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SURVIVIN - THE *INCONVENIENT* IAP

Dario C. Altieri

Tumor Microenvironment and Metastasis Program, The Wistar Institute, Philadelphia, PA 19104

Abstract

Although technically a member of the Inhibitor of Apoptosis (IAP) gene family, survivin has consistently defied assumptions, refuted predictions and challenged paradigms. Despite its more than 5,500 citations currently in Medline, the biology of survivin has remained fascinatingly complex, its exploitation in human disease, most notably cancer, tantalizing, and its regulation of cellular homeostasis unexpectedly far-reaching. An *inconvenient* outsider that resists schemes and dogmas, survivin continues to hold great promise to unlock fundamental circuitries of cellular functions in health and disease.

Keywords

Survivin; IAP; cell division; apoptosis; cancer; spindle assembly; mitotic catastrophe

INTRODUCTION

Inhibitor-of-Apoptosis (IAP) proteins are multifunctional molecules structurally identified by the presence of a ~70 amino acid Baculovirus IAP Repeat (BIR), a zinc finger fold coordinated by histidine and cysteine residues present at least once in each family member [1]. The eight IAP family members in the human genome contain one to three BIRs, typically arranged in the protein's amino-terminus. Additional protein domains found in IAPs include a carboxyl-terminus RING, which functions as an E3 ubiquitin ligase, a ubiquitin-associated domain implicated in binding to ubiquitinated proteins, and a caspase-recruitment domain (CARD, in c-IAP1 and c-IAP2), of less clear function.

At 142 amino acids, survivin [2-6] is the smallest member of the IAP family [1], containing a single BIR and a carboxyl-terminus α-helix, but no other identifiable protein domain (Figure 1). X-ray crystallography data have shown that survivin forms a stable homodimer in solution [7], but definitive evidence that this structure is actually required for function(s),

Correspondence: Dario C. Altieri, M.D., The Wistar Institute, 3601 Spruce Street, Philadelphia, PA 19104, USA, Tel. (215) 495-6970; FAX (215) 495-6863; daltieri@wistar.org.

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in vivo, is still lacking. To the contrary, there is evidence that some key protein-protein interactions, for instance the recognition of the chromosomal passenger protein, Borealin [8, 9], as well as mechanisms of subcellular localization [9], in particular nucleo-cytoplasmic trafficking [10], or apoptosis inhibition [11], require a monomeric survivin protein.

Located at the tip of chromosome 17 (17q25) in the human genome, a TATA-less *survivin* locus has been the subject of considerable studies [12]. This is more than an exercise since agents that shut down *survivin* gene expression have successfully entered the clinic as anticancer strategies [13]. Transcription of the *survivin* gene relies on three essential Sp1 sites [14], and canonical CDE/CHR boxes that impart sharp cell cycle periodicity of *survivin* gene expression at mitosis [15]. A CG-rich CpG island also in the proximal *survivin* promoter has been investigated for potential epigenetic modifications, but clear-cut implications for this mechanism are still lacking [12]. The regulation of the *survivin* locus is highly complex, and a plethora of transcription factors, many of which are intercalated in cell proliferation, cell survival or developmental pathways upregulate *survivin* gene expression [12]. An equally long list of molecules has been associated with actively repressing *survivin* gene transcription, in particular, p53 [16, 17], Pten [18], and BRCA1-SIRT1 [19]. This suggests that transcription of the *survivin* gene is a finely tuned process, carefully balanced between activators and inhibitors, and with potential unique cell type-specificities and developmental regulation. The fact that many of these transcriptional inhibitors are *bona fide* tumor suppressors, mutated or otherwise lost in cancer, suggests that repression of *survivin* gene expression is an important barrier against malignant transformation, and, by extension, that successful tumor suppression depends on ablation of this pathway [20].

