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Cohesins and cohesin-regulators: Role in Chromosome Segregation/Repair and Potential in Tumorigenesis

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Summary

Cohesin is the name of a multifunctional protein complex, which was initially discovered and characterized by its role in maintain cohered sister chromatids during chromosome segregation in cell division. However, in the last years a large number of studies and results have evidenced the implication of cohesin complexes in different crucial processes in cell life such as DNA replication, control of gene expression, heterochromatin formation, and DNA-repair. The canonical cohesin complex consists in four subunits named SMC1, SMC3 (**S**tructural **M**aintenance of **C**hromosomes) and SCC1, SCC3 (**S**ister **C**hromatid **C**ohesion). Two last subunits have also denominated RAD21 for SCC1 and STAG for SCC3 in mammals. These four subunits, named also cohesin individually, are able to form a ring-like structure (figure 1A), which could modulate different local chromatin conformations depending on the interactions with diverse cohesin-interacting proteins, which have been designated as cohesin cofactors and/or cohesin-regulators.
Chromosomal instability is one of the hallmarks of cancer, generating chromosomic aberrations including aneuploidy, loss of heterozygosity, chromosomal translocations etc. Mutations in genes encoding for proteins that control cell cycle are potential candidates in the generation of genome instability. Thus, cohesins and cohesin-regulators, which are key players in chromosome segregation and in DNA-damage repair, are obviously aspirant molecules for this research.

Basic concepts of cohesins in chromosome segregation and DNA-damage repair

Chromosome miss-segregation and aneuploidy are frequently observed in most of cancer cells. Perhaps the two cellular mechanisms more critical for chromosomal stability in which cohesins are involved are chromosome segregation during cell division and DNA-damage repair, therefore, in this paper, I will center on the cohesins and cohesin-interacting proteins involved in these two cellular important processes and their links with tumor formation and development.
Although the multiple roles of cohesins remodeling chromatin structure have been extensively and detailed revised in the last time (for two example reviews see Barbero, 2009 and Nasmyth and Haering, 2009), following, I describe here briefly the most relevant concepts of cohesin dynamic in order to understand their potential involvement in tumorigenesis.
Cohesin complexes preserve sister chromatid cohesion during cell division in mitosis and meiosis by binding along the arm and centromeres of chromosomes. For this function, cohesin needs to the action of other proteins; among the best characterized of these cofactors are the followings: the adherin complex formed by SCC2 and SCC4 proteins is required for the loading of cohesin complexes to chromosomes; the cohesion establishment/maintenance proteins Eco1 acetyltransferase in yeast and the mammalian

homologues ESCO1 and ESCO2, which, by acetylation of the SMC3 subunit of cohesin complex, stabilizes the binding of cohesin to chromatin; PDS5A and B (**P**recocious **D**issociation of **S**ister), WAPL (**W**ings **Ap**art-**L**ike) and SORORIN are proteins involved in the maintenance of cohesion through their interaction with cohesin complex subunits and/or with other cohesin-regulators (figures 1B and 2A); Shugoshin ("the guardian of the spirit" in Japanese) protein family SGO1 and SGO2, which are essentially implicated in the protection of sister chromatid cohesion at the centromeric regions and, finally, the cohesion removal proteins PLK1 (**P**olo **L**ike **K**inase 1), Aurora B and securin/separase complex (figure 2A). The two first molecules are protein-kinases that phosphorylate cohesin, essentially STAG subunit, triggering the removal of arm cohesins. Separase is a specific protease, which is inhibited by its cofactor securin; activation of the anaphase promoting complex/cyclosome (APC/C) leads to ubiquitination and degradation of securin, allowing cleavage of SCC1/RAD21 from centromeric cohesin complexes by separase and triggering the onset of anaphase.

