-S and G2/M checkpoint activation in mammalian cells [36]. Additionally, cohesin subunit SMC1A is phosphorylated at Ser957 and Ser966 by the ATM/ATR kinases, in association with NBS1 and BRCA1 [37-39]. Interestingly, ionizing radiation (IR) also induces phosphorylation at Ser1083 and acetylation at Lys105 and Lys106 of SMC3, in an ATM/ATR and ESCO1 dependent manner [40,41], reinforcing cohesion at DSB sites in human cells. In contrast to mammals, in budding yeast, cohesion establishment at DSB involves Scc1 Ser83 phosphorylation by DNA damage response kinase Chk1, and Lys84 and Lys210 acetylation by Eco1 [42]. Also, SUMOlyation of Scc1 by SUMO E3 ligase Nse2, is essential for cohesion at DSBs and genome wide [43]. Moreover, DNA damage during G2/M stabilizes Eco1 by preventing its phosphorylation and subsequent proteasome-mediated degradation [44]. Albeit different mechanisms operate in yeast and mammals, the ultimate goal is to reinforce cohesion, prevent mis pairing and aid in homologous recombination repair at DNA lesion sites.

A genome wide study of single nucleotide variants (SNVs) in leukemia, melanomas, small cell lung cancer and prostate cancer has identified positive correlation between SNV density and heterochromatin marks, suggesting a higher rate of mutation accumulation in repressive heterochromatin regions [45]. Cohesin modifications could possibly assist in recruitment of chromatin modifiers and nucleosome remodelers at DSB sites, thereby facilitating localized chromatin reorganization and increased accessibility for repair proteins.

Cohesin and gene expression

The first evidence that cohesion factors regulate gene expression and development came from studies on the *Drosophila cut* and *Ultrabithorax* homeobox genes [3,46,47]. Heterozygous *Nipped-B* mutants showed reduced *cut* expression, while loss of Rad21, Smc1 or SA resulted in increased *cut* expression. Mutations in *NIPBL* are the leading cause of Cornelia de Lange syndrome (CdLS), a neuro-developmental disorder with upper extremity malformations, hirsutism and other dysfunctions affecting cardiac, renal and gastroesophageal systems [48,49]. Hundreds of genes are indeed dysregulated in cell lines derived from CdLS patients, without any significant cohesion defects [50]. Cohesin also binds and facilitates expression of the *c-myc* gene, a function conserved across *Drosophila*, zebrafish, mouse and humans [51]. An obvious explanation for gene expression changes upon cohesin mutations is impaired cohesion and chromosome segregation. However, homozygous mutations in the *Smc1* and *SA* genes block ecdysone steroid hormone signaling, axon pruning and dendrite formation in γ neuron of the mushroom body in *Drosophila* [52,53]. Furthermore, genetic deletion of cohesin in non-dividing mouse thymocytes, resulted in reduced transcription and rearrangements at the T cell receptor α locus *(Tcra)*, thereby affecting thymocyte differentiation [54]. Clearly, the phenotype in non-dividing cells is independent of cohesin's role in cell division.

Using genome wide techniques, cohesin binding sites have been identified in *Drosophila* cell lines [55], *Drosophila* salivary glands [52], human lymphocytes [50], Hela cells [56], MCF-7 and HepG2 tumor cell lines [57], mouse pre-B cells, mouse embryonic stem cells (ESCs) [58],

Mammals	*D. melanogaster*	*S. cerevisiae*	*S. pombe*	Function
SMC1A	Smc1	Smc1	Psm1	core cohesin (mitosis)
SMC1B				core cohesin (meiosis)
SMC3	Smc3	Smc3	Psm3	core cohesin
RAD21	Rad21/Vtd	Mcd1/Scc1	Rad21	core cohesin (mitosis)
REC8	C(2)M	Rec8	Rec8	core cohesin (meiosis)
SA1/STAG1	SA (Stromalin)	Scc3	Psc3	core cohesin (mitosis)
SA2/STAG2	SA2 (Stromalin-2)			core cohesin (meiosis)
SA3/STAG3				

Table 1: Subunits of the core cohesin complex.