A mature survivin protein is extensively post-translationally modified (Figure 1), and phosphorylation plays an important role in survivin functions [21]. Best studied are the mitotic kinases Cdk1 [22-24], Aurora B [25, 26], casein kinase [27], and Polo-like kinase 1 [27] that phosphorylate survivin at different residues, regulating protein stability, subcellular localization, association with protein partners, various aspects of mitosis, and apoptosis inhibition. There may be potentially important roles for other kinases, for instance PKA [28] regulation of survivin cytoprotection, and even more phosphorylation events are predicted by consensus algorithms [21] (Figure 1). An additional post-translational modification of survivin involves acetylation of many lysine residues predominantly clustered in the -COOH terminus of the protein (Figure 1). Mostly mediated by Creb-binding protein (CBP) [21], cycles of survivin acetylation and deacetylation have been implicated in nucleo-cytoplasmic shuttling and a potential new mechanism of downstream regulation of gene expression [29] (Figure 1).

NEW TRICKS FOR *OLD SURVIVIN*: CELL DIVISION AND CELL SURVIVAL

That survivin is essential for cell division is established, inferred from its sharp cell cycle-dependent expression at G2/M, localization to various aspects of the mitotic apparatus and the plethora of mitotic defects ensuing from targeting survivin by many approaches and in disparate cell types [30, 31]. The phenotype of survivin-knockout embryos, which do not remain viable past blastocyst state [32], the extensive mitotic defects in adult tissues where

survivin has been conditionally ablated [33, 34], and the cell division defects caused by loss of survivin-like molecules in *C.elegans* [35, 36], and yeast [37], all support a model where a survivin pathway is indispensable at cell division.

Together with Aurora B, Borealin and INCENP, survivin is the fourth member of the chromosomal passenger complex (CPC) [38], a regulator of chromosome-microtubule attachment, spindle assembly checkpoint, and cytokinesis at cell division (Figure 2). Structurally, survivin recognizes the CPC through its dimerization domain, suggesting that it functions as a monomer in the complex [9]. Functionally, the CPC ensures a fidelity checkpoint that destabilizes errors in microtubule-kinetochore attachment via Aurora B-dependent phosphorylation of target substrates [38]. It derives from this model that a precise but dynamic localization of Aurora B to the inner centromere is paramount to ensure CPC checkpoint function. This centromere targeting activity is provided by survivin (Figure 2). It was first suggested that this could be accomplished by reversible mono-ubiquitylation of survivin. In this model, Ufd1 (ubiquitin fusion degradation protein 1) ubiquitylation of survivin promoted CPC centromere binding, whereas deubiquitylation by hFAM mediated its dissociation [39].

More recent studies, however, pointed to a very different scenario, in which survivin “reads” a mitotic histone mark introduced by Haspin phosphorylation of Thr3 on histone 3 (H3) [40-42]. By binding to phosphorylated H3, survivin then localizes the entire CPC to inner centromeres, precisely where is needed to correct errors in kinetochore-microtubule attachment [40-42]. Interference with the survivin-H3 recognition mislocalizes Aurora B, and causes many, but not all of the mitotic defects associated with survivin loss [40-42].

Although attractive, there may be more layers of complexity to this model. First, there is an additional mitotic histone mark created by Bub1 phosphorylation of histone H2A on Thr120 that may also promote CPC recruitment to centromeres through the adaptor protein Shugoshin (Sgo2) [40], itself another survivin-interacting molecule [43]. Second, at least in budding yeast, CPC targeting by survivin does not seem required for chromosomal bi-orientation, a function that may be accomplished just by clustering of Aurora B on chromatin or microtubules [44]. And, finally, the binding requirements of survivin to H3 may be exceedingly intricate, in vivo. In fact, the survivin region centered on Asp70 and Asp71 [42], which recognizes phosphorylated H3 [45, 46], is also the binding interface for the pro-apoptotic mediator, Smac [46]. It is still unclear how much of the anti-apoptotic function of survivin depends on sequestering Smac away from the caspase inhibitor, XIAP [1]. However, this mechanism has been repeatedly proposed [47], either involving monomeric survivin [11], thus the same structure recruited to the CPC [9], or mitochondria-localized survivin [48]. There may be differences in the affinity with which survivin binds H3 *versus* Smac [46]. However, this is controversial, as the dissociation constants for the survivin-Smac complex obtained from isothermal calorimetry [46] or NMR [49] do not agree. And to add another layer of complexity, Glu65 in survivin, which has also been implicated in binding phosphorylated H3 [46], is essential for the recognition of yet another survivin partner at mitosis, the GTPase Ran [50]. Functionally, this protein complex is important to deliver the Ran effector, TPX2 to microtubules, thus supporting bipolar spindle assembly [50], and, potentially, a scaffold function for CPC activation [51].

