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Survivin (BIRC5): Implications in cancer therapy

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ABSTRACT

Inhibitors of Apoptosis proteins (IAPs) were discovered through experiments aimed at rescuing apoptosis in insects. Classically associated with the inhibition of apoptosis, the IAP member Survivin also regulates cell cycle progression and is an essential component of the Chromosomal Passenger Complex (CPC), responsible for chromosomal segregation. Although undetectable in most adult tissues, Survivin is expressed in Adult Stem Cells (ASCs) and plays a crucial role in their maintenance. Survivin is overexpressed in most cancers, contributing to their clonal expansion. As a result, it has been proposed as a possible anticancer target for nearly two decades. In this discussion, we will explore the rationale behind Survivin as a therapeutic target, focusing on common cancer types such as carcinomas, sarcomas, and leukemias. We will delve into the modulation of Survivin by cancer pro-survival cell signaling, the association between SNPs and tumorigenesis, and its regulation by miRNAs. Finally, we will compare cell growth, clonogenic capacity, and apoptosis, along with different strategies for Survivin inhibition, including gene expression and protein activity modulation.

1. IAP, inhibitor of apoptosis

The discovery of the IAP family of proteins dates back to 1993, when experiments aimed at rescuing apoptosis in SF-21 insect cells were conducted. SF-21 cells were infected with a p35 mutant virus; however, they were unable to inhibit apoptosis. To identify the homologous genes of p35, which was one of the viral DNAs capable of protecting against apoptosis, several co-transfections with DNAs from other baculoviruses were performed. Sequence analysis revealed the presence of a polypeptide with a zinc finger-like motif found in other proteins with an apoptosis inhibitory function. This polypeptide was subsequently named Inhibitor of Apoptosis Protein (IAP) [1]. Subsequent studies have identified other IAPs homologous genes in fungi, nematodes and mammals [2,3], and eight family members are known in humans such as the NLR family apoptosis inhibitory protein (NAIP), the X-linked inhibitor of apoptosis (XIAP), the Baculoviral IAP repeat containing 2 (BIRC2), the Baculoviral IAP repeat containing 3 (BIRC3), the Baculoviral IAP repeat containing 5 (BIRC5) also known as Survivin, the Baculoviral IAP repeat containing 6 (BIRC6), the Baculoviral IAP repeat containing 7 (BIRC7), and the Baculoviral IAP repeat containing 8 (BIRC8) [4] (Fig. 1). The protein organization of IAP members is defined by up to four domains. One of these is the Baculovirus Inhibitor of the Apoptosis Repeat (BIR) domain, which comprises approximately eighty amino acid residues. The folding of the BIR domain results in three β sheets and four α helices, forming a compact structure. This structure is stabilized by coordination with a zinc ion, as illustrated in Fig. 2 [5]. There are two types of BIR domains, both playing a role in interacting with other proteins. They are characterized by the presence of a hydrophobic portion that facilitates interaction with proteins possessing the IAP-binding motif (IBM), including apoptotic effectors such as caspases and the Diablo IAP-binding mitochondrial protein (Smac/Diablo). Additionally, near the carboxy-terminal portion of the BIR domain, there is a RING domain comprised of eight residues of Cys and His that coordinate two zinc ions. This RING domain is crucial for dimerizing and catalyzing ubiquitin ligase activity [6]. The ubiquitin-associated (UBA) domain is involved in binding to poly-ubiquitine chains and finally the CARD (Caspase Recruitment Domain) one, which represents a protein-interaction surface.

2. Survivin has a unique structure

Unlike the other IAPs, Survivin possesses a unique structure, a single BIR domain and an α-helical folding of the caboxy-terminal region [7]. In addition to the full length wild-type transcript of Survivin, twenty

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variants originating from alternative splicing have been described [8]. Among them the best known in the literature are five: the ΔEx3 isoform, devoid of exon three; 2β, which includes the additional exon 2β; 3β, which includes the additional exon 3β; isoform 2α, which originates from the insertion of exon one and two at the distal end of intron two [9]; 2β + 32, which, with reference to the isoform 2β, inserts a portion of thirty-two nucleotide residues of intron two [10] (Fig. 3). The proteic products of the different isoforms exhibit structural variations when compared to the wild type. Exon three missing causes a frame shift and the structure of the carboxy terminal of the ΔEx3 isoform is altered. The partial insertion of exon two into 2β modifies the conformation of the BIR domain [11]. Isoform 3β, on the other hand, has a complete BIR domain and also possesses a sequence of seven additional amino acid residues [12]. The BIR domain is truncated in 2α, which loses the carboxy-terminal domain in its entirety [9].

3. Survivin, undetectable in most adult tissues, contributes to maintenance of adult stem cells (ASCS)

Survivin is expressed in ASCs and plays a role in maintaining their undifferentiated state. Studies in mice have shown that treatment with the Survivin gene expression inhibitor, YM155, leads to a significant decrease in the isolation of bone marrow-derived Mesenchymal Stem Cells (MSCs) and the formation of Colony Forming Units-Fibroblast (CFU-F). In ASCs, the loss of the antiapoptotic function of Survivin results in an increase in the expression of caspase-3 and caspase-7, observed in both murine and human MSCs [13]. The involvement of Survivin in regulation of stem cell differentiation capability has also been investigated in epidermal, hematopoietic and intestinal stem cells. Survivin expression is detected in keratinocytes lacking the Keratin 15 differentiation marker [14], whereas its upregulation induces the Notch pathway, classically involved in maintaining the undifferentiated state [15]. A Survivin Cre-Lox mouse model was created to investigate the involvement of Survivin in the regulation of adult hematopoiesis. The Survivin floxing in this model is linked to the complete absence of erythroid lineage progenitors. [16]. In intestinal epithelial stem cells, Survivin loss of function is associated with a reduction of the frequency of Leucine-rich repeat-containing G-protein coupled receptor 5^+ ($Lgr5^+$) stem cells and Transit-Amplifying (TAs) cells [17].