Mammals	*D. melanogaster*	*S. cerevisiae*	*S. pombe*	Function
NIPBL/SCC2	Nipped-B	Scc2	Mis4	Cohesin loading
MAU2/SCC4	Mau2	Scc4	Ssl3	Cohesin loading
ESCO1	Eco/Deco	Eco1/Ctf7	Eso1	Cohesion establishment
ESCO2	San			
PDS5A	Pds5	Pds5	Pds5	Cohesion maintenance
PDS5B/APRIN				
WAPL/WAPAL	Wapl	Rad61/Wpl1	Wpl1	Cohesion maintenance
SORONIN/CDCA5	Dmt (Dalmatian)	-	-	Cohesion maintenance
HDAC8	-	Hos1	-	Cohesindacetylase
Shugosin1	Sse1	Esp1		Protection of centromeric cohesion
Separase	Sse1	Esp1	Separase	Cohesin removal
Polo like Kinase 1 (PLK1)	Polo	Cdc5	Plk1	Cohesin removal

Table 2: Regulatory proteins involved in the cohesion cycle.

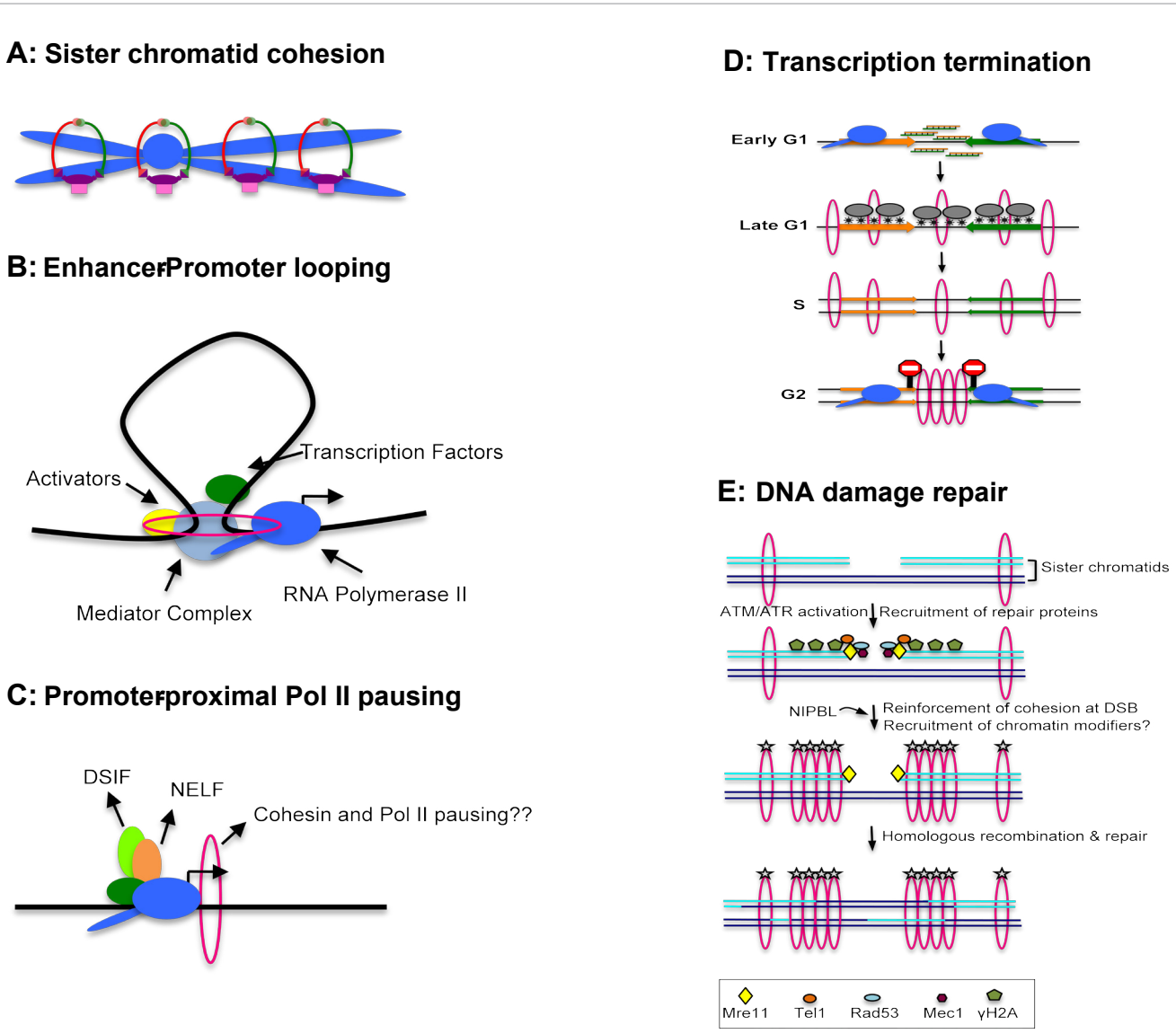

Figure 2: Interphase functions of cohesin. In addition to maintaining sister chromatid cohesion in *trans* (A) cohesin also mediates *cis* interactions between distal enhancers and promoter regions in association with activators and transcription factors (B). Additionally, cohesin is enriched at genes with high promoter-proximal Pol II pausing (C) and is likely to regulate the transition from initiation to productive elongation, in a DSIF and NELF independent manner. Apart from regulating initiation, cohesin is also responsible for efficient transcription termination between convergent genes throughout the cell cycle (D). Furthermore, cohesin maintains genome integrity via facilitating homologous recombination repair between sister chromatids (E), upon any DNA damage.

and mouse thymocytes [59]. In *Drosophila* and mammals, Nipped-B/NIPBL and cohesin colocalize to actively transcribed genes, with peaks near the transcription start site [55]. Additionally, in mammals there is an 89% overlap between cohesin and CTCF (CCCTC-binding factor) binding sites but no overlap between CTCF and NIPBL occupancy [56]. In a CTCF independent manner, RAD21 also colocalizes with tissue specific transcription factors (TFs) such as estrogen receptor α in breast cancer cell lines, hepatic nuclear factors in liver cells, and pluripotency factors in stem cells [57,60]. In addition to TFs, cohesin co-purifies with the mediator complex, which itself is important for transcription [58]. It is plausible that cohesin is loaded at NIPBL sites and slides away (as observed in yeast [61,62]), accumulating at CTCF or transcription factor sites. Or cohesin might recruit TFs to gene promoters or the TFs recruit NIPBL, which subsequently loads cohesin.