A CPC BAND OR A SURVIVIN ORCHESTRA?

Although dubbed as controversial [30], a potential mitotic role of survivin in spindle assembly has been proposed [31]. This was linked to a pool of survivin localized to centrosomes and microtubules [52], and which regulates bipolar spindle assembly [53] via active repression of microtubule dynamics [54]. This model is consistent with a large body of literature, where loss of survivin has been invariably associated with a plethora of microtubule defects, including centrosomal abnormalities, formation of multipolar spindles, misaligned spindles and, ultimately, polyploidy [4, 55] (Figure 2). Such “microtubule” phenotype is also seen in adult tissues after conditional ablation of survivin, in vivo [56, 57].

Fresh evidence has now uncovered a new pathway for how survivin may regulate microtubule integrity and cell viability at cell division (Figure 2). This involved a centrosomal localization of CUL7. Together with OBSL1 and CCDC8, CUL7 is a component of the so-called 3M complex [58], molecules that are mutated in rare growth retardation syndromes [59]. It turns out that centrosomal CUL7 is essential for microtubule dynamics, as its depletion causes a microtubule phenotype not dissimilar to what observed after survivin loss, with prometaphase arrest, tetraploidy, and, ultimately, death of cells attempting to traverse mitosis [58]. In further dissecting the pathway, it was shown that CUL7 inhibits the E3 ligase activity of its associated molecule, CUL9 [60], and this was functionally important because depletion of CUL9 rescued the microtubule phenotype induced by CUL7 silencing [61]. The third component of this response, and the actual effector of microtubule dynamics, was identified as survivin, in agreement with earlier data [54], which is destroyed by CUL9-mediated ubiquitylation [61]. Accordingly, loss of CUL9, dubbed as a tumor suppressor based on the cancer-prone phenotype of knockout mice, was sufficient to increase survivin levels, in vivo [61], and, conversely, re-expression of survivin in CUL7-silenced cells was sufficient not only to restore microtubule dynamics but also to rescue cell viability from apoptosis at cell division [61] (Figure 2).

That in addition to controlling CPC targeting (via H3 binding) and now microtubule/spindle dynamics (via TPX2 delivery and 3M complex regulation), survivin may have a third function at mitosis in countering cell death has long been proposed [15]. This idea has been vigorously challenged, and, at times, openly derided [62]. And yet, it is well known that when cells approach mitosis abnormally, whether because of a damaged mitotic apparatus, or under stress conditions, as the norm for tumor cells, they activate a dual necrotic and apoptotic suicidal pathway loosely defined as *mitotic catastrophe* [63]. This is likely a fail-safe mechanism to prevent the accumulation of an aneuploidy progeny, and survivin has long been recognized as an important antagonist of this process [3]. The reverse may also be true, and silencing of survivin has been associated with mitotic catastrophe [64] (Figure 2). Mechanistically, it may not be unexpected that survivin inhibits caspase-9 in concert with XIAP [28], and antagonizes p53-dependent cell death [65], two effector pathways of mitotic catastrophe [63].

