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Commentary

From mitosis to mutagenesis: Chromosomal passenger proteins at the crossroads of replication stress and cancer resilience

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Abstract

The chromosomal passenger complex (CPC), comprising Survivin, Aurora B kinase, INCENP, and Borealin, is classically known for its essential functions during mitosis. However, recent findings expand the CPC's role beyond cell division, uncovering novel functions in replication stress response and genome stability maintenance. In our recent study by Falke *et al.* [1], we demonstrate that CPC components, particularly Survivin and Aurora B, contribute to the protection of stalled replication forks and facilitate translesion synthesis (TLS) - a specialized DNA damage tolerance mechanism. This regulation involves a functional interaction with proliferating cell nuclear antigen (PCNA), a central coordinator of DNA replication and repair. The work not only reshapes our understanding of CPC biology but also reveals a mechanistic link how tumor cells may exploit CPC activity to maintain replication under genotoxic stress. These findings open new avenues for targeting CPC-PCNA interactions in cancers characterized by elevated replication stress.

Keywords: Aurora B kinase, Chromosomal passenger complex (CPC), Cancer therapy resistance, DNA damage tolerance, Proliferating cell nuclear antigen (PCNA), Replication stress, Survivin, Translesion synthesis (TLS)

Introduction

The chromosomal passenger complex (CPC) is a multifunctional regulator of mitosis, composed of four core subunits: INCENP, Borealin, Aurora B kinase, and Survivin [2]. This dynamic complex ensures correct chromosome alignment, segregation, and cytokinesis by regulating kinetochore-microtubule attachments and spindle checkpoint signaling [3]. Survivin, the smallest and most cancer-associated member of the CPC, is also a member of the inhibitor of apoptosis protein (IAP) family and frequently overexpressed in human tumors [2,4]. Although its mitotic functions have been extensively characterized, accumulating evidence suggests that the CPC also performs non-mitotic roles, particularly in the DNA damage response (DDR) and chromatin regulation [5-7]. In a recent study of our group [1], we provide compelling evidence that CPC components participate in replication stress tolerance (**Figure 1**) - a crucial adaptive response in cancer cells exposed to oncogene-induced replication perturbation or genotoxic therapies [8-10]. Specifically, the CPC was found to interact with proliferating cell nuclear antigen (PCNA), a sliding clamp that acts as a recruitment platform for DNA polymerases and repair factors during replication [11]. Through this interaction, the CPC appears to support translesion synthesis (TLS), an error-prone but essential mechanism that enables replication fork progression past DNA lesions [12,13]. This not only highlights an unexpected cytoprotective function of the CPC but also suggests that its inhibition may sensitize tumors to DNA-damaging agents by impairing TLS and fork stability. These findings broaden the therapeutic relevance of CPC proteins and support their evaluation as targets in replication stress-vulnerable malignancies like cancer.