Cohesin and CTCF play a pivotal role in the structural and functional organization of the nucleus. Direct evidence from knockdown experiments implicates CTCF and cohesin in maintaining long-range interactions at the imprinted *Igf2/H19* locus [63], Interferon gamma locus *IFNG* [64], *β-globin* locus [65], *APO* gene cluster [66], and *MHC* class II cluster [67]. In mouse embryonic stem cells, loss of cohesin and mediator subunits resulted in a decrease in enhancer-promoter contacts (Figure 2B), of key pluripotency genes and changes in gene expression [58]. However, ES cells are actively dividing and therefore the effects might be due to cohesin's role in the cell cycle. A subset of CTCF/cohesin sites are also bound by transcription factor TAF3, where long range looping is imperative for endoderm lineage differentiation and prevention of premature differentiation of neuroectoderm and mesoderm in mouse ESCs [68]. Upon induction of differentiation, cohesin and NIPBL bind to the β-*globin* locus control region (LCR) and regulatory sites, facilitating long-range interactions, which are lost upon partial reduction of NIPBL [65]. How cohesin mechanistically mediates such long-range interactions remains unknown. However, the simplest explanation is that cohesin entraps regulatory elements in *cis* (Figure 2B), similarly as it holds sister chromatids together in *trans* (Figure 2A).

Indisputably, cohesin exerts a direct influence on transcription. A recent PRO-Seq and ChIP-chip analysis in *Drosophila* shows a positive correlation between Rpb3 (Pol II subunit) and cohesin binding at actively transcribing genes [69]. Cohesin preferentially binds to genes with high promoter-proximal paused RNA Polymerase II (Pol II) and cohesin depletion results in increased pausing at cohesin binding genes, suggesting that cohesin might influence the transition from paused polymerase to elongation (Figure 2C). However, cohesin bound genes lack H3K36me3 modification (a mark of elongation) and pause release is independent of pausing factors DSIF and NELF [70]. Upon cohesin depletion, many of genes with paused polymerase decrease in expression and many increase in expression, indicating that the effect is context dependent.