Recent data further support this model, suggesting a unifying context for an integrated, tripartite role of survivin at mitosis. It turns out that stressed tumor cells exposed to low level, non-cytotoxic DNA damage recruit the essential autophagy regulator, ATG5 to the

nucleus [66]. Here, ATG5 forms a complex with nuclear survivin, and sequesters it, triggering hallmarks of mitotic catastrophe, including multipolar spindles, missegregated chromosomes, and cell death [66]. It is intriguing that mislocalization of the CPC, potentially contributed by ATG5 sequestration of survivin in the nucleus [66], has also been implicated in the activation of mitotic catastrophe [63], and this is the type of cell death seen with small molecule CPC antagonists pursued as anticancer agents [67] (Figure 2).

Taken together, these results point to a complex model for a simultaneous tripartite role of survivin at cell division, overseeing faithful chromosomal segregation by CPC targeting (i), bipolar spindle formation via centrosomal regulation of microtubule dynamics (ii), and inhibition of mitotic catastrophe through suppression of caspase 9 and sequestration of Smac (iii) (Figure 2). Whether this integrated survivin pathway is uniquely exploited in tumor cells, compared to the normal tissues, remains to be demonstrated. It could be argued that aneuploid and genetically deranged tumor cells, constantly exposed to disparate stress stimuli in their microenvironment, may become especially dependent or“ addicted” to the anti-apoptotic function of survivin at mitosis, a prediction consistent with the phenotype of transgenic mouse models [68]. On the other hand, survivin is also essential roles to maintain the viability of specialized compartments of normal cells (see below), potentially through the same integrated, tripartite pathway (Figure 2).

NEW TRICKS FOR *NEW SURVIVIN*

For its role at the crossroads of multiple signaling pathways [4], it is not surprising that fresh experimental evidence continues to uncover novel roles for survivin in cellular homeostasis. One of these emerging trends involves an essential developmental role in stem cell maintenance.

STEM CELL MAINTENANCE

Stemming from its abundant expression during embryonic and fetal development [69], and the panoply of developmental signaling pathways that target survivin, in particular Wnt/β-catenin [70], Hedgehog[71], Hippo [72], and Notch [73], it may not be surprising that human [74, 75], and mouse [76] embryonic stem cells contain high levels of survivin. Although the biochemical wiring of this pathway is not completely defined, survivin is clearly indispensable for the integrity of stem/progenitor cells. This has been demonstrated for pluripotent stem cells, where expression and subcellular localization of survivin and its splice variants [77] may be regulated by microRNAs [78], as well as neural [79], hematopoietic [80, 81], epidermal [82], and intestinal [83] stem cells. Other data point to a pivotal role of survivin in stem cell-driven malignancy, initiating hematopoietic transformation in transgenic mice [84], conferring a drug-resistant phenotype in acute lymphoblastic leukemia [85], cooperating with Myc-driven signaling in mesenchymal transformation [86], and enabling survival of stem/progenitor-like cells during gliomagenesis [87]. Consistent with these observations, survivin is a reliable indicator of poor prognosis in stem cell-derived tumors, including acute leukemia [88], and gliomas [89]. Based on these results, targeting survivin may provide a viable strategy to deplete a potential cancer stem cell reservoir, often linked to disease recurrence and drug resistance.

Accordingly, interference with survivin expression or function inhibited pluripotent stem cell-derived teratomas [90], eradicated acute leukemia [85], or suppressed gliomagenesis using small molecule [87] or oncolytic viral [91] approaches.

More work is required to dissect how survivin maintains a stem cell compartment. However, stem cells seem to need survivin predominantly, if not exclusively, for protection against apoptosis [84, 87, 90, 92]. Second, there may be an unexpected *upstream* role of survivin in controlling pluripotency at the level of gene expression. Although this is a novel field of investigation, it is intriguing that survivin expression in $CD34^{+}38^{-}$ myeloblastic stem cells is associated with extensive transcriptional reprogramming and upregulation of regulators of cell proliferation, PI3K, and cell migration/invasion [88]. Conversely, deletion of survivin in hematopoietic stem cells disrupts an Evi-1-dependent transcriptional program, resulting in loss of downstream target genes, Gata2, Pbx1 and Sall2 [81]. A potential upstream role of survivin in controlling gene expression, including in stem cells, clearly remains to be fully elucidated. However, earlier studies have shown that modulation of survivin acetylation by CBP suppresses STAT3-dependent gene transcription [93], and transgenic expression of survivin in the urothelium was sufficient to produce a transcriptional gene signature of increased inflammation and heightened cell motility [94].

