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Structure and Function of Chromosomal Passenger Complex: An Orchestrator of Systematic Cell Division, Mitotic Exit and Cytokinesis

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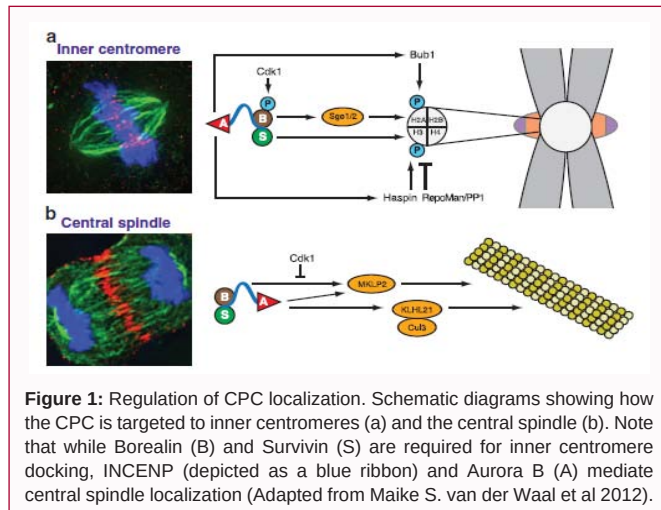
Abstract

Transferring of duplicated genetic material to a pair of newly formed daughter cells is one of the ultimate goals of cell division in living organisms. For ensuring cell division and genomic stability in organisms, numerous surveillance mechanisms are present. Chromosomal passenger complex (CPC) is one of the highly conserved complexes that is believed to have an essential role in non erroneous chromosome segregation and execution of cytokinesis. Astonishingly, CPC has a dynamic pattern of localization during cell division and it also achieves other functions during different stages of cell cycle. Structurally, CPC consist of four proteins i.e. Inner Centromere protein (Incenp), Survivin, borealin and Aurora B Kinase. Functionally, it facilitates accurate and correct segregation of duplicated chromosome at metaphase by numerous methods which includes mitotic checkpoint regulation throughout cell division, destabilization of erroneously attached spindle fibers and via endorsing apical shortening of chromosomal arms in anaphase. CPC most likely delays the abscission checkpoint to prevent chromosome breaks and damages if chromatin is lagging behind or trapped inside the furrow regression during cytokinesis. In this way, CPC avoid tetraploidization by strictly observing the cytoplasmic division. In this review, both structure and function of CPC is described that how it is proficient of executing its numerous functions during cell cycle to avoid genomic instability and ensure accurate chromosome segregation.

Keywords: Chromosomal passenger complex; Cytokinesis; Surveillance mechanisms; Chromosome segregation

Introduction

A cell has to be confronted of transferring the error free replica of its genetic information to daughter cells upon each round of partition. In general, cancer cells have been evident for faults in chromosomes segregation. The phenomenon is termed as numerical chromosomal instability (CIN) that results either because of loss or gain of entire chromosome. Another type is called structural chromosomal instability characterized with structural aberrations [1-3]. Numerical CIN results in aneuploidy and evidence is accumulating that it can generate tumour initiation and progression by loss of heterozygosity of tumor suppressor genes [4]. The defects that could lead to such instabilities in chromosome can be revealed by unraveling how a dividing cell ensures normal chromosomal stability. One of such mechanism includes the segregation of chromosomes non-erroneously during mitosis that has to be followed by appropriate cytokinesis [4]. Correct bi-orientation and attachment with spindle poles of duplicated chromosomes is indispensable for correct chromosome separation. The division of cell has to be delayed until all the sister-chromatids attach properly to the mitotic spindle fiber and let the cell machinery to continuously check the spindle-kinetochore attachment and correct it in case of errors. Furthermore, both temporal and spatial coordination of cytokinesis and mitosis is crucial to warrant the clearing of metaphase chromosomes from the equator before the actual separation of two newly forming cells. This coordination is essential to ensure that chromatin is not damaged and properly segregated as tetraploidization may resulted which can give rise chromosomes separation errors in the next round of cell cycle [2,5]. All these regulatory processes ensuring maintenance of stable genome are highly reliant on the functioning



of CPC. This review focuses on the regulatory role of CPC that how it performs numerous function during cell division. Moreover, the structure of the complex will also be discussed regarding how it assists localization of the complex to various sites during mitosis for exerting functions that ensures genomic stability.

