

The Critical Role of Survivin as an Anti-Apoptotic Biomarker and Therapeutic Target in cancer

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ABSTRACT: Apoptosis is a finely regulated physiological process responsible for keeping tissue homeostasis by removing damaged, abnormal, or unnecessary cells. Disruption of apoptotic pathways is a hallmark of cancer, enabling malignant cells to evade programmed cell death and continue their uncontrolled proliferation. Survivin, the minimum member of the inactivating protein (IAP) inhibitor family, has emerged as a key regulator of both apoptosis inhibition and cell cycle progression. Because of its marked overexpression in a wide range of human malignancies and its limited expression in most normal adult tissues, Survivin has garnered significant attention as a potential diagnostic, prognostic, and therapeutic biomarker. This review aims to summarize and evaluate current evidence regarding the biological functions of Survivin, its role in cancer development and progression, and its clinical significance in predicting treatment response and patient outcomes. Relevant scientific literature published in peer-reviewed journals was collected and analyzed using major biomedical databases, including PubMed, Scopus, and Web of Science. Studies concerning the expression of the servifin protein, its molecular mechanisms, its predictive value, and its therapeutic targeting in various types of cancer were reviewed and summarized. The reviewed evidence indicates that elevated survivin protein expression is strongly associated with tumor aggressiveness, resistance to chemotherapy and radiotherapy, poor disease prognosis, and reduced survival rates in multiple cancer types. Furthermore, its selective expression pattern and multifunctional role make survivin an gorgeous target for developing novel cancer control strategies. The present review highlights the growing importance of incorporating survivin protein assessment into cancer research and clinical practice and supports further research into survivin-targeting approaches to improve cancer prognosis, prognosis, and treatment outcomes.



Keywords: Survinin, Apoptosis, cell line, cancer

1. INTRODUCTION

Survivin, a participant of the programmed cell death protein inhibitor group encoded by BIRC5 gene, is a 142-amino-acid polypeptide which theatres a pivotal role in cancer biology. Although its expression is essential during early embryonic development, it is virtually invisible in most differentiated adult tissues, with its appearance restricted for certain stem and progenitor cells. But, Survivin is markedly overexpressed in the mainstream of human malignancies, where it significantly contributes to tumor progression and treatment resistance [1, 2]. Survivin survives in 3 homologous isoforms as a result of alternative overlapping transcription processes. Survivin-Ex-3 is found primarily in the nucleus, while full-length survivin and survivin-2B are found mainly in the cytoplasm [3]. These immunohistochemically distinct groups may explain the variation in the ability of the servifin protein to perform its roles as a Mitotic Spindle-Associated Protein also a kinetocorre-Associated Chromosomal protein, Figure 1.

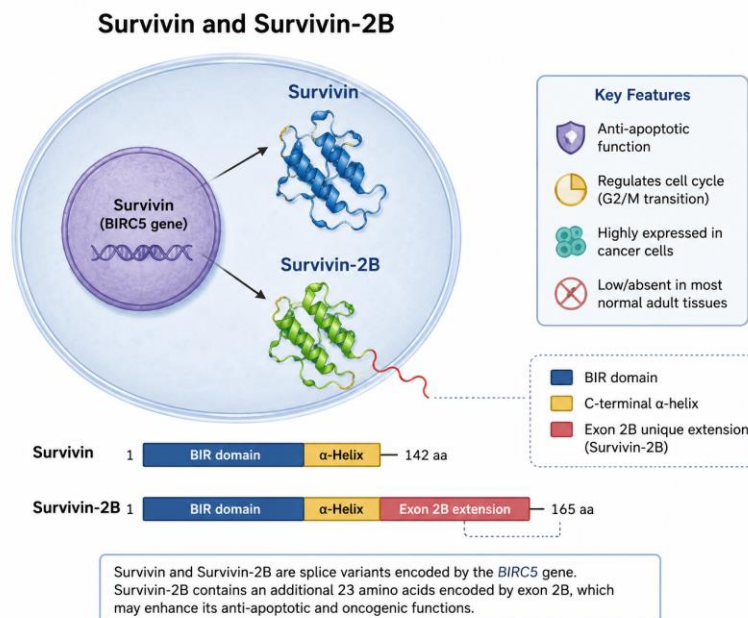


FIGURE 1. - Structural and Functional Comparison of Survivin and Survivin-2B Isoforms