CELL MOTILITY AND METASTASIS

A fairly unanimous consensus is that expression of survivin in virtually every human tumor is associated with poor prognosis [95]. There could be various mechanisms for this correlation, and some have been documented, including inhibition of apoptosis, including mitotic catastrophe [96], enhanced drug resistance [6], and maintenance of cancer stem cells [88]. However, the main cause of cancer death comes from disease dissemination to distant organs, i.e. metastasis. Retrospective studies and meta-analyses have consistently shown that survivin expression correlates with metastatic disease in breast [97], colorectal [98], gastric [99], thyroid [100], esophageal [101], and non-small cell lung [102] cancer. Even assuming that this is a direct effect, the mechanistic underpinning of how survivin may influence metastatic competency is not firmly established. In fact, a role of IAPs in general in cell motility has been intensely debated [103]. Although these molecules may inhibit cell migration under certain conditions, potentially via ubiquitination of Rac1 [104], or regulation of RAF destruction [105], most data suggest that IAPs [106, 107] function as potentially evolutionary-conserved [108] enablers of cell motility [103]. Data on how survivin may participate in this response are still scant, but emerging evidence also points to survivin as an important mediator of tumor cell motility and invasion, potentially affecting metastatic competency, in vivo [109].

A survivin pathway in controlling cell motility may be entirely separate from other functions in this molecule in apoptosis inhibition and mitosis. Instead, experimental data have mechanistically linked survivin expression in tumors to increased production of matrix metalloproteinase(s) for digestion of the extracellular matrix [110], upregulation of $\alpha 5$ integrin combined with Akt activation [111, 112], or NFκB-dependent paracrine release of fibronectin by a survivin-XIAP complex, which resulted in a highly metastatic phenotype, in vivo [113]. Intriguingly, a new function of survivin in regulating cell motility may not be

restricted to tumors. Accordingly, silencing of survivin in vascular smooth muscle cells did not affect cell proliferation or cell viability, but caused disorganized actin filaments, changes in cell shape, and impaired chemotaxis [114].

CONCLUDING REMARKS AND THE NEXT SURVIVIN WAVE(S)

If nothing else, the remarks in this contribution should highlight the humbling complexity of survivin biology. Despite considerable efforts over almost two decades, the last chapter of how survivin works in normal or tumor cells has not yet been written. New, unexpected, and sometimes bewildering findings continuously emerging in the literature make us rethink what we really know about this unique signaling network in health and disease. Attempts to (over)simplify the biology of survivin, discount its diversity and artificially categorize its consequences have created biased perceptions. Just because survivin-like molecules in lower organisms do not affect cell death, this does not mean that survivin is not an apoptosis inhibitor, but simply that it targets a cell death pathway not operative in those models. And just because cell division is a carefully orchestrated cascade, it does not mean that it is error-free, especially under stress, and that does not couple to a fail-safe mechanism of mitotic cell death, of which survivin is an integral part.

Perhaps an unwelcomed consequence of these preconceived ideas has been the paucity of therapeutic strategies to disable the survivin pathway in cancer. This is a curious deficiency, especially when one considers the urgency for new, more effective treatments in oncology, the undisputable importance of survivin as a disease driver in virtually every human tumor, and our better understanding of some of its functions. Although the lack of progress in this area may reflect a broader risk-avulsion and redundancy of current oncology drug discovery efforts, there is confidence that the pace of survivin discovery will continue unabated in the years to come, refining its biochemical pathways, uncovering new functions, and opening innovative prospects for personalized therapeutics.