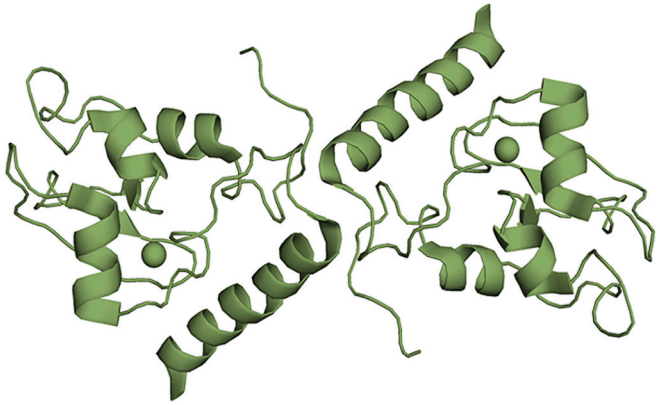

Fig. 2. Dimeric structure of the BIR domain obtained from RCSB PDB database and oriented by PyMOL software.

4. Survivin plays different roles

Classically associated with inhibition of apoptosis, Survivin expression is required in all phases of the cell cycle and regulates its progression.

4.1. Survivin in cell cycle

Sequence analysis upstream of Survivin's transcription initiation site has uncovered the presence of a TATA-less promoter. Additionally, multiple cell cycle-dependent elements were identified, indicating that Survivin is a cell cycle-regulated protein [18] modulated by Cyclin dependent kinase 1 (Cdk1) [19,20]. In ASCs Survivin is regulated at all stages of the cell cycle as demonstrated in umbilical cord blood $CD34^+$ cells [21]. In contrast, in cancer, Survivin is highly expressed during the G2/M phase but its expression levels drop significantly during the G1 phase (Fig. 4) [22].

4.2. Survivin in chromosomal passenger complex (CPC)

It has been proposed that the diverse functions of Survivin in apoptosis regulation may be linked to its distinct cellular

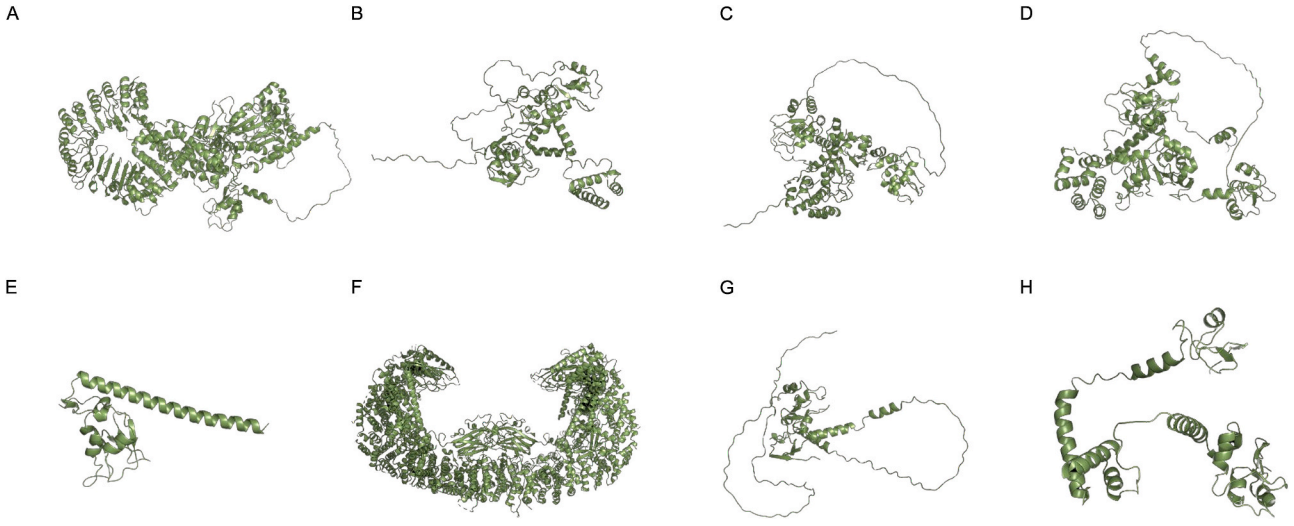

Fig. 1. The structural representations of the eight members of the IAPs family identified in humans are shown. These include a) NLR family apoptosis inhibitory protein (NAIP), b) X-linked inhibitor of apoptosis (XIAP), c) Baculoviral IAP repeat-containing 2 (BIRC2), d) Baculoviral IAP repeat-containing 3 (BIRC3), e) Survivin Baculoviral IAP repeat-containing 5 (BIRC5), also known as Survivin, f) Baculoviral IAP repeat-containing 6 (BIRC6), g) Baculoviral IAP repeat-containing 7 (BIRC7), and h) Baculoviral IAP repeat-containing 8 (BIRC8). The respective Protein Data Bank (PDB) files were obtained from the RCSB PDB database, and the molecules were oriented using PyMOL software.

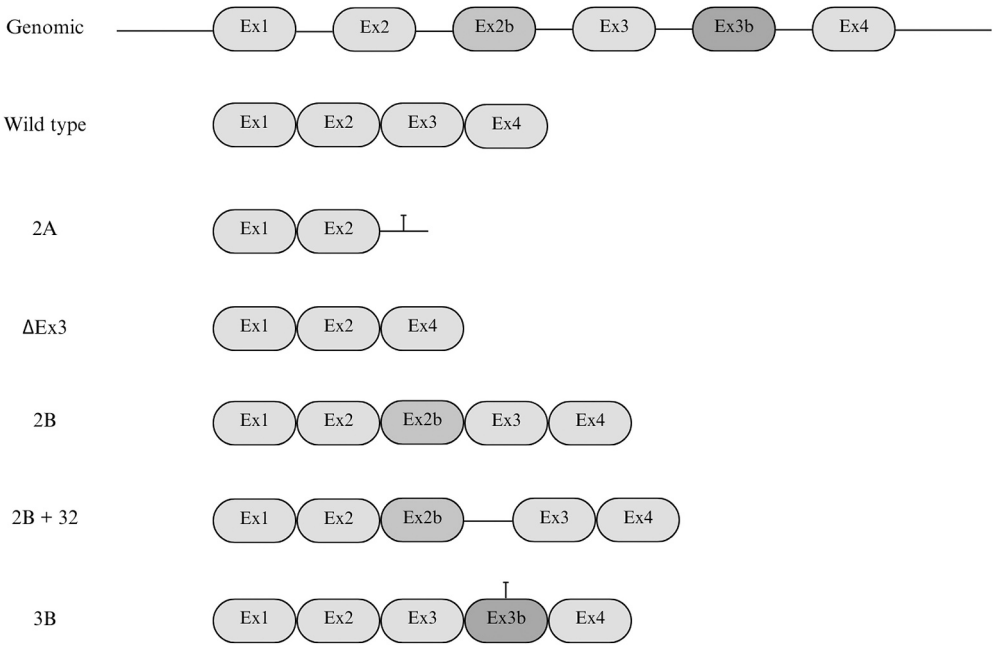

Fig. 3. This figure illustrates the arrangement of Survivin exons, wild type transcript, and the results of alternative splicing, such as 2A, ΔEx3, 2B, 2B + 32, and 3B.