2. SURVIVIN STRUCTURE

The servifin protein and its variant, servifin-2B, are derived from the BIRC5 gene. Belonging to a family of inhibitors of IAPs, servifin productions a pivotal role in inhibiting programmed cell death [apoptosis] and regulating the cell cycle, particularly throughout the G 2- M transition [4]. Servifin protein consists of a BIR domain [viral IAP repeat], responsible for anti-apoptotic activity, and a carbon-terminal alpha-helix region essential for protein stability and cellular function. The servifin-2B variant contains an additional extension resulting from the insertion of exon 2B during alternative splicing, leading to structural and functional differences compared to the native protein. Servifin exhibits high expression levels in many human tumors, while its expression is low or absent in most normal adult tissues [5]. Therefore, it is a crucial biomarker for diagnosis and prognosis, allso a promising therapeutic target in cancer research. Analyzing its various variants, including Survivin-2B, helps in understanding the molecular mechanisms involved in tumor development and response to treatment,see Figure 1. Figure 2. Replication occurs through interactions involving parts of the N - Terminal Region as well as the linker connecting the B-I-R domain to the C-terminal alpha Helix, giving this protein its characteristic bow tie shape [6].

Post-translational regulation plays a significant role in survivin's functional dynamics. For instance, ubiquitination of lysine remains indoors the BIR domain has been related to its centromeric localization [7].

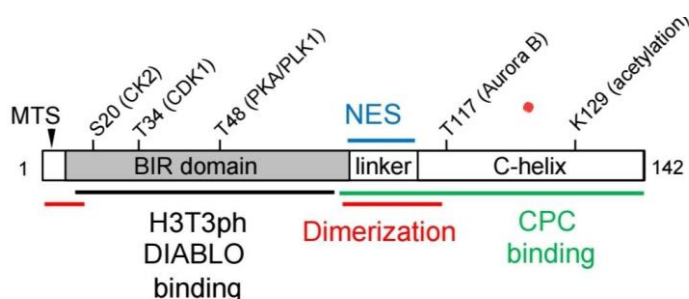


FIGURE 2. - Survivin structure [8]

Survivin also participates in forming a heterotrimeric complex with Borealin and I N C E NP, in which its C-terminal coiled-coil α -helix assembles into a three-helical bundle in a strict 1:1:1 stoichiometry. This organization is necessary in order to be able to target a complex appropriately to central spindle and midbody during cell division. Moreover, structural analysis has shown that BIR domain of survivin harbors certain binding determinants to N-terminal Tail of Histone H 3 upon phosphorylation of threonine 3 (H3.T3.ph), which is involved in chromosomal control [9].

Several phosphorylation steps regulate cellular functions of survivin. Phosphorylation of CDK1 at threonine 34 is important in its antipoptotic effect, and PKA phosphorylation of serine 20 facilitates cell survival through increased association with XIAP. Aurora B kinase alters threonine 117, which affects centromeric localization and mitotic activities of survivin to the disadvantage. The CK2 phosphorylates threonine 48 in BIR domain, which is necessary in mitotic regulation & apoptotic inhibition. Besides, phosphorylation of PLK1 at threonine 20 helps in proper chromosome alignment during mitosis [10].

In addition to phosphorylation, surviving protein undergoes various other post-translational changes. The lysine 129 acetylation interferes with homodimer formation, Crm1 binding, and nuclear export. Besides, K48- and K63-linked ubiquitination in the course of mitosis regulate centromeric recruitment of survivin and provides a normal mitotic progression [11]. These morphological and regulatory studies underscore the multifaceted roles of Survivin in cell division and regulation of apoptosis [12].

3. SURVIVIN FUNCTION

Survivin is an indispensable regulator of cell division, and its loss leads to catastrophic cell division failure and cell death. This protein plays a pivotal role in the Chromosomal Passenger Complex [CPC], a multiprotein complex that too includes Aurora B kinase, INCENP, TDP60, and Borealin. Survivin contains a viral phosphatase uptake inhibitor [BIR] repeat domain that specifically binds to the phosphorylated form of histone H3 at threonine 3, that is phosphorylated via histone H3-associated kinase, Haspin [13]. This phosphorylation is necessary for the polarization of other CPC proteins to the inner centromere region, Figure 3.