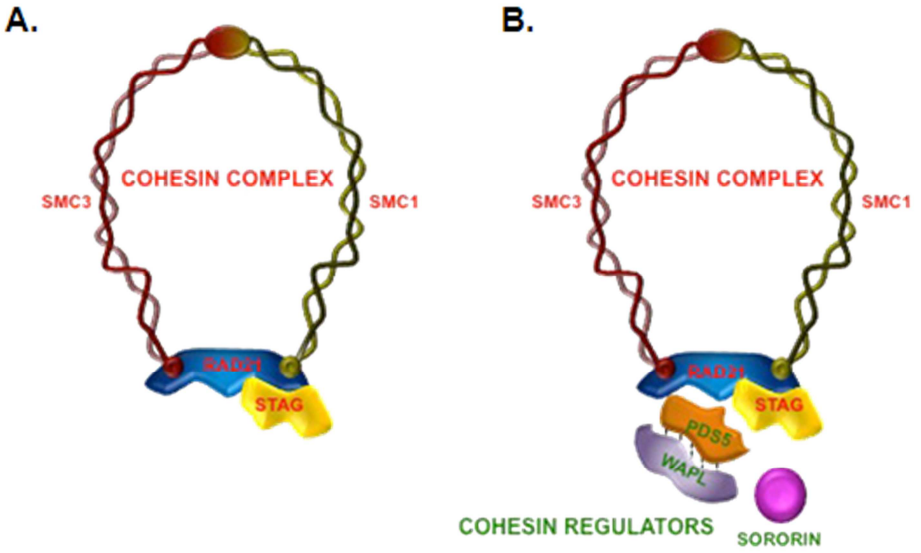

Figure 1. Cohesin complex and cohesin-regulators. A. Ring model of cohesin complex formed by four subunits SMC1, SMC3, RAD21/SCC1 and STAG/SCC3. Subunits SMC1, SMC3 and RAD21 conform the ring-like structure. STAG protein interacts with RAD21 to complete the cohesin complex. **B.** Examples of cohesin-regulators. PDS5 and WAPL form a protein complex, which is associated to the cohesin complex by STAG interaction. Sororin is other cohesin-regulator that is also involved in the control of cohesin ring dynamic.

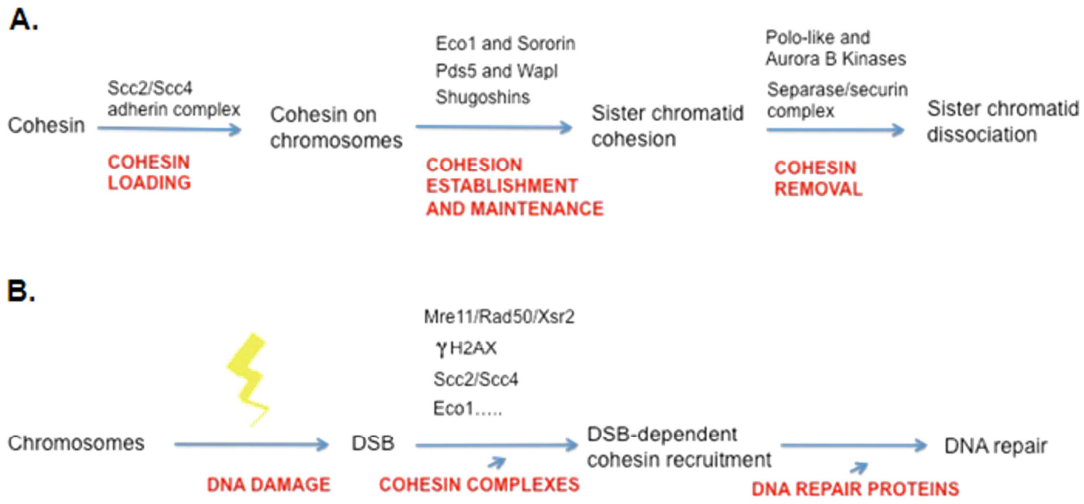

Figure 2. Scheme of cohesin metabolism during chromosome segregation and DNA-damage repair. A. Dynamic of cohesin complex in chromosome segregation indicating the characterized cohesin-regulators involved in cohesin loading to chromosomes, sister chromatid cohesion establishment and maintenance, and cohesion dissolution during cell division. **B.** Involvement of cohesin complexes during DNA-damage repair. Cohesin are recruited to double strand break (DSB) areas to facilitate the repair process. Some cohesin-regulators, such us Scc2/Scc4 loading complex and Eco1 cohesion establishment factor are also required for new cohesin loading in these chromosome damaged regions. See text for more details.