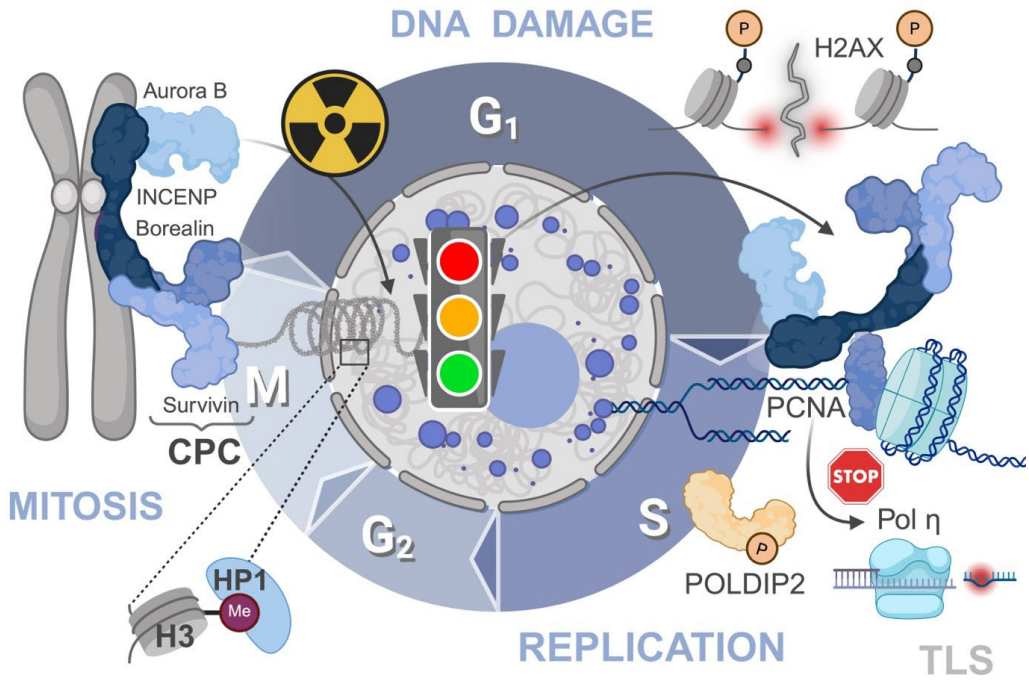

Figure 1. At the crossroads of mitosis and replication stress, Survivin and Aurora B - key components of the chromosomal passenger complex (CPC) - promote translesion synthesis (TLS) at stalled replication forks, presumably through a direct interaction of INCENP with PCNA. This emerging function expands the traditional mitotic role of the CPC and underscores its crucial involvement in maintaining genome stability and facilitating replication stress tolerance in cancer cells.

CPC: Beyond Mitosis and into the Nucleus

Survivin, the smallest member of the inhibitor of apoptosis (IAP) family, exerts its physiological functions primarily through protein-protein interactions, lacking intrinsic enzymatic activity [4]. In mitosis, Survivin anchors the CPC to centromeres by recognizing histone H3 phosphorylation [14,15]. The CPC itself functions as a stable, obligate heterotetramer of its four subunits essential for chromosome alignment, centromere integrity, and cytokinesis [3,14]. In contrast, emerging evidence indicates that the CPC does not maintain this canonical tetrameric configuration throughout the entire cell cycle. Instead, its individual subunits or partial assemblies are redistributed and repurposed during interphase in a context-dependent manner. For instance, low-level Aurora B kinase activity persists into G2 and early interphase and is often associated with chromatin-modifying or DNA damage response (DDR) complexes [16]. Similarly, both Survivin and Borealin are detectable in the interphase nucleus and have been observed to form foci independent of INCENP and classical mitotic substrates [1,6,17]. Most notably, our recent work demonstrates that INCENP interacts with PCNA via a functional PIP-box motif during S/G2, providing mechanistic support for subunit-specific repurposing at replication forks. While comprehensive proteomic or structural characterization of interphase CPC assemblies remains lacking, former findings support a model in which CPC components undergo dynamic reorganization and participate in non-canonical nuclear processes as subcomplexes or monomers, rather than persisting as a fixed mitotic complex.

Our own research was however the first to demonstrate that multiple CPC components form joint nuclear foci during interphase. We uniquely showed their co-localization within centromeric heterochromatin regions and their spatial association with replication zones. This novel finding highlights an underappreciated role of the CPC in the S-phase DNA damage response. The subnuclear redistribution of Survivin and other CPC members, independent of classical DNA damage markers such as γH2AX or 53BP1, reflects a functional shift from canonical checkpoint signaling toward active DNA damage tolerance mechanisms. Notably, Survivin foci co-localize with PCNA, the central replication clamp, particularly during late S-phase and G2, thus linking CPC activity directly to replication-associated processes. This observation complements the growing recognition that mitotic regulators participate in interphase nuclear functions including chromatin remodeling [18], centromeric transcription [19], and DNA damage surveillance [20], and *vice versa* [21]. Furthermore, Aurora B kinase activity persists beyond mitosis, modulating responses to replication-blocking lesions [22]. Taken together, our data challenge the traditional view of the CPC as a mitosis-exclusive entity. Instead, they position its components as dynamically reconfigurable modules that engage with replication and repair machinery during interphase to maintain genomic stability under stress.

Replication Stress and the CPC-PCNA Axis

A central discovery in the study is the interaction between CPC and PCNA, mediated specifically by a PCNA-interacting protein-(PIP-)box motif in INCENP [1]. This interaction serves as a functional bridge that enables CPC recruitment to replication forks and facilitates efficient fork progression under replicative stress. In contrast, there is no current evidence for a direct interaction between