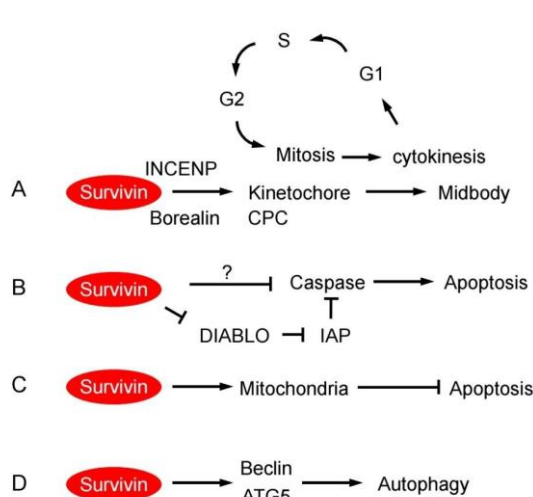


FIGURE 3. - Survivin function

The interaction of the survivin protein with histone H3t3ph leads to aurora kinase-B misalignment, causing chromosome misalignment and errors during mitosis. At the onset of mitosis, survivin protein assembles at the centromeres. This process requires the intrinsic Centromere Protein and its interaction with aurora kinase-B also other members of the central centromere complex [CPC] to help regulate spindle assembly and correct centromere positioning [14]. Therefore, the crucial role of survivin in the assembly of the central centromere complex and the progression of mitosis—mediated by its BIR domain—represents a promising target for developing anticancer therapies that specifically target survivin [15].

During anaphase, the centromere loses survivin protein, which then migrates to the midspindle region, ultimately concentrating at the centromeres of the centromere. Although the precise molecular pathway for this repositioning has not yet been fully studied, it has been shown that the survivin protein interacts with non-muscle myosin II [16]. In this regard, it is hypothesized that the centrosome-localized survivin protein is involved in the construction of the contractile Ring throughout cell division [17].

Aneuploidy is often related to an abnormal survivin activity, once again proving the necessity of survivin in normal checkpoint regulation of mitosis, & cytokinesis. Notably, p53-loss seems to be pre-condition cells to re-enter the cell cycle after survivin-depletion, which indicates a complicated interdependence between survivin-dependent mitotic regulation and p53-dependent cell cycle control [18].

4. SURVIVIN AND CANCER

Increased survivin has been invariably linked to bad prognosis, metastasis and presence of circulating tumor cells in different cancers [19]. Functionally survivin aids the evasion of cell cycle checkpoints, aneuploid cell survival, & resistance to radiation therapy. It is needed in the immune system in B-cell expansion, T-cell development, & homeostasis, which has been shown by research on conditional knockout mouse models. It also plays important roles in the proliferation of certain cell types including pancreatic b-cell and intestinal epithelial progenitors, as well as roles in the early brain development [20].

The expression of survivin genes is precisely regulated at the molecular level by a TATA-free promoter containing Sp1 sites saturated with CpG islands that undergo epigenetic changes, and CDE/CHR elements that provide cell cycle-dependent expression [21]. Various cancer pathways frequently involved in upregulating survivin expression include EGFR, HER2/neu, PI3K, MAPK, NF- κ B, and mTOR. Additionally, the Wnt / β -Catenin, Notch, Y-A-P, as well as Hedgehog Signaling Pathways play a role in its transcriptional activation [22]. Conversely, survivin expression is inhibited by major tumor suppressors that are often mutated or inactivated in cancer, including TP53, PTEN, Rb, and BRCA1. All these complex regulatory functions and functional roles underlie survivin as a bio-marker plus therapeutic target in cancer studies [23].

Several variants of the survivin gene that undergo alternative splicing have been identified, such as survivin-DEx3, survivin-2a, survivin-3a, survivin-2B, and survivin-3B. These splicing processes produce protein isoforms lacking certain structural components, either the complete BIR domain, the nuclear export signal (NES), or the C-terminal coiled helix domain, resulting in variations in their intracellular locations [24]. For example, survivin-DEx3 lacks an NES signal but possesses a characteristic dual nuclear localization (NLS) signal, allowing it to be localized to the nucleus [25]. In contrast, survivin-2B contains an in-frame insertion of a cryptic exon that weakens the BIR subunit, resulting in a protein that is primarily cytoplasmic. Interestingly, survivin-DEx3 and survivin-2B have low interaction with the chromosomal passenger complex (CPC) and cannot completely replace the loss of the wild-type survivin [26].