All these cohesin-regulators were firstly characterized studying its function in sister chromatid cohesion, but shortly after has been found evidence of its involvement in DNA repair and other cohesin tasks. The initial result on the participation of cohesins in theses mechanisms was already reported before cohesins were known to mediate sister chromatid cohesion; the Scc1 ortholog from *Schizosaccharomyces pombe* was first identified as a protein whose mutation causes sensitivity to radiation because damaged DNA cannot be properly repaired and, thus, called Rad21 (**Rad**iation-sensitivity) (Birkenbihl and Subramani, 1992). Following experiments, essentially in budding yeast, showed that cohesin mutants are defective in repair damaged DNA and provided evidence that DNA repair depends on the function of cohesin to mediate sister chromatid cohesion. In addition, studies of Rad21-depleted chicken cells have shown that vertebrate cohesin also functions in both segregation and repair (Sonoda et al., 2001). This cohesin requirement could be explained because DNA double strand breaks (DSB) are preferentially repaired by recombination between sister chromatids and the cohesion between them would facilitate this process. In this sense, cohesin complexes are recruited to sites of DSB to contribute to DNA repair of these damaged regions of chromosomes (figure 2B). This cohesin recruitment also required: from Eco1/ESCO acetyltransferase (Heidinger-Pauli et al., 2009) and from a functional SCC2/SCC4 adherin complex (Ström et al., 2004). In addition to machinery of chromosome cohesion, another specific DNA-damage repair proteins are necessary for the cohesin localization to DSB sites (figure 2B). A component of the DNA-damage sensing complex MRX (Mre11/Rad50/Xsr2) is required for cohesin assembly around the DSB. Phosphorylation of histone H2AX by Mec1/Tel1 generates what is known as gH2AX. Yeast strains expressing a non-phosphorylatable H2AX fail to recruit cohesin, thus suggesting that gH2AX may act as a signal for cohesin assembly (Unal et al., 2004). Interestingly, some modifications by phosphorylation of SMC1 and SMC3 cohesin subunits are carried out by specific kinases following IR and UV damage. Mutations in SMC1 or SMC3 that prevent phosphorylation result in abrogated DNA-damage responses (Kitagawa et al., 2004).

Although, currently the participation of other chromosome cohesion cohesin-regulators in DNA repair is poorly understood, probably future research will incorporate also some of these molecules to control of DNA repair mechanisms (figure 2B).

Cohesins: chromosome segregation, DNA-damage repair and cancer

Obviously, the multiple roles of cohesins (figure 3) make it difficult to determine how their lack of function contributes to the generation and development of tumors and probably in many cases, were involved several processes. In this review, I focus on the two functions of cohesins most clearly related to genome stability, chromosome segregation and DNA-damage repair, and on the currently available data and results linking mutations on cohesin and cohesin-regulators genes and tumorogenesis.

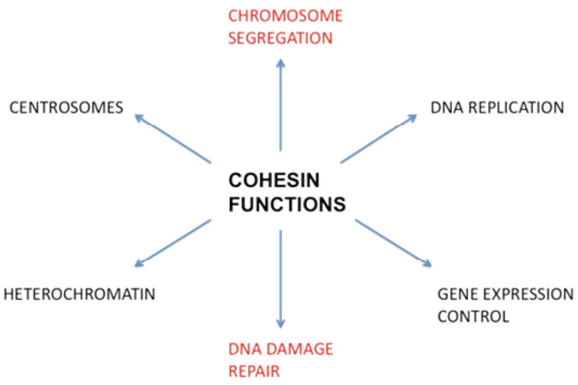

Figure 3. Cohesin functions. Scheme of the main cell life processes in which cohesins have been functionally characterized. The two cohesin tasks in red are the principal focus of this review.

Cohesin complex subunits

RAD21 cohesin subunit has long been linked with cancer chemotherapy; inhibition of RAD21 expression by RNA interference in human breast cancer cells enhanced the cytotoxicity of etoposide and bleomycin in these cells (Atienza et al., 2005). In agreement with this result, Xu et al. (2011) reported that overexpression of RAD21 gives resistance to chemotherapy in high-grade luminal, basal and HER2 breast cancers. Mice lacking *Rad21* gene function present early embryonal lethality, but heterozygous *Rad21*$^{+/-}$ animals were obtained by breeding. *Rad21*$^{+/-}$ mice were viable and developed to apparently normal adulthood without morphological defects. However, *Rad21*$^{+/-}$ mice have enhanced sensitivity to whole body irradiation, indicating that *Rad21* gene dosage is critical for ionizing radiation (IR) response (Xu et al., 2010).

The study of 11 somatic mutations in 132 human colorectal cancers identified 6 of them mapping to 3 cohesin, *SMC1a*, *SMC3* and *STAG3*, genes and 4 to a cohesin-regulator *SCC2* gene (Barber et al., 2008).