PCNA and the other CPC subunits, Survivin or Borealin. Both lack canonical PCNA-binding motifs, such as the PIP-box or APIM, and no PCNA association was observed in assays excluding INCENP. Instead, Survivin and Borealin are likely recruited indirectly via the CPC scaffold organized by INCENP. Their localization to replication-associated foci and their functional impact on fork dynamics, such as reduced replication speed upon Survivin depletion, are thus likely dependent on CPC integrity rather than direct PCNA engagement. Supporting this, DNA fiber assays following Survivin knockdown revealed a significant reduction in replication fork speed, underscoring the role of the CPC in maintaining fork stability and genome maintenance during replicative stress. This discovery expands the role of the CPC from a mitotic master regulator to a guardian of replication fidelity. Notably, Survivin-depleted cells resort to mitotic DNA synthesis (MiDAS) to complete replication of under-replicated regions that escape resolution in S and G2 phase. MiDAS is a Rad52- and POLD3-dependent salvage pathway that initiates break-induced replication (BIR)-like DNA synthesis in early mitosis, particularly at common fragile sites (CFSs), where canonical origin firing is suppressed [23,24] can salvage replication, it is error-prone and often results in ultrafine anaphase bridges and structural chromosome aberrations, implicating it in genomic instability and cancer evolution [23,25,26]. The dependency on MiDAS in CPC-compromised cells highlights a critical non-mitotic role of the complex in replication completion and stress adaptation.

Indeed, genetic studies in *Schizosaccharomyces pombe* provide early evidence for a functional connection between CPC components and DNA replication. The fission yeast Survivin homolog Bir1p was shown to interact with Psf2p, a GINS complex (derived from the Japanese numbers 5-1-2-3/go-ichi-ni-san) subunit, a key component of the eukaryotic replisome essential for replication initiation. Overexpression of Psf2p suppressed a temperature-sensitive bir1-46 allele, while Psf2p loss disrupted Bir1p localization and caused chromosome missegregation. Similarly, the INCENP homolog Pic1p rescued bir1-46 defects and exhibited canonical CPC localization. These findings suggest that replication-linked CPC recruitment may be evolutionarily conserved and influenced by centromere replication timing [27]. Furthermore, studies on replication fork restart pathways suggest that proteins like FANCD2 and BRCA1 function in concert with PCNA and TLS effectors [28-30]. Given CPC's direct interaction with PCNA, this raises the possibility that it may interface with these broader genome integrity networks across cell cycle phases. Such potential integration points would position CPC not only as a structural modulator but as a regulatory node within replication stress resilience pathways, particularly in the context of cancer-specific replication dynamics. Importantly, recent studies have begun uncovering mechanistic parallels: for example, dysregulated Aurora B activity has been linked to DNA damage response signaling and replication stress resilience in cancer [16,31-33], and components of the CPC have been implicated in stabilizing stalled replication forks via interactions with repair factors. Moreover, global analyses of replication stress in cancer reinforce that tumor cells selectively exploit replication stress response pathways involving ATR/CHK1/WEE1 and nucleases like MUS81-contexts in which CPC activity may interface synergistically [32,34-36]. This positions our work as not only novel but timely in providing an explanatory mechanistic insight into how CPC subunits (via INCENP-PCNA) facilitate fork progression and prevent reliance on MiDAS under genotoxic stress.

Aurora B Phosphorylation of POLDIP2: A TLS Trigger

Perhaps the most striking mechanistic insight is the identification of POLDIP2 as a direct substrate of Aurora B kinase [1]. Through phosphorylation, Aurora B facilitates the release of DNA polymerase eta (Pol η), a TLS polymerase, enabling replication across damaged DNA. This places the CPC at the regulatory apex of damage bypass pathways. TLS is a double-edged sword: while it allows replication to continue in the face of DNA lesions, it is inherently error-prone and mutagenic [37]. The regulated activation of TLS by CPC components introduces a potential mechanism by which tumors balance survival with genomic plasticity, contributing to both resistance and clonal evolution [38]. Importantly, several cancers exploit TLS upregulation to evade genotoxic therapies [39], making Aurora B-mediated TLS regulation an attractive vulnerability. Modulating TLS fidelity via post-translational modifications is emerging as a pivotal mechanism for tumor cell adaptation [40].