These intertwining alternatives were associated with a sure clinical outcome as well as malignant phenotype. Nevertheless, the current research has mostly targeted the identification of their RNA transcripts, and little is achieved in synthesizing isoform-selective antibodies [27]. Consequently, presence and biological importance of these protein variants on the endogenous level are not sufficiently proven in cell lines and in clinical samples. More so the specific role of the survivin isoforms in cancer growth and progression remains a controversial topic of discussion [28].

5. SURVIVIN LOCALIZATION

Survivin covers a Nuclear Export Signal (NES) which interrelates with the export receptor CRM1, which is necessary in establishing its cytoplasmic localization in interphase. It is an NES that is located in between the BIR Domain also the C-terminal Coiled-Coil region, which is vital in ensuring correct subcellular trafficking [29]. Mutations in this pattern hinder nuclear export, resulting in the mislocalization of survivin, preventing its targeting for the centromere or midbody, while not impacting its homodimerization or interaction with "chromosomal passenger complex" (CPC) proteins [30].

These mutations cause a shift towards nuclear localization, which is now lost in favor of cytoplasmic localization, and this shift is associated with the loss of survivin protective activity against apoptotic stress caused by genotoxic stress, or external insults [31]. However, interestingly, survivin engineered in a manner that it is localized in the nucleus alone was revealed to render Cancer Cells more vulnerable to apoptosis. The findings indicate the cytoplasmic survivin is the largest functional pool that facilitates the embarrassment of Apoptosis [32].

However, a subcellular localization of Survivin is debatable as far as clinical significance is concerned. Both nuclear and cytoplasmic localization pattern has linked with both positive and negative prognoses in cancer patients, suggesting that localization is not a conclusive prognostic biomarker [33].

6. SURVIVIN IN APOPTOSIS

The first protein to be described as member of Inhibitor of Apoptosis (IAP) protein family-or alternatively, Baculoviral IAP Repeat-Containing (BIRC) proteins-was Survivin by virtue of containing one Baculovirus IAP Repeat (BIR) motif at N-terminus. An outstanding feature of all IAP family members is that, they have at least one BIR domain, structural module that is inherently conserved, comprising approximately 70 amino acids and enables protein-protein interactions [34].

Functionally, depletion of survivin can trigger apoptotic cell death, whereas its overexpression has been shown to confer resistance to apoptosis under diverse experimental conditions, figure 4. Some inhibitors of apoptosis (IAPs) exert their anti-apoptotic effects via straight compulsory to activated caspases then blocking their catalytic activity. Just like that, the second BIR domain as well as its adjacent binding region in XIAP straightly interact with caspases, preventing substrate access to their active sites [35].

In addition to BIR domains, many IAPs contain either a R I N G domain which functions as the e3 ubiquitin ligase or a ubiquitin-binding domain, both of which contribute to the proteolysis of caspases by the Ubiquitin-dependent proteasome. In contrast, the survivin protein contains only one BIR domain, and current evidence does not conclusively support its ability to directly bind to caspases and inhibit their activity [36].

It is noteworthy that survivin protein was reported to interact with mitochondrial protein DIABLO/SMAC, a pro-apoptotic factor that promotes caspases by antagonizing the function of inactivating inhibitors of apoptosis (IAPs). This has led to the hypothesis that survivin protein may indirectly inhibit apoptosis by sequestering DIABLO/SMAC, thereby preventing it from amplifying apoptotic signals. However, whether such survivin–DIABLO interactions occur at physiologically relevant expression levels and actively contribute to apoptosis inhibition remains to be definitively demonstrated [37].