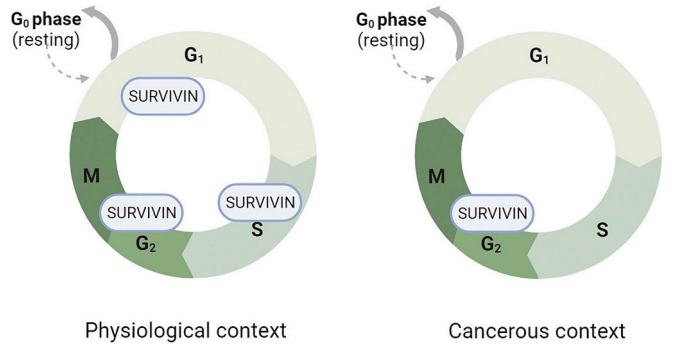

Fig. 4. Survivin is expressed at all stages of the cell cycle in physiological context. By contrast, in cancer, Survivin is highly expressed during the G2/M phase and its level drops significantly during the G1 phase.

compartmentalization. Specifically, when localized in the cytoplasm, it functions as an inhibitor of apoptosis; in contrast, nuclear localization of Survivin is associated with regulation of mitosis and organization of the CPC (Fig. 5) [23]. CPC plays crucial roles during mitosis, encompassing the phosphorylation of substrates involved in chromosome condensation, microtubule attachment to kinetochores, activation of the Spindle Assembly Checkpoint (SAC), and cytokinesis. Structural analysis of the CPC reveals two modules: a kinase module represented by Aurora kinase and a localization module consisting of Inner centromere protein (INCENP), Cell division cycle associated 8 (also known as Borealin), and Survivin. The localization module is characterized by a bundle of three helices from each protein, with Survivin contributing through its BIR domain. The regulation dynamics of CPC are complex, and Survivin is an essential component. Among its functions, Survivin acts as a sensor of centromeric histone H3 phosphorylation, facilitating recruitment of CPC to the inner centromere [24]. Dysregulation of CPC compromises chromosomal stability, as demonstrated by the Survivin loss of function that leads to chromosomal aberrations indicative of the mechanism of Non-Homologous End Joining (NHEJ) recombination repair [25].

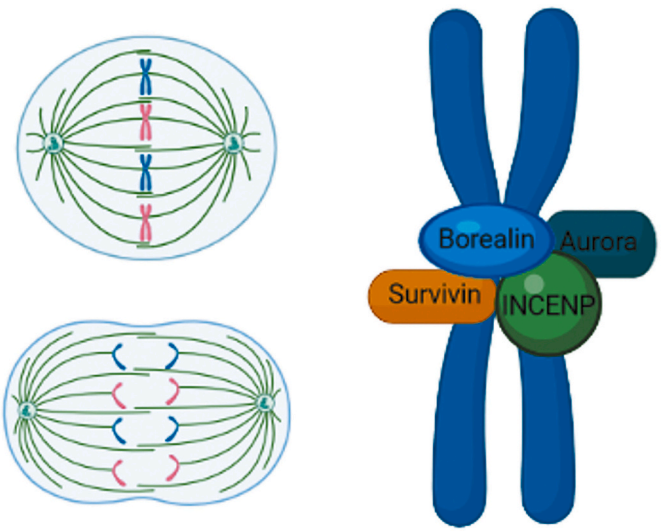

Fig. 5. Survivin constitutes the CPC by interacting with Aurora, INCENP and Borealin. Dysregulation of CPC compromises chromosomal stability.

4.3. *Survivin in apoptosis*

In tumor cell lines, a pool of Survivin was observed to colocalize within a mitochondria fraction with Smac/Diablo, rather than with Aurora kinase. This observation supports the hypothesis of a cytoplasmic antiapoptotic function for Survivin, not directly related to the CPC [26]. In umbilical cord blood $CD34^{+}$ cells, upregulation of Survivin by several growth factors is associated with inhibition of apoptosis, whereas its downregulation is associated with stimulation of apoptosis [21]. In line with the previous consideration, transgenic expression experiments revealed that $Survivin^{+/-}$ heterozygous liver cells derived from the murine model exhibit pronounced apoptosis in response to the Fas-associated death domain protein (Fas) [27]. Survivin exerts its antiapoptotic effects through various mechanisms, involving both caspase-dependent and independent pathways. Specifically, when forming a complex with Smac/Diablo, Survivin promotes inhibition of

caspase-9 and caspase-3 activity. Additionally, experimental evidence suggests that Survivin can inhibit the activity of *Apoptosis inducing factor* mitochondria associated 1 (Apoptosis Inducing Factor, AIF) independently of caspase-mediated apoptosis. In response to apoptotic stimuli, AIF translocates from the mitochondrion to the nucleus, initiating DNA fragmentation [28,29] (Fig. 6).

5. Survivin is overexpressed in cancer and plays a role in self-renewal

Survivin is overexpressed in a large number of cancers including breast cancer [30], melanoma [31], squamous cell carcinoma [32], ovarian cancer [33], glioma [34], lung cancer [35], prostate cancer [36], thyroid [37], and hematological [38] and gastric [39] cancers (Table 1). In glioblastoma, Survivin expression is increased in $CD133^{+}$ cells, expressing a specific Cancer Stem Cell (CSCs) marker [40], and in *Stem cell* antigen 1^{+} ($Sca\text{-}1^{+}$) prostate cancer cells its overexpression correlates with the ability to self-renew [41]. Considering its involvement in regulation of cell cycle progression, inhibition of apoptosis and regulation of CPC, Survivin has been proposed as anti-cancer targeted therapy for about two decades.