Implications for Therapy and Translational Outlook

The connection between CPC activity and TLS has profound therapeutic implications. Survivin is already a validated target in oncology, with multiple strategies aiming at its inhibition, degradation (e.g., PROTACs), or immunologic targeting [41]. The novel findings linking Survivin and Aurora B to replication stress responses suggest that CPC-targeted interventions may not only impair mitosis but also explain the sensitization of tumor cells to replication stress-inducing therapies such as radiation or chemotherapeutics like cisplatin and gemcitabine [42,43]. Moreover, interfering with CPC-PCNA interactions or Aurora B-mediated phosphorylation of TLS regulators such as POLDIP2 [1] may offer a novel route to suppress error-prone DNA damage bypass. By limiting TLS activity, this strategy could reduce mutational burden and combat therapy resistance, as replication fork stability is increasingly recognized as a key determinant of chemoresistance [44]. Further investigation into synthetic lethality between CPC inhibition and TLS disruption could enhance precision oncology approaches [45]. Preclinical models may benefit from combining CPC modulators with agents targeting DNA polymerase switching [46] or PCNA-interacting peptide mimetics [47]. CPC-targeted interventions, particularly Aurora B kinase inhibitors (e.g., barasertib/AZD1152 [48], Hesperadin [49]) and Survivin degraders (e.g., YM155 [50], PROTACs [51]), may synergize with TLS modulators. For instance, combining Aurora B inhibitors with Rev1-Pol ζ interaction blockers such as JH-RE-06 may impair both damage bypass and replication fork recovery [52]. Similarly, targeting Survivin alongside PCNA-TLS interaction inhibitors (e.g., T2AA [52]) could enhance synthetic lethality in replication-stressed tumor contexts. These strategies warrant further preclinical investigation. Nevertheless, targeting CPC components may also affect normal proliferative tissues. Aurora B and Survivin are expressed in hematopoietic progenitors and gut epithelium [53-56], where CPC inhibition could induce on-target toxicities such as myelosuppression and mucositis [57,58]. To mitigate these risks, approaches such as tumor-selective delivery systems (e.g., nanoparticle carriers, tumor-specific PROTACs [51]), patient stratification based on replication stress biomarkers (e.g., RPA foci, γH2AX) [59,60], intermittent dosing regimens to allow recovery of normal proliferative compartments, and combination therapy with protective agents or use of lower-dose combinations with TLS inhibitors to enhance therapeutic index should be considered. These strategies aim to enhance the therapeutic index of CPC-targeted therapies.

Unanswered Questions and Limitations

While the current evidence supports a model in which the chromosomal passenger complex (CPC) engages with translesion synthesis (TLS) polymerases during replication stress, several key mechanistic questions remain. Most notably, how do individual CPC components interface with the TLS machinery in molecular terms? Survivin and Borealin lack canonical PCNA-interacting motifs such as PIP-boxes or AlkB homolog 2 PCNA interacting motif (APIM) sequences, raising the question of whether their recruitment to replication forks is indirect via INCENP, largely scaffold-mediated, or further regulated through post-translational modifications. Additionally, the spatial and temporal orchestration of CPC subunits with TLS polymerases remains largely undefined. Are these interactions constitutive or induced only upon replication fork stalling, and how are they integrated into broader cell cycle checkpoints and fork surveillance systems? For instance, it is currently unknown whether the CPC modulates polymerase switching, influences TLS fidelity, or functions as a signaling hub coordinating ATR/CHK1 activation, Fanconi anemia pathway engagement, or chromatin remodeling in S-phase. Our current model proposes that CPC binding to PCNA facilitates polymerase switching through two non-exclusive mechanisms: (1) allosteric modulation of PCNA, potentially displacing high-fidelity polymerases or inhibitors such as CAF-1 and enabling TLS polymerase access; and (2) phosphorylation-guided regulation via Aurora B kinase, which phosphorylates POLDIP2 and may similarly affect additional TLS-related substrates. Although TLS regulation by Aurora B beyond POLDIP2 remains largely unexplored, proteins such as REV1, Pol κ, and UBC13 contain putative Aurora B motifs, suggesting broader regulatory potential. Structural studies or proteomic approaches using proximity labelling, engineered PCNA/CPC variants or phosphoproteomics may be required to unravel the precise molecular grammar of this axis. In parallel, several technical and conceptual limitations constrain the interpretation of our current findings. The mechanistic insights, such as the INCENP-PCNA interaction and its effect on replication fork dynamics, are primarily based on correlative assays in transformed cell lines. Definitive causality and biochemical reconstitution of CPC function at stalled forks are still lacking. Moreover, the extent to which the CPC integrates with canonical fork protection networks involving ATR, BRCA1, FANCD2, or TLS effectors is inferred rather than directly demonstrated. Although MiDAS activation upon Survivin depletion supports a role for CPC in replication completion under stress, genome-wide mapping of under-replicated loci and chromosomal breakpoints (e.g., via Repli-seq or γH2AX profiling) is needed to contextualize its functional impact. Finally, *in vivo* validation in non-transformed or tumor models is required to confirm whether CPC- mediated fork protection is a universal mechanism or a cancer-specific adaptation to replication stress. These limitations delineate critical future directions toward defining the CPC's non-mitotic roles in genome stability maintenance.