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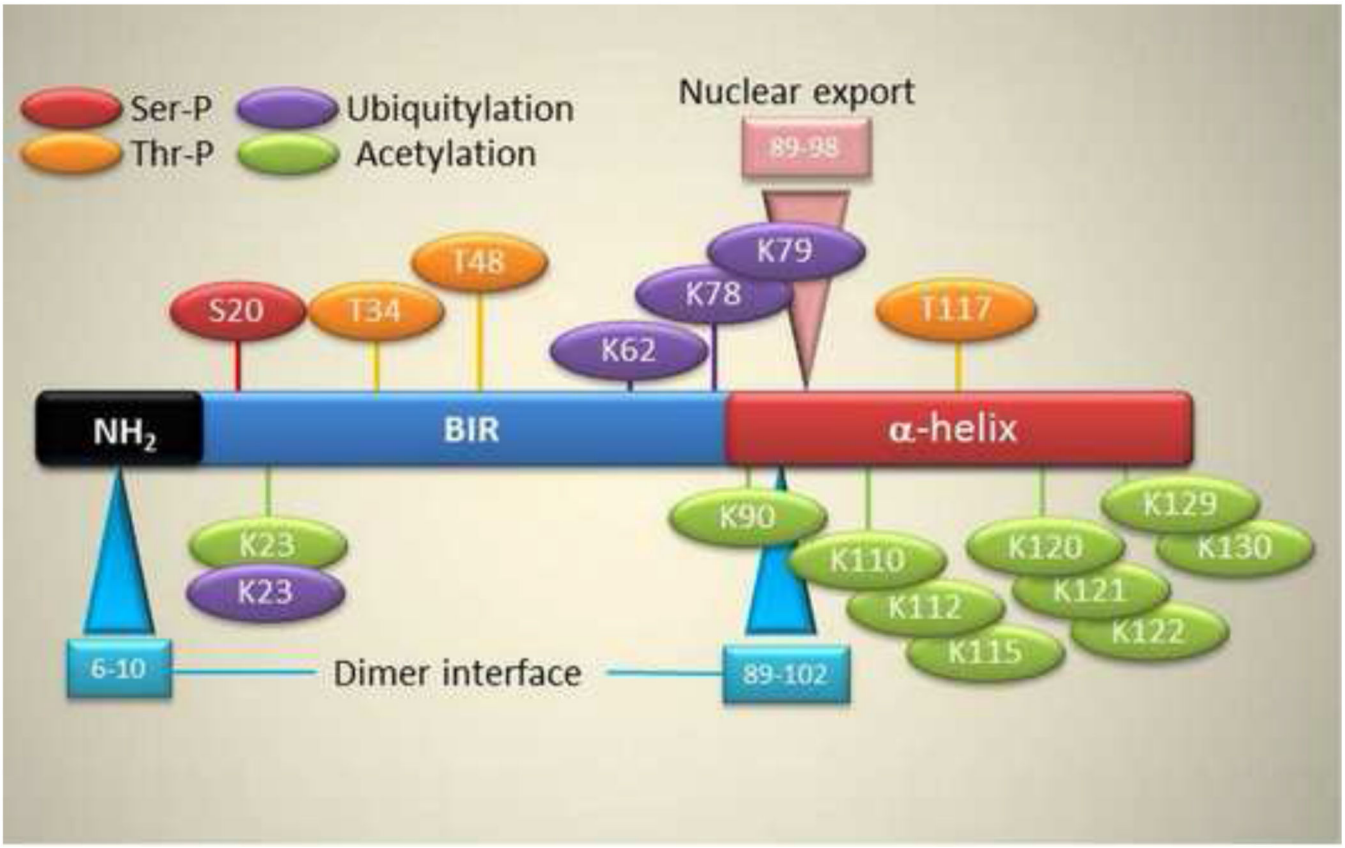

Figure 1. Post-translational modifications in survivin

Amino acids undergoing Ser/Thr phosphorylation, acetylation or ubiquitylation are indicated. The positions of the proposed dimer interface and nuclear export sequence (NES) are shown.