6. Survivin isoforms can be differentially expressed in cancer: putative roles in tumorigenesis

The expression of the Survivin isoforms appears dysregulated in various tumors. For example, in ovarian cancer isoforms 2α, 2β, 3β, and ΔEx3 are differentially expressed [42] as are 2β and ΔEx3 in colorectal carcinoma [43]. In oral squamous cell carcinoma (OSCC) and in cervical cancer, isoforms 2β and ΔEx3 are upregulated, although isoform 3β undergoes a minor increase in OSCC [44,45]. It has been hypothesized that the different expression of alternative isoforms of Survivin in cancer might result in a negative Trans-Dominant effect (TD). This effect could arise from the formation of inactive dimers, potentially compromising the normal functions of Survivin [46]. Notably, isoforms 2β and ΔEx3 can interact with the wild-type isoform; however, they exhibit reduced affinity with the constituents of the CPC and do not localize in the respective subcellular compartment like the wild-type monomers. In osteosarcoma and cervical cancer, overexpression of these isoforms does not prevent cell cycle progression. Additionally, the reduction in the proliferative rate induced by Survivin knock-down is only rescued by the wild-type isoform [11]. As regards the apoptotic function, Végran et al. demonstrated an inverse correlation between expression of isoform 3β and expression of pro-apoptotic genes in breast cancer. Further *in vitro* experiments showed that the gain offunction of the 3β variant was able to inhibit drug-induced apoptosis [47]. By contrast, the hypothesis of the antagonistic function of the ΔEx3 isoform holds particular significance. In cervical cancer, overexpression of this isoform demonstrates an inhibitory effect on cell growth and clonogenic potential [48].

7. Modulation of Survivin expression by cancer pro-survival cell signaling pathways

Extensive analyses of pro-survival signaling in cancer have been conducted over the years, and this section summarizes some of the main signaling pathways that regulate survival of cancer cells and expression of Survivin (Fig. 6). In mammals, there are at least a dozen Mitogen-Activated Protein Kinase (MAPK) genes, with three well-known families such as extracellular signal-regulated kinases 1 and 2 (ERK1/2), c-Jun N-terminal kinase (JNK 1, 2, 3), and p38 (a, b, c, and d). Experimental evidence suggests that MAPK signaling may or may not be pro-survival in cancer, and the correlation with Survivin expression is not entirely clear. It is known that Deguelin stimulates apoptosis in colorectal cancer by activating the p38 pathway and concurrently suppressing the expression of Survivin [49]. On the other hand, an inverse correlation between JNK signaling and tumorigenesis has been demonstrated. In prostate cancer, the use of siRNA directed against JNK impaired cell viability and decreased the expression of Survivin and other JNK-related genes such as Cdk1, Matrix Metallopeptidase 1 (MMP1), and the proto-oncogene c-Myc. Supporting the pro-survival

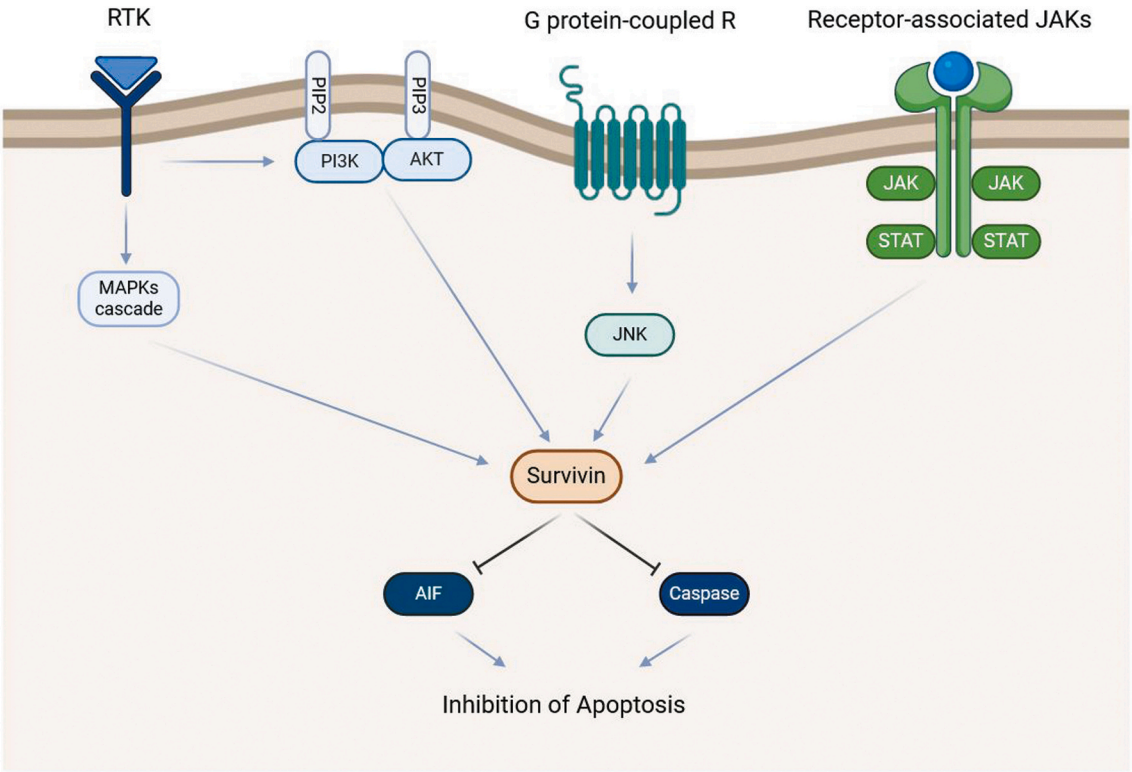

Fig. 6. Survivin is modulated by several cellular signaling pathways, including the MAP kinase cascade, PI3K/AKT signaling, JNK, and JAK/STAT.

Table 1
Summary of some study concerning overexpression of Survivin in several tumor models.