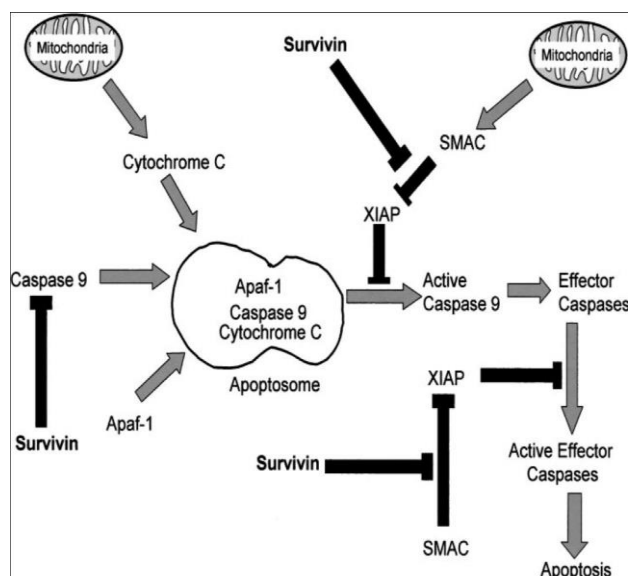


FIGURE 4. - Possible Mechanisms by which the Survivin protein prevents Apoptosis: The Survivin protein can prevent apoptosis via binding to caspase-9 or it may prevent S mac , so preventing this apoptosis-inducing protein from inhibiting I A P proteins

7. REGULATION OF SURVIVIN

Studies have shown that activation of the MAPKp42/22 protein kinase signaling pathway leads to a decrease in survivin protein expression in CD34⁺ cells stimulated by growth factors prior to cell cycle arrest. This observation suggests that these pathways are actively involved in the cytokine control of survivin protein appearance in CD34⁺ cells, which regulation is not only a byproduct or echo of changes in cell cycle dynamics [38], Figure 5.

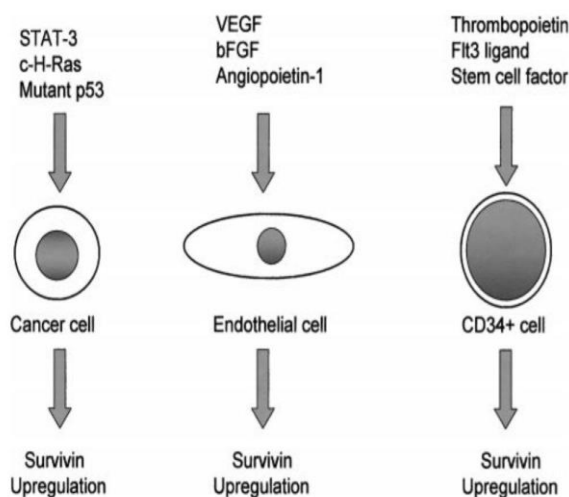


FIGURE 5. - regulation of survivin

Interestingly, survivin is not only expressed during active cell proliferation but can also be induced in quiescent endothelial cells (ECs) when exposed to mitogenic stimuli such as Vascular Endothelial Growth Factor (VEGF) and Basic Fibroblast Growth Factor (bFGF). Experimental inhibition of survivin expression through antisense targeting abolishes the cytoprotective effects conferred by VEGF against apoptotic stimuli like ceramide or tumor necrosis factor (TNF) [39]. This finding strongly suggests that one of VEGF's mechanisms for protecting ECs during angiogenesis involves the upregulation of survivin, THAT theatres a key role in apoptosis preventing.

Furthermore, VEGF-mediated cytoprotection extends to defense in contradiction of chemotherapeutic drugs like as Taxol as well as vinblastine (VBL), both of which disrupt microtubule dynamics. In this case, VEGF stimulates the PI3-K/PKB signaling pathway, resulting in elevated survivin levels, which subsequently preserve the structural integrity of microtubules, thus safeguarding the cellular architecture from drug-induced damage [40]. A comparable process is noted with angiopoietin-1, which also stimulates survivin production in endothelial cells through the activation of the PI3-K/AKT pathway. This overexpression subsequently safeguards endothelial cells from various apoptosis-inducing substances. Behavioral interference with a dominant-negative survivin construct negates this protective effect, demonstrating that survivin is a crucial mediator of angiopoietin-1-induced endothelium survival [41].

From an effective perspective, this dual function of survivin offers both prospects and obstacles. Targeting survivin may offer a way to reduce tumor cell proliferation and induce death in proliferating endothelial cells that constitute the tumor vasculature, hence obstructing tumor angiogenesis. Conversely, the overexpression of survivin in endothelial cells, although possibly facilitating tumor proliferation, also serves a vital protective function in non-malignant clinical conditions, such as ischemic brain injury [42].