Structure of the CPC

CPC is composed of enzymatic and non enzymatic components i.e. Aurora Kinase B (AURKB) an enzymatic core protein, Borealin (CDCA8) and Survivin (BIRC5) which are non enzymatic subunits and the inner centromere protein (INCENP) that serves as a scaffold protein. Being a scaffold structure, INCENP allows the other subunits to physically interact with it through its C and N-terminals. The IN-box of INCENP at the C terminal is responsible for interaction with AURKB while the N-terminal of INCENP hold on interactions with CDCA8 and BIRC5. Between these two regions, there is a long unstructured region that contains a binding motif for Heterochromatin Protein 1 (HP1), numerous CDK1 phosphorylation sites and an expected coiled-coil domain [6,7]. As protein interactions are very crucial for the functional stability of a complex thus CPC supports its subunits stability via inter proteins interaction. Depletion and silencing or chemical inhibition of any of the CPC member protein in various organisms could lead to the analogous phenotypes [8,9].

AURKB is a member of an Aurora (Serine/Threonine kinases) conserved family that also includes Aurora A and Aurora C. All the family members are the main regulator of mitosis and cytokinesis in eukaryotes [10]. AURKB phosphorylates a number of substrates that includes histone proteins, MCAK mitotic centromere-associated kinesin (reviewed in [11], vimentin [12] and the MKLP1 which is a microtubule motor protein both at the midbody and central spindle [13,14]. The interaction of AURKB with its substrates both in appropriate time and space is very important during the cell division process and it is achieved via interacting with the other passenger subunits of the CPC.

The second component of CPC is INCENP. There are two functional modules in INCENP. The conserved part also known as IN-box is located in the C terminal region and is responsible for activating AURKB [15,16]. While the opposite side i.e. the N terminal region is where Survivin and Borealin binds and is crucial for centromere targeting. *In vitro* analysis showed that INCENP can also bind with microtubules [17].

The third component, survivin was originally known as anti apoptotic protein and usually found over expressed in numerous human cancers. However, its role in regulating apoptosis is controversial despite having (IAP) inhibitor of apoptosis domain and (BIR) baculovirus IAP repeat domain (18). Structural studies have revealed the participation of BIR domain in provoking Survivin homodimerization thus raising the possibility of a totally altered function as an oligomer [19].

Borealin which is also known as Dasra was identified as a CPC component almost a decade ago and yet no orthologs have been revealed so far both in *C. elegans* and in yeast [20,21]. It can bind directly with survivin and INCENP but cannot bind with AURKB. Borealin has been found to have a DNA binding properties *in vitro* (22) and its C terminal can help CPC targeting to the centromere during metaphase [20].

Different aberrations and defects could result in a dividing cell if CPC function is compromised. More prominently, the disturbance will result in segregation faults and chromosome compression because of the inappropriate spindle formation, erroneous microtubule-kinetochore attachment, and spoiled function of the mitotic checkpoints. In addition, impaired cytokinesis results because of the abnormal function of CPC leave the cells in the tetraploidy condition that ultimately die or senesce. Upon partial inhibition, certain regulatory properties of the CPC lost like correction of merotelic attachments. In contrast, the complete inhibition of CPC may be required for compromising its role at other places e.g. at the mitotic check points [23-25]. However, the severity of the aberrations that can accumulate into a dividing cell depends upon the intensity of inhibiting or knocking down the kinase ability of the complex. Significantly, the relationship between heterozygous knockout mice for AURKB and the high incidence of cancer is emphasizing the important function of CPC in sustaining the genome stability [26].