Samples	Methodology	Number of patients or samples	Clinical laboratory association or clinical outcome
Ductal carcinoma *in situ* (DCIS) and invasive ductal carcinoma samples (Breast Cancer)	Immunohistochemistry	26 + 26	Cancer Progression
Mouse model (Melanoma)	Implantation of cell lines overexpressing Survivin		Increased tumor size
HSC-3, KB, SCC-4, SCC-9, SCC-15, and SCC-25 cell lines (Squamous cell carcinoma)	Western Blot	6	Relationship between Survivin expression and oral carcinogenesis and aggressiveness
A2780 and OVCAR-3 cell lines (Ovarian cancer)	pCDH-Neo-Venus-survivin lentivirus	2	Survivin overexpression raises the survival rate of ovarian cancer cells
Patients (Glioma)	Meta-analysis	1260	Higher Survivin expression was associated with worse overall survival in patients with glioma
Patients (Lung cancer)	Immunohistochemistry, *in situ* hybridization and RT-PCR	7 eligible studies	The level of Survivin expression correlated with the Overall Survival (OS) of NSCLC patients
Patients (Prostate cancer)	Immunohistochemistry	62	Overexpression of Survivin was associated with a significantly increased risk for the subsequent development of distant metastasis
Human thyroid carcinomas samples (Thyroid Cancer)	Immunohistochemistry	56	A statistically significant association was found between nuclear Survivin expression and anaplastic thyroid cancer
Transgenic Mices (Hematological cancer)	Immunohistochemistry		High-grade aggressive tumor in the thymus with involvement of the bone marrows and infiltration into the spleens and liver
Primary samples (Gastric Cancer)	Immunohistochemistry	322	The expression of Survivin was significantly associated with gross type, depth of invasion, distant metastasis, TNM stage and vascular invasion

role of JNK in cancer, two other evidences are discussed: in human bladder cancer, stimulation of the JNK pathway attenuated the activity of the chemotherapeutic agent Gemcitabine, exerting an anti-apoptotic effect [50] as well as in hepatoma, where JNK stimulation confers resistance on chemotherapeutic Sorafenib [51]. Expression of Survivin is regulated within the Phosphatidylinositol-4,5-bisphosphate 3-kinase/AKT serine/threonine kinase (PI3K/AKT) axis, both in physiological and cancerous contexts [52,53]. In breast cancer, inhibition of PI3K signaling by Wogonin resulted in decreased Survivin gene expression, induced mitotic arrest, and reduced clonogenic potential [54]. Survivin expression can also be regulated by Janus kinase/Signal transducer and activator of transcription (JAK/STAT) signaling. In leukemia, inhibition of the JAK/STAT pathway manifested antitumor properties by decreasing Survivin expression [55]. However, in colorectal cancer, inhibition of JAK/STAT signaling affected cell proliferation without a change in Survivin gene expression [56].

8. Similarities and discrepancies between onset of SNPS in Survivin and clinical outcome

The Single Nucleotide Polymorphisms (SNPs) we will examine in this section can arise in both non-coding regions, 5′- and 3'-UTRs, and the coding sequence of Survivin. The occurrence of such SNPs may be associated with tumorigenesis, both high and low risk, or may instead play a protective role. Notably, in a case-control study aimed at investigating the association between polymorphisms in Survivin and the risk of developing hepatocellular carcinoma (HCC), three SNPs were examined: rs8073069 and rs9904341, both occurring in the promoter sequence, and rs1042489, located in the 3'-UTR. Strong Linkage Disequilibrium (LD) was established between these SNPs. Analyses under different genetic models (dominant, recessive, additive, and multiple) revealed that the G-C-T haplotype for the mentioned SNPs is associated with a low risk for HCC [57]. In oral squamous cell carcinoma the SNP rs9904341 was not considered a risk factor [58], just as it was not in non-small cell lung cancer the SNPs rs9904341 and rs8073903 [59]. In breast cancer, SNP rs8073069 was significantly associated with subjects showing tumor necrosis [60]. According to another study, the SNP rs9904341, which was not considered a risk factor in the tumors mentioned earlier, could indeed be associated with an increased risk in prostate cancer [61], and in bladder cancer it is also associated with high-grade tumor (Table 2) [62]. SNPs in gene promoters can directly influence binding of transcription factors, leading to alterations in gene expression levels. This regulatory role makes them significant players in determining an individual's predisposition to various conditions. For instance, variations in the promoter region of cancer-related genes, such as Survivin, have been associated with an increased or decreased risk of developing certain types of cancer. Cell cycle-dependent (CDE) and cell cycle homology region (CHR) cis-regulatory elements were identified in the Survivin promoter sequence. The SNP rs9904341, located in the CDE/CHR region, was found to compromise interaction with related transcriptional repressors. Both in physiological conditions and in cancer, this SNP led to an increase in Survivin gene expression. [22]. The association between the occurrence of the SNP in the Survivin promoter and cancer has also been demonstrated in ovarian [63] and esophageal [64] tumors. A meta-analysis conducted on gastric, colorectal, bladder,

Table 2
Occurrence of SNPs in Survivin and the risk of tumorigenesis.

SNPs	Cancer	Factor of risk
rs8073069 rs9904341 rs1042489	Hepatocellular carcinoma	Low risk
rs9904341 rs8073903	Non-small cell lung cancer	Low risk
rs9904341	Bladder cancer	High risk

and other tumors aimed to investigate the susceptibility to cancer associated with specific SNPs in Survivin. Although the SNP rs17878467 is positioned in the Survivin promoter, it is not cis-acting element or located in a putative transcription factor binding site and does not manifest as a risk factor; rather, it appears to play a protective role [65]. The occurrence of SNPs in Survivin also takes place within the 3'-UTR region and a correlation with miRNA was suggested. In lymphoblastoid cell line, it was *in silico* described that several SNPs located in the 3'-UTR of Survivin, *i.e.* rs1042489, rs1042542, rs17882360, rs2239680, rs2661694 and rs4789560, might represent miRNA binding sites [66]. This finding implies that these specific SNPs could modulate Survivin expression by serving as binding sites for miRNAs. However, it is crucial to acknowledge the limitations of *in silico* predictions and the need for experimental validation to confirm the functional impact of these SNPs as miRNA binding sites. While computational analyses provide valuable insights, empirical evidence is essential to establish the biological relevance of these interactions. The presence of SNPs in the coding region, rs2071214, is a significant factor in understanding genetic variations and their implications in molecular biology. Specifically, the SNP involves an amino acid substitution located in the C-terminal region of the protein. The specific localization in the C-terminal region of the protein could influence its three-dimensional structure, potentially altering its functions and interactions.

9. Several miRNA regulate Survivin expression

In recent years, the focus on regulation of gene expression has shifted toward the role of microRNA (miRNA) post-transcriptional regulators. In laryngeal carcinoma cells, miR-203 was identified as a suppressor of Survivin gene expression, effectively blocking progression of the cell cycle in the G1 phase [67]. The tumor suppressor activity of miR-203 has also been reported in hepatocellular carcinoma cells (HCC) [68]. Indeed, miR-34a has been shown to decrease the expression of Survivin in breast cancer. Moreover, it exhibited a synergistic effect with the chemotherapy drug Selexinor, also resulting in reduced tumor growth in a mouse model. This highlights the potential of miRNA as a therapeutic approach [69]. Other miRNAs inhibit Survivin expression and exert anticancer effects such as miR-708 [70], double chain miR-138-5p in bladder cancer [71] and miR-214-3p in breast cancer, as demonstrated by analyzing its loss of function [72].