Chromosomal instability is a characteristic of colorectal cancer cells, resulting in chromosome gain or loss. It is possible to argue that abnormal cohesin pathway activity leads to chromosome missegregation and chromosome instability. This hypothesis is supported by the observation that colorectal cancer cells exhibit up to 100-fold higher rates of missegregation than normal cells. In addition, using a microcell mediated chromosome transfer and expression microarray analysis, Notaridou et al. (2011) identified the cohesin subunit *STAG3* gene as one of the nine genes associated with functional suppression of tumorogenicity in ovarian cancer cell lines and as a candidate gene associated with risk and development of epithelial ovarian cancer. Kalejs et al. (2006) found aberrant expression of meiotic-specific genes, including the meiotic specific cohesin genes *REC8* and *STAG3* in a lymphoma cell model.

The other two members of the STAG cohesin family (STAG1 and STAG2) have been also implicated in cancer. The most frequent cause of familial clear cell renal cell carcinoma (RCC) is von Hippel-Lindau disease and the VHL tumor suppressor gene (TSG) is inactivated in most sporadic clear cell RCC. To identify candidate genes for renal tumorigenesis, Foster et al. (2007) characterized a translocation, t(3;6)(q22;q16.1) associated with multicentric RCC without evidence of VHL target gene dysregulation. The gene encoding for the human cohesin subunit STAG1 map within close proximity to the breakpoints and thus it is a candidate gene involved in RCC. In array studies searching for genome alterations in a series of 167 malignant myeloid diseases, Rocquain et al. (2010) found recurrent deletions of *RAD21* and *STAG2* genes, suggesting that cohesin components are new players in leukemogenesis.

Chromosomal translocations are also frequently found in different cancer cells. The results studying a novel non-TCR chromosome translocations t(3;11)(q25;p13) and t(X;11)(q25;p13) activating *LMO2* by juxtaposition with *MBNL1* and *STAG2* are consistent with *LMO2* upregulation via capture of *MBNL1* or *STAG2* regulatory elements effected by t(3;11) or t(X;11), respectively (Chen et al., 2011). With the aim to identify genomic alterations, associated with exposure to radiation, Hess et al. (2011) used array comparative genomic hybridization to analyze a main (n=52) and a validation cohort (n=28) of PTC from patients aged <25 y at operation and matched for age at diagnosis and residency. Both cohorts consisted of patients exposed and not ex-posed to radioiodine fallout. The study showed association of a gain on chromosome 7 (7q11.22-11.23), which correlates with the expression of *STAG3L3*, a *STAG3*-truncated loci previously characterized and reported in our laboratory (Pezzi et al., 2000).

Very recently, Solomon et al. (2011) found harbor deletions or inactivating mutations of *STAG2* in a diverse range of human tumor types including glioblastomas, Ewing's sarcomas, melanomas, lymphomas, medulloblastomas and colorectal carcinomas. Although it is has been thought that inactivation of genes that control chromosome segregation is involved in generation of aneuploidy in human cancers, however, until this work, only few examples of human tumors confirming this hypothesis had been reported. These authors compared the *STAG2* gene function as a "caretaker" tumor suppressor gene that when inactivated results in chromosomal instability.

So far, we have shown different studies that link cancer development to disorders in the four core cohesin subunit genes, but there are also several experimental data linking cohesin-interacting proteins with tumorigenesis.

Cohesin-regulators: cohesin loading, cohesion establishment and maintenance

Because the essential function of adherin complex SCC2/SCC4 in loading cohesin complexes to chromosomes during chromosome segregation and in DNA-damage repair, it is logical to assume that its lack of function have an impact on genomic stability, however, until I know, there are not experimental results implicating mutation in *SCC2* and/or *SCC4* genes in human tumors.

The study of gene expression profiling is very useful to molecularly classify primary tumors. In such a study in melanoma cells, upregulation of activators of cell cycle, including *ESCO2* cohesion establishment gene, has been reported and implicated in melanoma progression Ryu et al. (2007). Loss of the p-arm of chromosome 8 is frequently observed in breast, prostate, and other types of cancers. In a study of 273 genes expressed on p-arm of chromosome 8 (five breast and three prostate human cancers) downregulation of *ESCO2* gene was observed (Yamamoto and Yamamoto, 2008).

PDS5B expression is lost in many cancers and *PDS5B* mutations in germ line provoke birth defects. Based on these results, Denes et al. (2010) hypothesized that PDS5B plays a role in stem cell differentiation and in embryonic carcinoma. *PDS5B* knockdown disrupted Oct4, Nanog and SOX2 patterns, in addition to others stem cell differentiation mechanisms. Their results suggested that the link between the PDS5B-related birth defects that shows Cornelia de Lange syndrome (CdLS; OMIM: 122470, 300590, 610759) and cancer is a disrupted early stem cell differentiation program. On the other hand, PDS5A, the other PDS5 member, is overexpressed in high-grade gliomas, which are characterized by a high degree of genome instability and aneuploidy (Hagemann et al., 2011), linking again lost of chromosome cohesion with genomic instability.