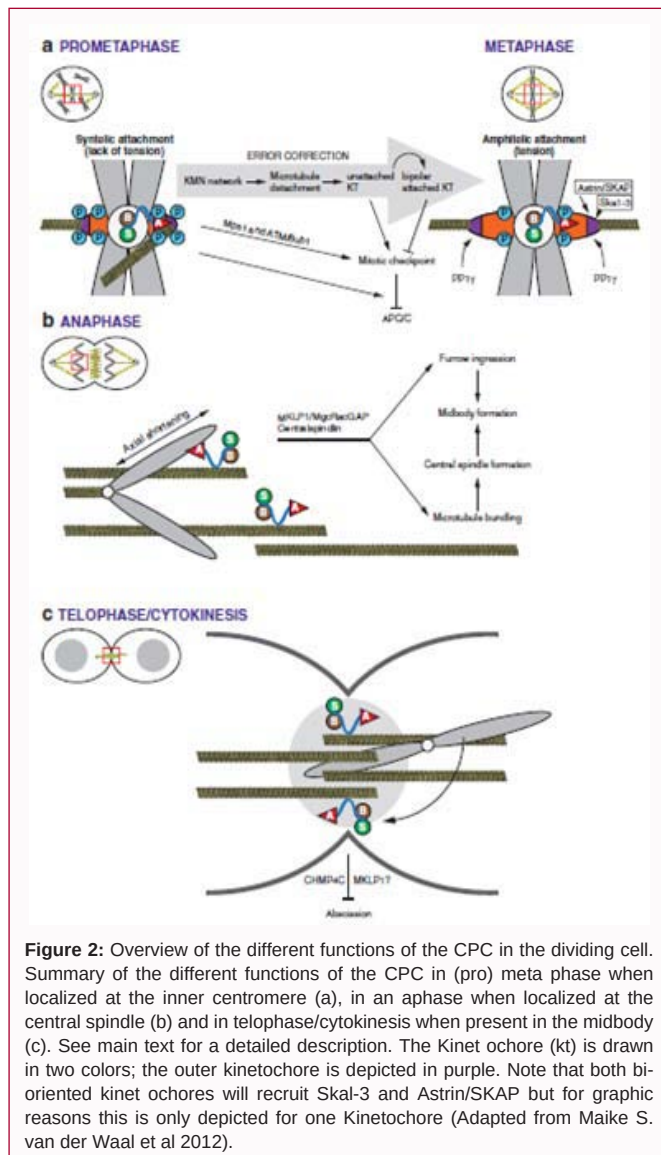
Function

Regulatory role of CPC in a dividing cell

AURKB gets activated and drives certain processes after the dividing cell successfully exits the interphase. These processes assist in ensuring the chromosomal stability. During this whole process, dynamic localization of CPC is crucial for exerting its multifunctional role. Except early prophase where it can be found on the chromosomal arms, it is localized to the inner centromere onward till metaphase. Anaphase onset CPC translocated from the centromere to the central spindle where it perform very important role at the interpolar and overlapped microtubules. Afterwards, it concentrates at a special structure called midbody during telophase (reviewed in 27 and Figure 1). In early mitosis, the regulatory role of CPC includes maintenance of chromosome morphology, removal of cohesion from the arms of chromosomes, spindle fibers formation followed by kinetochore assembly, correcting spindle-chromosomes bi polar attachments and more importantly the regulation of mitotic check points. Morphological changes in chromosome promoted by CPC continue till anaphase where shortening of metaphase chromosomes occur. Moreover, CPC plays an indispensable role at the cytokinesis by maintaining abscission check point preventing chromatin non disjunction errors [27-29].

Correcting kinetochore-microtubule attachments in prometaphase and metaphase

The duplicated chromosomes, in early mitosis have to be



bi-oriented and correctly attached on a bipolar spindle fibers (amphitelic attachments) i.e. multiprotein structure-kinetochore at the centromere of the sister chromatids must attach to the spindles emanating from the opposite poles [30,31], Figure 2a. However, segregation errors may have occurs in anaphase in case of erroneous microtubule-kinetochore attachments e.g. merotelic attachments: when oppositely directed microtubules become attached to a kinetochore of a one-sister chromatid, and Syntelic attachments: when uni-directed spindles attached to both sister-chromatids [32,33]. CPC role is to stabilize the correct bipolar attachments and promoting chromosomes bi-orientation through subverting the merotelic and Syntelic attachments via number of mechanisms and signaling cascades [34,35]. For instance, it is necessary to generate a tension across sister-chromatids kinetochore and CPC substrates like KNL1, Ndc80/Hec1, Dsn1/Mis13 (KMN network components) which are located at the inner centromere for correctly detachment and movement of the chromatids but such tension is failed to produce in case of erroneous microtubule and kinetochore attachment [36,37] (Figure 2a). Microtubule binding ability is reduced upon continuous phosphorylation of KMN network proteins and facilitates the liberation of incorrectly attached microtubules.

Importantly, amphitelic attachments results in generating tension across sister-kinetochores allowing dragging out of the kinetochore associated substrates from the influential range of CPC. Afterwards, KMN network dephosphorylation by PP1 gamma isoform through interacting with Knl1 is no longer inhibited. This whole signaling pathway is thought to be a promoter for stabilizing the bi-oriented attachments [38-40].

Role of CPC onset of metaphase

On successful bi-orientation of chromosomes followed by silencing of mitotic checkpoint and the degradation of cyclin B and securing in APC/Cdc20 dependent manner promotes anaphase entry. Unlike in both fission and budding yeast where check point silencing is achieved via kinetochore associated PP1 phosphates activity for neutralizing the aurora B actions [41,42], it is obtained through dephosphorylation of Aurora B substrate at kinetochore i.e. Zwint-1 in human cells. This dephosphorylation is necessary for the movement of RZZ complex (ZW10, ROD and Zwilch) and BubR1 and Mad2 (check point proteins) to their respective poles from spindle attached kinetochores during late metaphase [43]. Now the CPC has travelled and localized to the mid zone microtubules in anaphase and will subsequently travel to midbody during telophase after silencing of mitotic check point in metaphase. CPC continues to control the normal cell division by endorsing cytokinesis and maintaining the abscission check point (Figure 1 and Figure 2b and 2c).