Cohesin depletion reduces *myc* transcription and *MYC* has emerged as the universal regulator of transcriptional programs in mammalian cells [51,71]. Interestingly, genes with the highest cohesin levels produce nearly 2-fold more steady-state RNA than genes lacking cohesin [69]. Yeast two-hybrid and mass spectrometry experiments in *Caenorhabditis elegans* identified novel interactions between RAD21 and RNA processing factors but their functional implication and species conservation has not been explored [72]. In fission yeast, cohesin promotes efficient transcription termination between convergent genes during the cell cycle [73]. During G1 phase, overlapping transcripts at convergent gene loci produce double strand RNA (Figure 2D), followed by RNA interference dependent transient heterochromatin formation (including histone H3 lysine 9 trimethylation marks and Swi6 association). Subsequently, Swi6 recruits cohesin either via a direct interaction or by first recruiting Mis4 (fission yeast cohesin loader), which then loads cohesin. In G2, cohesin is concentrated into the intergenic regions of the convergent genes, where it promotes gene-proximal transcription termination. It would be exciting to investigate such a possibility between sense and antisense transcription units in mammals.

Cohesin deregulation in cancer

A multitude of mutations, uncontrollable cell division and genome instability, are the hallmarks of cancer cells. Genome wide sequencing analysis has identified nearly 140 genes mutated in solid tumors (those derived from colon, breast, brain, or pancreas), squamous cell carcinoma, melanomas, leukemia and lung cancer [74]. About 95% of these non-synonymous mutations are single-base substitutions (such as C:G) resulting in splice site alterations, missense and nonsense changes; whereas the remainder is insertion-deletion polymorphism. Most tumors also display widespread copy number variations, as well as homozygous deletions, translocations, inversions and gene amplifications. Fundamental to its role in faithful chromosome segregation, cohesin deficient cells exhibit widespread chromosomal instability (CIN), impaired DNA damage repair and high sensitivity to ionizing radiations.

Mutations in *SMC1A, SMC3, STAG2, RAD21*, *NIPBL, STAG3* and *SMC5* (plays a role in DNA damage repair, along with SMC6) have been identified in patients with acute adult *de novo* myeloid leukemia [75,76]. SMC1A has also been implicated in the pathogenesis of gliomas, where SMC1A expression is upregulated and reducing its levels suppresses glioma cell growth *in vitro* [77]. Several authors have documented aberrant expression of RAD21 in cancer. RAD21 was found to be overexpressed in undifferentiated cancers of the breast, lung, bladder, brain and ovaries [78]. Contrarily, RAD21 was downregulated in oral squamous cell carcinoma tumor samples and cell lines with high invasive and metastatic potential [79]. Interestingly, studies in zebrafish have revealed *rad21* to be a regulator of *runx1* [80]. RUNX1/AML1 (runt-related transcription factor 1/ acute myeloid leukemia 1) belongs to the family of RUNX transcription factors that regulate the transcription of genes involved in cell differentiation, growth and survival. *RAD21* and *RUNX* mRNA levels were indeed deregulated and surprisingly co-dependent in endometrial cancers [81]. Glioblastoma cell lines, melanomas and Ewing's sarcomas also display cohesion defects, lagging chromosomes and anaphase bridges (classic signs of aneuploidy) due to mutations in the X-linked *STAG2* gene, which has been proposed to function as a "caretaker" tumor suppressor gene [82]. Somatic mutations in *SMC1A, SMC3, SA3,* and *NIPBL* have also been documented in colorectal cancers characterized by almost 100-fold higher CIN than normal cells [83]. Conversely, downregulation of *SMC1A, STAG3, STAG2* and *RAD21* has been found in ovarian cancer, acute myeloid leukemia and in chronic myelomonocytic leukemia [79,84-87].