10. Actual and potential therapeutic approaches to inhibit Survivin

10.1. Inhibition of gene expression

Inhibition of gene expression can be achieved through various mechanisms operating at multiple levels, including epigenomic, genomic, transcriptomic, and translational regulation. Here, we show several examples of molecular strategies to inhibit Survivin.

10.2. Epigenetic silencing mechanism

Apigenin, a natural flavonoid found in various fruits and vegetables, has demonstrated tumor suppressor activity by modulating the epigenome. Independent studies have clarified that Apigenin also possesses the potential to inhibit the gene expression of all IAP members, including Survivin. This suggests that Apigenin may play a role in regulating key proteins associated with apoptosis and cell survival [73]. Treatment with Apigenin in prostate cancer has been associated with several beneficial effects. It leads to a reduction in gene expression of Histone deacetylase 1 (HDAC1), whose protein product is involved in histone deacetylation and gene repression. Furthermore, Apigenin treatment results in increased histone acetylation above the promoter region of Cyclin dependent kinase inhibitor 1 A (CDKN1A), the protein product p21 is known to regulate cell cycle progression. The observed changes suggest that Apigenin may contribute to regulation of gene expression related to cell cycle control. Moreover, treatment with Apigenin is also associated with a reduction in cell growth and stimulation of apoptosis *in vivo*, in mouse models. This highlights the potential anticancer effect of Apigenin in prostate cancer [74]. Administration of dietary supplementation with bioflavonoids, including Apigenin, in humans was proposed within the trial NCT00609310, for prevention of recurrence of neoplasia in patients with resected colorectal carcinoma, however, the trial has been suspended [75].

10.3. Knock-out approach

The Clustered Regularly Interspaced Short Palindromic Repeats/Associated Protein 9 (CRISPR/Cas9) system for gene silencing of Survivin has been used in two tumor models, hepatocellular carcinoma and acute myelocytic leukemia (AML). The CRISPR/Cas9 mechanism has been utilized to inhibit Survivin gene expression in hepatocellular carcinoma in a mouse model too. In this approach, a plasmid encoding the single-guide RNA (sgRNA) directed against the Survivin gene and the sequence encoding the Cas9 enzyme was incorporated into a charge-reversal vehicle, heparin-based, to transfect hepatocarcinoma cells. Induction of out-of-frame insertions/deletions (in/del mutations) and suppression of Survivin gene expression confirmed successful silencing. Following the treatment, the proliferation rate and invasive capacity of the hepatocarcinoma cells decreased, while apoptosis was induced. In a xenografted murine model, the knock-out approach to inhibit Survivin *via* vein injection demonstrated a significant antitumor effect. This highlights the potential therapeutic application of CRISPR/Cas9-mediated gene editing for targeting Survivin in hepatocellular carcinoma [76]. Expression of Survivin has been permanently silenced in two AML cell line models, namely HL-60 and KG-1, using the CRISPR/Cas9 system. For gene knock-out, a nickase mutant of Cas9 (Cas9n) was employed along with a dual-guide RNA. After verifying potential off-targets of the sgRNAs, using BLAST, the Surveyor nuclease assay was utilized to confirm the presence of in/del mutations. Upon confirming double-strand breaks (DSBs) and activation of the NHEJ repair mechanism, Survivin silencing was validated through Real-Time PCR. The effect of gene silencing was manifested in cellular viability and growth. Both cell lines exhibited a drastic reduction in cellular viability, increased apoptosis, and necrosis [77]. In conclusion, based on the existing literature, we can assert that the knock-out of Survivin, through the implementation of the CRISPR/Cas9 system, has exerted a substantial anti-tumor effect in the two cancer models mentioned above.

10.4. Inhibition of transcription

YM155, also known as Sepantronium Bromide, has been found to induce dissociation of p54 (nrb) from Interleukin enhancer-binding factor 3 (Ilf3). This molecular interaction leads to the inhibition of Survivin transcription (Fig. 7). Dissociation of these proteins and subsequent downregulation of Survivin transcription could potentially contribute to the anti-cancer effects of YM155. Modulation of Survivin expression by compounds like YM155 represents a potential strategy for cancer treatment [78,79]. Treatment of hepatoblastoma cells with YM155 has been reported to yield several anti-cancer effects. Specifically, YM155 inhibited proliferation and formation of CFU-F, which are indicative of reduced clonogenic potential. Additionally, YM155 treatment induced apoptosis in hepatoblastoma cells, and this apoptotic effect was attributed to downregulation of Survivin expression. Therefore, the findings suggest that YM155 has potential therapeutic benefits in hepatoblastoma by targeting Survivin and influencing key cellular processes [80]. In oral squamous cell carcinoma, YM155 has been found to inhibit cell growth and induce apoptosis, particularly in cells expressing Survivin. Additionally, it attenuated the expression of Nuclear factor kappa B subunit 1 (NFKB1), a gene that encodes for a transcription factor associated with cell survival and inflammation. In a