WAPL was also identified as an oncogene in uterine cervical cancer and it is induced by human

papillomavirus (HPV) E6 and E7 oncoproteins. *WAPL* overexpression induces apparition of multinucleated cells and increases the number of chromatid breaks in the cell, contributing to molecular mechanisms of tumor progression from HPV-infected cells to cervical carcinoma (Ohbayashi et al., 2007). Later, these authors reported that human *WAPL* gene encodes a large number of spliced variants and that the expression patterns of these variants could have diagnostic potential for cervical lesions (Oikawa et al., 2008).

Sororin, also known as cell division cycle associated 5 (CDCA5) protein, has been recently identified as an up-regulated gene in mostly lung cancers using a cDNA array containing 27648 genes or expressed sequence tags (Nguyen et al., 2010). Sororin is phosphorylated by extracellular signal-regulated kinase (ERK) at Ser79 and Ser209 *in vivo*. The suppression of sororin expression by siRNAs or the inhibition of the interaction between sororin and ERK inhibited the growth of lung cancer cells indicating a functional role of activation of CDCA5/sororin in lung cell cancer proliferation.

To investigate the putative role of the centromere cohesion guardian shugoshin 1 (SGO1) in human colorectal cancer, Iwaizumi et al. (2009) performed *SGO1* knockdown using shRNA expression vector. Human *SGO1* knockdown cells proliferated slowly and presented marked of chromosomal instability (CIN) in the form of aneuploidy. Other characteristics of these transfected cells were increased centrosome amplification, the presence of binucleated cells, and mitotic catastrophes. The results of this study showed that SGO1 down-regulation leads CIN in human colorectal cancer cells and it could be a molecule involved in the CIN pathway found in colorectal cancer progression.

Cohesin-regulators: cohesion dissolution

The complex separase and its inhibitor securin are responsible for the total dissolution of sister chromatid cohesion in anaphase. Mammalian securin gene was originally identified in 1997 and characterized as pituitary tumor-transforming gene (*Pttg1*), which encodes the PTTG protein, from rat pituitary tumor cells (Pei and Melmed, 1997). PTTG/securin is highly expressed in various tumors and it can induce human cellular transformation. PTTG/securin is associated with more aggressive tumor behavior and has been identified as one of 17 key signature genes associated with metastatic disease (Ramaswamy et al., 2003). In addition, a PTTG binding factor (PBF) was identified through its interaction with PTTG and it was characterized as a proto-oncogene that is upregulated in several cancers (Smith et al., 2010). PTTG1/securin is also overexpressed in hepatocellular carcinoma. Chronic infection with hepatitis B virus (HBV) is the main causal factor for hepatocellular carcinoma and the viral protein HBx plays an essential role in the pathogenesis of hepatic tumors. To investigate the putative correlation between the abnormal expression of PTTG1 and the tumorigenic mechanism of HBx, Molina-Jiménez et al. (2010) analyzed the PTTG1 expression in biopsies from patients chronically infected with HBV in different disease stages and from HBx transgenic mouse model. These authors found that HBx viral protein promotes an accumulation of PTTG1 by inhibition of PTTG1 ubiquitination and degradation. The molecular mechanism/s by which HBx carried out this inhibition is currently under research.

Separase is the endopeptidase that cleaves RAD21 cohesin subunit during to metaphase/anaphase transition causing the removal of cohesins and the separation of sister chromatids. Overexpression of separase induces premature separation of chromatids, lagging chromosomes, and anaphase bridges. In a mouse mammary transplant model, induction of separase expression in the transplanted FSK3 cells for 3-4 weeks results in the formation of aneuploid tumors in the mammary gland (Zhang et al., 2008). In a later report, Meyer et al. (2009) showed that separase is significantly overexpressed in osteosarcoma, breast, and prostate tumor specimens. There is a strong correlation of tumor status with the localization of separase into the nucleus throughout all stages of the cell cycle. In addition, overexpression of separase transcript strongly correlates with high incidence of relapse, metastasis, and lower 5-year overall survival rate in breast and prostate cancer patients, suggesting that separase is an oncogene.