Additionally, several reports link cohesin regulatory/accessory proteins to tumorigenesis. Overexpression of WAPL and ESCO2 is associated with tumor progression in cervical cancer and melanomas, respectively [88,89]. Separase upregulation is sufficient to induce tumorigenesis in mammary epithelial cells in a p53 mutant background [90]. Pituitary tumor transforming gene *(PTTG1)* has been classified as a proto-oncogene, as PTTG1 abundance correlates with metastasis

in multiple tumors, while siRNA mediated inhibition of *PTTG1* suppresses growth of lung and ovarian cancer cells both *in vitro* and *in vivo* [91-94]. Interestingly, cohesin associated Pds5 paralog; APRIN (Pds5B) is also downregulated in a variety of cancers and loss of APRIN affects stem cell differentiation by disrupting Oct4, Nanog and SOX2 patterns [84]. Certainly, the cohesin pathway seems to be a common target in a variety of cancer types and in the next section we discuss how cohesin misregulation can result into tumorigenesis.

Cohesin at the telomere: aging and cancer

Unlike yeast cohesin, vertebrate mitotic cohesin is composed of two different Scc3/SA proteins, namely SA1/STAG1 and SA2/STAG2. Emerging evidence suggests functional disparity between cohesin-SA1 and cohesin-SA2. Remeseiro et al. demonstrate that cohesin-SA1 null mice are embryonic lethal and SA1 knockout mice that survive to late stages of embryogenesis (E17.5-18.5) recapitulate pathological features observed in CdLS patients and *Nipbl* heterozygous mice [95]. Such phenotypic changes possibly arise due to misregulation of transcription factors such as *c-myc*, *Pax2*, *MafB* and altered expression of the protocadherin gene family, involved in central nervous system development [96]. Interestingly, cohesin-SA1 is essential for telomeric cohesion, while cohesin-SA2 is important for centromeric cohesion and both are required for cohesion on the arms [97].

Telomeres are DNA-protein structures at the ends of chromosomes, pivotal for the maintenance of genome integrity. Each cell division involves progressive shortening of telomeres because replication cannot proceed through the chromosome ends. In vertebrates, the telomeric DNA sequence is a track of six-nucleotide unit sequence TTAGGG, extending for thousand of bases at chromosome ends, which forms G-quadruplexes and T-loop structures protected by the shelterin protein complex [98]. Telomere dysfunction can elicit DNA damage response and telomere shortening can promote genome instability by gene fusions and breakage. Conversely, most mouse studies emphasize a tumor suppressive role for short telomeres, by triggering senescence and aging [98]. Cancer cells rely on telomere lengthening mechanisms in order to gain uncontrolled cellular proliferation. Most human tumors have upregulation of telomerase (enzyme dedicated to telomere replication) and 10-20% human tumors also activate alternative pathways for telomere lengthening (ALT) [99]. Interestingly, ALT is mediated via homology-directed repair (HDR) and sister-telomere proximity is undoubtedly crucial for this process. ChIP-Seq analysis shows that most human subtelomeres contain a CTCF- and cohesin-binding site within 1-2kb of the TTAGGG repeat [100]. Additionally, loss of CTCF or cohesin results in telomere-induced DNA damage foci (TIF) formation and destabilizes telomere repeat binding factor 1 (TRF1) and TRF2 binding to the subtelomere DNA. In association with repressor/activator protein 1 (RAP1), TRF1-interacting nuclear protein 2 (TIN2), TIN2-interacting protein 1 (TPP1) and protection of telomeres 1 (POT1), TRF1 and TRF2 constitute the shelterin complex [101]. Cohesin-SA1 maintains telomere sister chromatid cohesion by interacting with TIN2 [97]. Telomere dysfunction, mutations in cohesin and tumor suppressor genes, and activation of oncogenes, can collectively contribute to chromosome instabilities, genetic chaos and immortal growth.

Concluding Remarks

To summarize, the cohesin complex and associated proteins are fundamental to the establishment and maintenance of a hale and hearty biological system. Apart from chromosome segregation, we are beginning to understand the plethora of regulatory functions executed by cohesin. Further work will be necessary to understand the mechanisms underlying cohesinopathies and gain insights into a potential therapeutic role of cohesin in cohesinopathies and cancer.

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