Following blockage of the middle cerebral artery in murine models, survivin expression is detectable in the microvessels of infarcted cerebral regions. This induction appears to occur through both VEGF-dependent and VEGF-independent mechanisms. Heterozygous survivin-deficient mice have markedly diminished microvessel density in ischemic areas relative to their wild-type peers. The findings indicate that augmenting survivin expression in endothelial cells may serve as an effective strategy for facilitating angiogenesis and vascular repair in ischemic situations, hence potentially accelerating tissue recovery [43].

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8. THERAPEUTIC STRATEGIES TO TARGET SURVIVIN

Several therapeutic strategies have been explored to directly target the survivin protein, yielding promising results in preclinical and early clinical studies. One important approach utilized the shrapin protein, which induced rapid cell death without causing any significant disruptions to cell division. Another approach relied on virtual screening to identify small mixes that impersonator the D I A B L O / S M A C interaction with XIAP. These drugs, which reduce survivin levels and, to a lesser extent, XIAP, demonstrated tumor growth inhibition in preclinical models. Additional small compounds engineered to interfere with the survivin-DIABLO/SMAC interaction have also shown anticancer activity [48].

High-throughput nuclear magnetic resonance imaging (NMR) revealed several survivin-binding compounds targeting the survivin subunit interaction region. These compounds inhibited cancer cell propagation as well as persuaded G0/G1 Cell Cycle arrest. Using cavity-induced synergistic modification (CIAM), a binding pocket was discovered near the survivin subunit interaction region, leading to the development of direct survivin inhibitors. Among these inhibitors, compound S12 demonstrated significant anti-cancer activity in both in-vitro plus in-vivo, producing effects similar to those of survivin depletion. Furthermore, YAP inhibition enhanced cell sensitivity to compound S12,

suggesting potential synergistic therapeutic benefits. Modified derivatives of compound S12 were also developed for SPECT tumor imaging applications [49].

Recently, virtual screening has revealed new compounds targeting the dimer interface, including L Q Z -7 F and L Q Z -7 I, which promote proteasomal squalor of Survivin, induce apoptosis, and inhibit tumor development in xenograft models. Nonetheless, the exact mechanism by which these medications disrupt survivin is ambiguous, and their impact on cell cycle dynamics has not been thoroughly elucidated [50].

Immunotherapy targeting the survivin protein has shown promising potential in cancer treatment [40]. Specific cytotoxic T-cell (CTL) responses to survivin can induce the destruction of cancer cells expressing this protein. In preclinical studies, survivin-based DNA vaccines and synthetic peptides stimulated CD8⁺ and CD4⁺ T-cell responses, causing tumor regression also reduced recurrence. Additionally, the survivin peptide vaccine SurVaxM demonstrated significant efficacy against brain tumors and showed encouraging results in early clinical trials. Dendritic cell vaccines loaded with the complete survivin protein have also been evaluated, highlighting the potential applications of survivin-targeted immunotherapy in cancer treatment. [43].

9. CONCLUSION

The survivin protein contains a Nuclear Export Signal that interacts WITH the CRM1 export Receptor, letting protein to translocate into the cytoplasm during interphase. This signal is located between the BIR domain and the C-terminal coiled HELIX region. Mutations in the NES disrupt the export of survivin from Nucleus, leading to its mislocalization within the nucleus and impairing its proper routing to the centromere or centrosome, but not to homologous dimer formation or binding to other CPC proteins. Disruption of the nuclear export signal is functionally linked to the translocation of survivin from the cytoplasm to the nucleus, which is associated with the loss of survivin's protective effect against apoptosis induced by cytotoxic stress or other harmful external factors. Furthermore, artificial expression of survivin in the nucleus was found to predispose Cancer Cells to apoptosis. These findings support the hypothesis that cytoplasmic survivin is a key inhibitor of apoptosis. However, it is unclear whether the subcellular distribution of survivin has prognostic significance. Cytoplasmic or nuclear localization has been associated with both good and poor prognostic outcomes for cancer in clinical studies, suggesting that survivin localization alone may not be a reliable predictive biomarker.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest

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