Polo-like kinase 1 (PLK1) and Aurora B are two protein-kinases that have as substrates cohesins and other proteins involved in chromosome segregation. PlK1 is overexpressed in various human cancers, and this is mostly associated with poor prognosis (Strebhardt and Ullrich, 2006). The first data to associate PLK1 with neoplastic growth were generated by studies showing that PLK1 concentrations are also increased in primary cancer tissues (Holtrich et al., 1994). This prompted a number of studies that subsequently demonstrated that PLK1 is overexpressed in a broad spectrum of human tumors compared with normal controls. Furthermore, some reports have indicated that PLK1 expression is a reliable marker for identifying a high risk of metastasis (Dai et al., 2000). More recently, Ito el al. (2010) described the post-transcriptional regulation of *Plk1* expression by RNA interference mediates by miR-593* and *Plk1* downregulation in EC cells decreases cell proliferation *in vitro* via G2/M cell cycle arrest, and drastically suppresses tumor formation *in vivo*.

Aurora B kinase is involved in different key functions during chromosome segregation to preserve genomic stability. Examples of these functions are: sister chromatid cohesion, chromosome condensation, mitotic spindle assembly, syntelic chromosome attachments and spindle assembly checkpoint (for a review see Vader and Lens, 2008). Aurora B is overexpressed in

cancer cells, and an increased level of Aurora B correlates with advanced stages of colorectal cancer. Overexpression of Aurora B results in multi-nucleation and polyploidy in human cells (Tatsuka et al., 1998) and, additionally, it has been reported that Aurora B overexpression induces chromosomes lagging in metaphase, chromosome segregation error, and errors in cytokinesis, and thus suggesting a direct link between Aurora B and carcinogenesis (Ota et al., 2002). These findings and the crucial roles of Aurora B and PLK1 in chromosome dynamics during cell cycle have led to consider these two kinases as important targets for cancer therapy (de Cárcer et al., 2007; Strebhardt, 2010; Libertini et al., 2010).

Concluding remarks

Cohesin complex, initially characterized as a ring protein complex that maintains sister chromatids together during chromosome segregation, is now considered a real architect of chromatin structure during essential dynamic DNA processes. In many cases, these processes are designed to safeguard the stability of genetic material and its proper distribution to the daughter cells. Thus, it is not surprising that when there are errors/problems in the cohesin complex metabolism related with this guardian function, one of the likely results was the formation of a tumor. Although this review focuses essentially on the role of cohesins in chromosome segregation and DNA-damage repair and their connection with tumorigenesis, other functions of cohesins are also possibly related with the development of human tumors. In this sense, recently Baysal et al. 2011, described that germ line mutations in *SDHD*, a mitochondrial complex II (succinate dehydrogenase) subunit gene at chromosome band 11q23, cause highly penetrant paraganglioma tumors when transmitted through fathers. In contrast, maternal transmission rarely, if ever, leads to tumor development. They observed that hypermethylated adrenal tissues show increased binding of the chromatin-looping factor cohesin relative to the hypomethylated tissues, suggesting that this differential allelic interaction may result in maternal downregulation of *SDHD* and the parent-of-origin dependent tumor susceptibility.

In recent years, an increasing number of scientific works showed that cohesin functions are mediated by the action of other proteins. These molecules can be subdivided into two kind of cohesin-interacting proteins: those that regulate different aspects of the cohesin metabolism and necessary for several functions (such as SCC2/SCC4, Eco1/ESCO) and those that contribute to one cohesin specific role by a spatial-temporal interaction with cohesin complex (such as CCCTC-binding factor (CTCF) and MEDIATOR in the control of gene expression (Wendt et al., 2008; Kagey et al., 2010)). In addition, post-translational modifications, such as acetylation and phosphorylation, in specific residues of cohesin subunits are also required for specific cohesin functions, suggesting the putative existence of a cohesin code similarly to well established histone code.

All these findings point to the initial denomination of cohesin is currently very limited and therefore some authors are beginning to use other terms, such us *chromatin-looping factor* (Baysal et al., 2011) or, from my point of view, more convenient *chromosome architectins*, which, by interaction with specific regulator proteins, model precise tridimensional structures at local regions of chromosomes to perform different and specific functions depending on the spatial-temporal requirements of cell life. The future research on the molecular mechanisms of both, the cohesin-interacting proteins and the specific cohesin post-translational modifications, and on the alterations in the cohesin network during pathological conditions is crucial in determining the relationships between this interesting ring protein complex and the formation/development of tumors in humans.

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