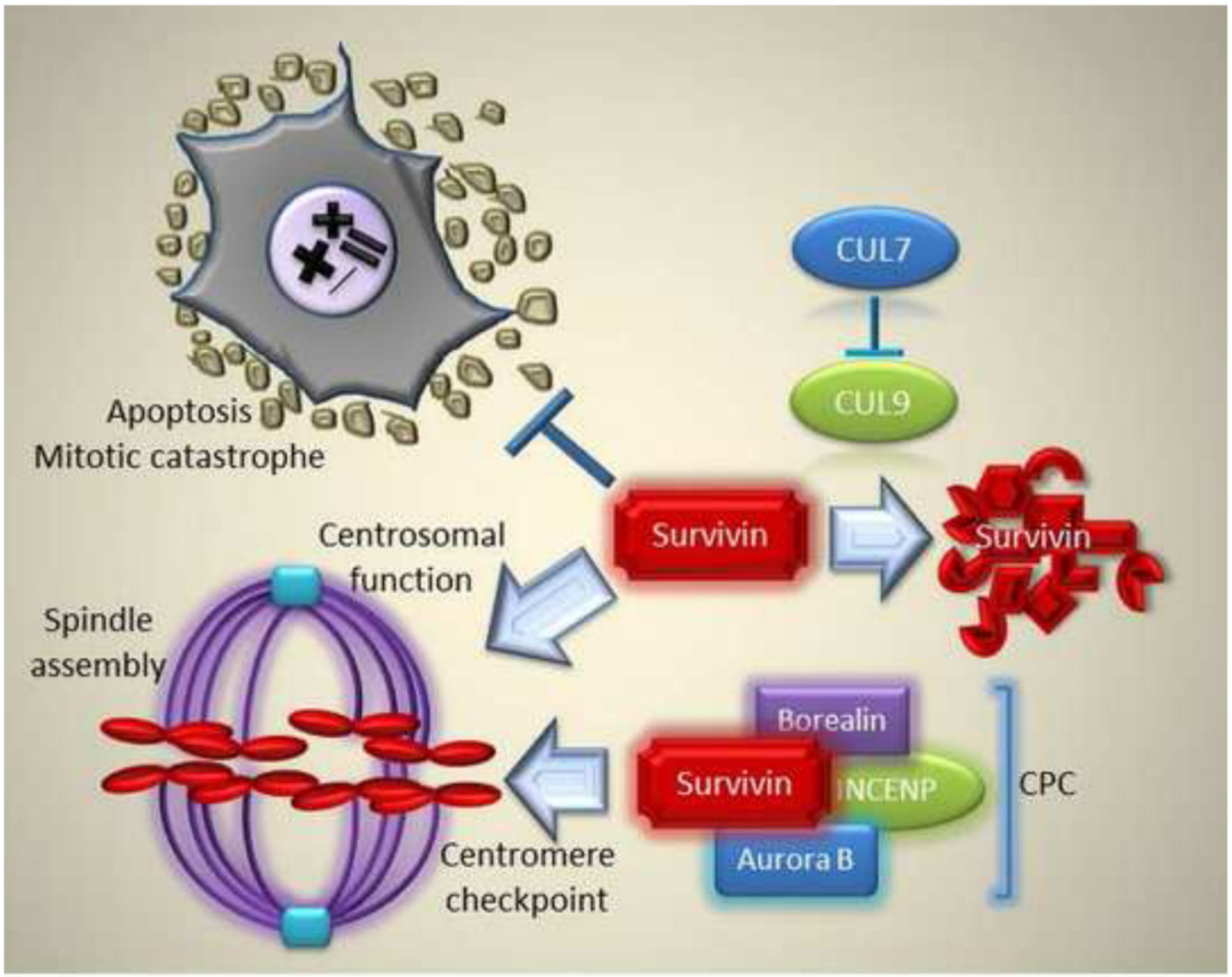

Figure 2. Tripartite role of survivin at mitosis

A proposed role of survivin in inhibiting apoptosis/mitotic catastrophe (i), regulating spindle assembly (ii) and CPC targeting for a centromere checkpoint (iii) are indicated. See text for additional details.