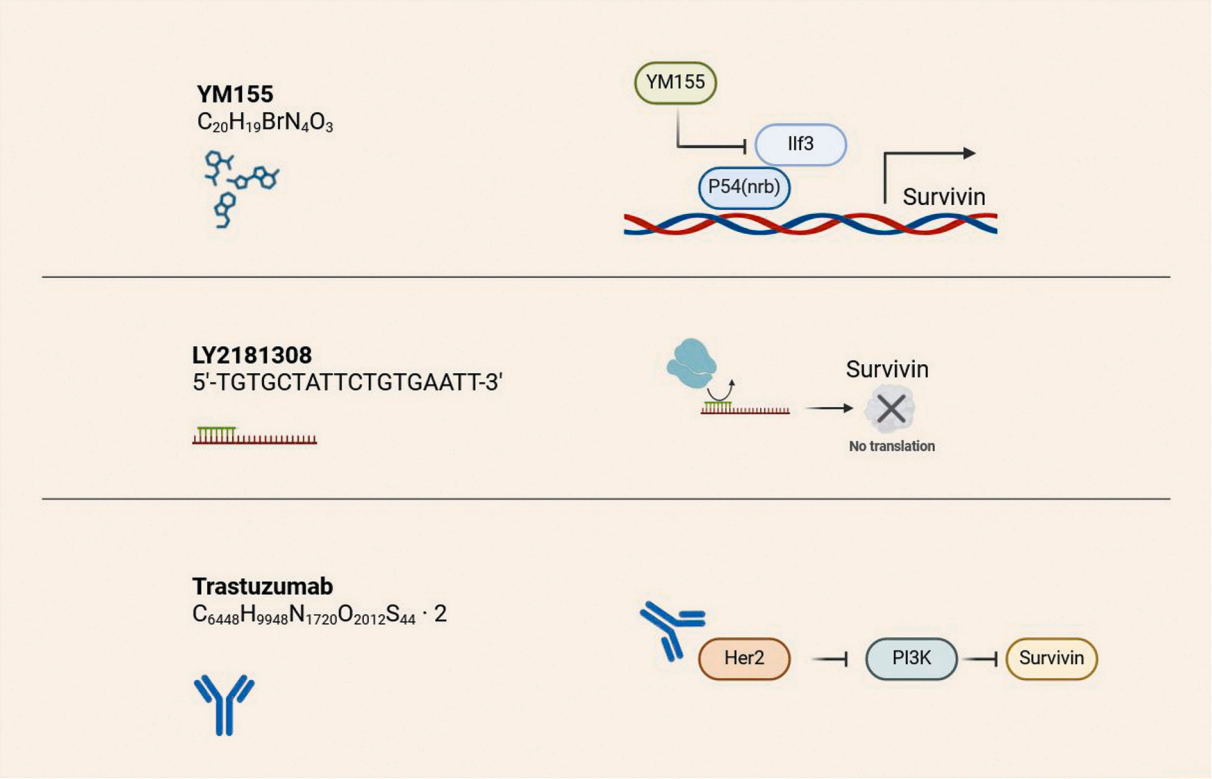

Fig. 7. YM155 inhibits the gene expression of Survivin by dissociating, at the promoter level, Ilf3 from p54(nrb). LY2181308 is designed to interact with Survivin mRNA. This interaction initiates an RNA interference mechanism, where the heteroduplexes are recognized by ribonucleases that degrade the messenger RNA. Trastuzumab inhibits PI3K signaling and inhibits Survivin gene expression.

related murine model, YM155 exhibited antimetastatic effects. Interestingly, it did not affect survival of cells expressing reduced levels of Survivin. The specificity of its effects on cells expressing reduced Survivin levels suggests a selective impact on cancer cells, emphasizing its potential as a targeted treatment in this context [81]. YM155 has been studied in numerous clinical trials, mostly completed, one concluded, and another still in the recruitment phase. Within the NCT00818480 trial, the drug was administered to subjects for the treatment of prostate cancer, melanoma, and non-hodgkin lymphoma [82]. According to another trial, treatment with the drug was also effective in subjects with castrate-resistant prostate cancer, non-small cell lung cancer, metastatic melanoma, muscle-invasive bladder cancer, follicular lymphoma, and diffuse large B-cell lymphoma. The study examined the pharmacokinetics, safety, and tolerability of the drug [83]. Within the NCT01100931 trial, the effectiveness of the combination of Carboplatin, Paclitaxel, and YM155 in the treatment of NSCLC was determined [84]. The combination showed a favorable safety profile but failed to demonstrate an improvement in the response rate in advanced NSCLC [85]. Other clinical trials have been conducted and completed on both solid and non-solid tumors, including NCT01038804 [86], NCT01009775 [87], NCT01007292 [88], NCT00514267 [89], NCT00257478 [90], NCT00328588 [91], NCT00281541 [92]. The NCT00498914 trial was terminated because the futility boundary at interim analysis was not met [93]. Finally, The NCT05263583 trial is currently ongoing to evaluate the safety and efficacy of YM155 in patients with relapsed/refractory c-Myc rearranged high-grade B-cell lymphoma [94].

FL118, a camptothecin derivative, appears to act as a degrader of ATP-dependent RNA helicase DDX5 (DDX5) a positive regulator of Survivin. The mechanism involves stimulation of ubiquitination, inhibiting the transcription of DDX5. As DDX5 is a positive regulator of Survivin, its degradation would likely lead to a reduction in Survivin expression [95]. In colorectal carcinoma, treatment with FL118 has been reported to exert anticancer effects *in vivo*. This suggests that the compound activity extends beyond *in vitro* cell culture systems and has a meaningful impact on growth and survival of colorectal cancer cells within an animal model. The *in vivo* efficacy of FL118 further supports its potential as a therapeutic agent for colorectal carcinoma and underscores the importance of understanding its mechanisms of action in a broader physiological context [96]. In pancreatic cancer, FL118 has demonstrated the ability to overcome resistance to Cisplatin, a commonly used chemotherapeutic agent. Furthermore, in combination with Cisplatin, FL118 reduced formation of spheroids, which are three-dimensional structures often associated with increased resistance to treatment. In a patient-derived tumor xenograft mouse model, FL118 exhibited a substantial antitumor effect. These findings suggest that FL118 may have potential applications in addressing resistance issues in pancreatic cancer treatment and could enhance the efficacy of standard chemotherapeutic agents like Cisplatin, emphasizing its potential as a novel therapeutic approach for pancreatic cancer [97]. FL118 is currently undergoing testing in the NCT06206876 trial to assess safety, side effects, and optimal dosage for treating patients with pancreatic adenocarcinoma [98].

10.5. Inhibition of translation

LY2181308 is a second-generation antisense oligonucleotide. It is an 18-mer antisense oligonucleotide where the hydrogen atom at position two of the ribose is replaced with a methoxyethyl group. This modification enhances its stability and binding affinity. LY2181308 is designed to interact with Survivin mRNA. The mechanism of action involves the formation of high-melting heteroduplexes between LY2181308 and Survivin mRNA. This interaction triggers an RNA interference mechanism, where the heteroduplexes are recognized by ribonucleases (RNases) that subsequently degrade the messenger RNA [99–101] (Fig. 7). LY2181308 has demonstrated its effectiveness in various tumor models,

including lung, colon, pancreas, liver, breast, prostate, ovary, cervix, skin, and brain. These findings highlight the versatility of LY2181308 in targeting critical pathways involved in cancer progression [102]. In lung cancer cell samples obtained by Fiber Optic Brushing (FOB), the protein expression level of Survivin decreased following LY2181308 treatment, as compared to subjects treated with conventional Cisplatin-Gemcitabine therapy. This observation suggests that the specific treatment, possibly involving LY2181308, led to a reduction in Survivin expression [103]. In prostate cancer no differences in progression-free survival were observed in castration-resistant prostate cancer (CRPC) in response to treatment with LY2181308 when compared with Docetaxel plus Prednisone alone therapies [104]. LY2181308 has been studied in various clinical trials, such as NCT00642018 for treatment of hormone-refractory prostate cancer patients [105], NCT01107444 for non-small cell lung cancer [106], and NCT00620321 for relapsed or refractory AML [107]. The NCT00415155 study for hepatocellular carcinoma was withdrawn [108].