Future Directions

Having outlined these unresolved mechanistic aspects, we now consider how they could inform future research and translational efforts. One critical avenue will be mapping the dynamics of CPC interactions with S-phase regulatory networks such as the ATR-CHK1 axis [61,62] or the Fanconi anemia pathway [63]. The CPC may act not only as a downstream responder but also as an upstream modulator of polymerase recruitment, replication fork stability, or DNA damage bypass fidelity. Survivin's dual role in cell survival and mitotic fidelity is well established, yet its contribution to replication fork protection and DNA damage tolerance remains underexplored - even though growing evidence hints towards engagement in DNA damage repair pathways [64,65]. Recent evidence further suggests that Survivin may stabilize multi-protein assemblies at stalled forks, potentially bridging TLS polymerases with chromatin remodelers like SMARCAD1 [66-68]. In parallel, Aurora B kinase has been shown to phosphorylate repair-associated proteins such as H2AX [69] and POLDIP2 [1], suggesting that its kinase activity could extend beyond mitosis to orchestrate fork-associated signaling events TLS polymerases such as Pol η, Pol κ, and Rev1 are tightly regulated by post-translational modifications (PTMs), including ubiquitination and phosphorylation, which influence their recruitment, processivity, and exchange dynamics [40,70]. The CPC may modulate these modifications indirectly, either by shaping local chromatin architecture or by compartmentalizing key signaling kinases during replication stress.

Clinically, replication stress represents a therapeutic vulnerability in many cancers, particularly those harbouring defects in ATR, BRCA1/2, or other DNA damage checkpoint genes [71,72]. Notably, Survivin and Aurora B are frequently overexpressed in solid tumours and hematologic malignancies, where they correlate with poor prognosis, increased mutational burden, and therapy resistance [73]. These findings raise the possibility of therapeutic combinations that jointly target CPC components and replication stress pathways, including ATR inhibitors, DNA-damaging agents, or TLS modulators such as T2AA and JH-RE-06 [74,75]. Furthermore, patient stratification based on Survivin/Aurora B levels, replication stress biomarkers (e.g., RPA foci, γH2AX), or TLS polymerase expression could enhance personalized treatment strategies [76]. Incorporating pharmacodynamic monitoring of TLS activity may also enable real-time prediction of therapeutic response and the emergence of resistance.

Conclusion

Chromosomal Passenger Complex (CPC) proteins, long celebrated for their roles in mitotic regulation, are now emerging as multifaceted players in genome surveillance and replication stress response. In our study, we reposition the CPC as a critical component of the DNA damage tolerance network, integrating mitotic regulators into the replication stress response (**Table 1**). These findings not only deepen our mechanistic understanding of Survivin and its partners but also open translational avenues in targeting the CPC beyond mitosis.

By participating in replication fork stability, translesion synthesis, and checkpoint orchestration, CPC components such as Survivin and Aurora B contribute not only to chromosomal segregation but also to the cellular capacity to tolerate genotoxic stress, potentially driving therapy resistance. In cancers characterized by high Survivin expression and replication stress, such as glioblastomas or triple-negative breast cancers, therapeutic modulation of CPC-mediated TLS may offer a two-pronged strategy to curb tumor growth and limit therapy resistance. These insights necessitate a conceptual shift: from viewing CPCs solely as mitotic guardians to recognizing them as dynamic regulators of genome integrity across cell cycle phases. Future research should clarify their mechanistic interplay

Table 1. Replication-specific functions of CPC components and supporting experimental evidence [1].

CPC Component	Replication-Specific Function	Key Experimental Evidence
INCENP	Recruits CPC to replication forks via PIP-box-mediated interaction with PCNA	Pulldown assays, site-directed mutagenesis of PIP-box, co-coimmunoprecipitation with PCNA
Survivin	Stabilizes stalled replication forks; limits MiDAS activation; forms foci at replication zones	DNA fibre assays showing reduced fork speed upon knockdown; increased EdU incorporation during mitosis
Aurora B	Triggers translesion synthesis (TLS) by phosphorylating POLDIP2, promoting Pol η recruitment	*In vitro* kinase assays; mutational analysis of POLDIP2 phosphorylation sites; Pol η foci quantification under replication stress
Borealin	Maintains CPC integrity; facilitates subnuclear CPC localization to replication-associated foci	Co-localization studies with PCNA; dependency on full CPC for fork protection (indirect evidence)

*Function inferred based on CPC disassembly phenotype and Survivin/Borealin co-localization with PCNA.

with replication machinery, explore context-specific vulnerabilities in tumors, and assess whether CPC inhibitors can be rationally combined with DNA damage response (DDR)-targeting agents. Together, these efforts may unlock new avenues for precision oncology.

Conflict of Interest

The authors declare no competing financial interests. They hold no patents or patent applications related to therapeutic targeting of the chromosomal passenger complex (CPC) or translesion synthesis (TLS) pathways.

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