Role of CPC in central spindle assembly

In anaphase, in between packs of separated chromosomes, a special structure called central spindle is formed when anti-parallel plus ends of microtubules between two opposite poles bundled in the mid zone. This special structure is of utmost importance for the correct assembly and positioning of actomyosin based contractile ring. This ring structure is crucial for ingression of cleavage furrow and regulation of abscission and cytokinesis [44]. In this regard, the role of CPC is indispensable for formation of appropriate central spindle by translocating to the midzone. KIF20A/MKLP2 kinesin-6 achieved this transport of CPC to the midzone in mammalian cells [45,46]. It has been revealed that near the midzone, the microtubules stability is enhanced by the polarization of these microtubules by Aurora B that is probably achieved by elevated bundling activity of spindle fibers of the central spindle complex composed of MKLP1 heterotetramer, KIF23 homodimer and Rho family GTPase activating protein dimer [44]. Furthermore, clustering of central spindlin is necessary for microtubules bundling that is maintained by Aurora B mediated phosphorylation of MKLP1 [47].

CPC role in regulating cleavage furrow ingression

CPC has believed to be involved in the inhibition of polar cortical ingression and promotion of cleavage furrow ingression at the equatorial cortex simultaneously [48,49]. Same as the microtubule bundling, these effects are also controlled by central spindling regulation through CPC (Figure 2b). Moreover, appropriate and controlled RhoA activity is necessary in earlier and later stages of cytokinesis for both formation and ingression of contractile ring [50,51]. In addition, studies suggest the possible contribution of Aurora B in furrow ingression via polymerization of actin and maintaining myosin activity by phosphorylating proteins like form in FHOD-1 and myosin regulatory light chain-2 respectively [52,53].

Role of CPC in chromosome condensation

The role of CPC is not only confined to the regulation and

formation of central spindle and furrow ingression, it can also further help in segregating chromosomal arms condensation. The purpose may be to avoid any chromosomal breaks that could happen due to cytoplasmic ingression by quickly clearing the chromatids arms from the cell equator. In human and fission yeast cells, condensin I is recruited to chromatin and phosphorylated in Aurora B dependent manner to facilitate the chromatid compaction in contrast to the budding yeast cells where this response is achieved via phosphorylating serine 10 of Histone 3 protein [54-56].

CPC role in regulating abscission time

Upon CPC localization to the midbody during cytokinesis, aurora B mediated abscission checkpoint gets activated to prevent against conditions like tetraploidization and chromosomal breaks once the two daughter cells are connected by a chromosomal bridge. Other tension like nuclear pore defects and DNA damage can also invoke an abscission halting by sending signals to aurora B. In one of the recent study has unraveled an upstream signaling cascade of Aurora b necessary for successful and correct scission of two dividing cell [57]. Initially, if there is chromatin trapped inside the cleavage furrow, Cdc like kinase 1, 2 and 4 gets activated and phosphorylates aurora b at serine 331 which further phosphorylate CHMP4C at S210 to inhibit its translocation to the abscission zone [58]. CHMP4C is an ESCRT-III subunit and a known substrate for aurora B. This CHMP4C holds on along with ANCHR (abscission/no cut checkpoint regulator) the VPS4 protein that is thought to be very crucial for doing the final cut between two cells. S331ph of Aurora B applies a brake to the division by delaying the abscission until the trapped chromatin is resolved. Protein Kinase C isoform epsilon PKCε is responsible for counteracting this abscission delay by achieving phosphorylation of aurora B at S227 [57]. The S227ph of aurora B release the CHMP4C from its closed inactive conformer to an active open conformer by phosphorylating CPC subunit borealin at S165. The CHMP4C along with VPS4 now localize to the abscission zone where final cut has to occur between two dividing cells. Finally, chemical inhibition of Aurora B increases the abscission in absence of trapped chromatin. This lead to the decrease of AURKB activity below a certain level before the abscission can occur. In short, by responding to various cues, an aurora kinase B appears to be a central regulator of the abscission timing and mitotic exit.

Conclusion

The fundamental reason of the chromosomal fault like aneuploidy which is present in numerous human tumours is because of the disturbed CPC function as it has involved in maintaining genome stability. The condition may be caused either by over expression of CPC or by devastating mutations in the subunits of CPC (reviewed in 59). In addition, the misregulation of the CPC regulatory kinases and phosphatase could also be taken into consideration. Infact, in a number of tumours, highly expressed Aurora B and survivin has been found to be associated with poor prognosis [59]. It is worth to know whether over expression of these subunits of CPC is proficient enough to initiate tumourgenesis in animals as it is still unknown. Strikingly, aneuploidy is usually witnessed in mice through over expression of Bib1 that result into hyperactivation of Aurora B which can proposed that CPC increased activity could lead to carcinogenesis. In contrast, heterozygous AURKB depleted mice have been observed with high cancer development ability, specifying that reduced AURKB expression can also generate tumourous phenotype [60]. Therefore, only proper and an unbiased CPC activity can ensure genome

integrity and protection from carcinogenesis.

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