11. Inhibition of Survivin expression by turning-off canonical signaling

11.1. Inhibition of MAPK pathway

CI-1040, also known as PD184352, was the first MAPK inhibitor to enter clinical trials. The discovery of CI-1040 involved *in vitro* studies where the addition of the molecule, in the presence of ATP and a phosphorylating protein, led to inhibition of phosphorylation of MAPK and expression of Survivin. This inhibition of MAPK phosphorylation is significant because the MAPK pathway plays a crucial role in cellular processes, including cell proliferation and survival. By inhibiting this pathway, CI-1040 has the potential to modulate cellular responses and impact expression of key proteins such as Survivin [109]. In Papillary Thyroid Carcinoma (PTC), CI-1040 has demonstrated its ability to inhibit cell growth. Additionally, in a xenografted PTC mouse model, the administration of CI-1040 resulted in a decrease in the size of the tumors [110]. In spheroidal models of neuroblastoma, CI-1040 has been observed to inhibit cell growth in a dose-dependent manner. Spheroid models are three-dimensional cellular structures that more closely mimic the *in vivo* environment compared to traditional two-dimensional cell cultures. The dose-dependent inhibition of cell growth by CI-1040 in neuroblastoma spheroids suggests its potential as a therapeutic agent for neuroblastoma, possibly by targeting key signaling pathways involved in cell proliferation and survival, such as the MAPK/ERK pathway. These observations contribute to an understanding of CI-1040's anticancer effects across different cancer models [111]. CI-1040 was studied in the clinical trial NCT00034827 for advanced colorectal and lung cancer patients who failed a prior chemotherapy regimen, breast cancer patients who had failed regimens, and patients with pancreatic cancer who had received no prior chemotherapy [112]. With the aim of assessing the efficacy in patients who have metastatic or unresectable breast, colon, pancreatic, or non-small cell lung cancer, the drug was evaluated in the clinical trial NCT00033384 [113]. PD0435901, as the second generation of the CI-1040 molecule has been reported to be effective in downregulating expression of Survivin [114].

11.2. Inhibition of JNK pathway

AS602801, also known as Bentamapimod, is an ATP-competitive inhibitor of JNK (c-Jun N-terminal kinases), a family of protein kinases that play a role in various cellular processes, including apoptosis and inflammation. It has been reported that AS602801 inhibits gene expression of Survivin [115,116]. The observation that AS602801 exhibits strong cytotoxicity and inhibits self-renewal in mouse xenograft models derived from human pancreatic cancer, non-small cell lung cancer, ovarian cancer, and glioblastoma is noteworthy. This suggests a broad spectrum of potential efficacy across different cancer types. The ability to impact self-renewal in cancer cells is particularly significant, as it targets a key feature of cancer stem cells that contribute to tumor growth and recurrence [117]. The observation that AS602801 suppressed tumor growth in glioma cell xenografted mice is notable, particularly in combination with Temozolomide and Vincristine [118].

11.3. Inhibition of PI3K/AKT pathway

Trastuzumab, commonly known as Herceptin, is a monoclonal antibody that targets the Human epidermal growth factor receptor 2 (Her2). In Her2-positive breast cancer, Trastuzumab has been shown to inhibit PI3K signaling, a crucial pathway involved in cell survival and proliferation. Additionally, reduction in Survivin gene expression has been observed as part of the molecular changes induced by Trastuzumab [119,120] (Fig. 7). This suggests that in breast cancer, Trastuzumab treatment resulted in reduced cell growth and a decrease in the frequency of CSCs in mice [121,122]. Trastuzumab has been extensively studied in many clinical trials for treatment of various tumors, alone or in combination with other drugs. Many studies are still in the recruitment phase. Here are some examples: within the NCT01959386 trial, the drug underwent an observational study to verify the efficacy, safety, and tolerability in participants with $HER2^{+}$ early breast cancer [123], additionally it has also been proposed for conditions in patients with operable breast cancer (NCT01785420) [124].

The statement that LY294002 inhibits gene expression of Heat Shock Proteins (Hsp)-27 and − 72, heat-induced Akt phosphorylation, and Survivin gene expression aligns with the known functions of the PI3K/AKT pathway. Heat shock proteins, including Hsp-27 and -72, are often upregulated in response to cellular stress, and the PI3K/AKT pathway can influence their expression. Akt phosphorylation is a downstream event in the PI3K pathway, and inhibition of PI3K can prevent this phosphorylation. Survivin is often regulated by the PI3K pathway [125,126], and could therefore be identified as a PI3K/AKT signaling inhibitor. In nasopharyngeal carcinoma cells, treatment with LY294002 resulted in decreased proliferation and increased apoptosis, as indicated by the activation of caspase-9. Furthermore, in a mouse model where tumors were generated by implanting cells from a metastatic line of nasopharyngeal carcinoma, the treatment with LY294002 led to a reduction in tumor size in a dose-dependent manner. This reduction in tumor size was accompanied by an increase in caspase-9 expression, suggesting induction of apoptosis in the treated tumors. These findings highlight the potential anticancer properties of LY294002 in inhibiting tumor growth and promoting apoptosis, in the context of nasopharyngeal carcinoma and metastatic tumors [127,128]. LY294002, the PI3K inhibitor, had positive effects in gastric cancer and breast cancer by enhancing the chemotherapeutic effects of Oxaliplatin and Tamoxifen [129,130].

11.4. Inhibition of JAK/STAT pathway

TG101209 interacts with the Asp-Phe-Gly activation loop of the ATP binding domain in JAK. This interaction is evidenced in a molecular docking model, a computational approach used to predict the preferred orientation of one molecule to a second when bound together to form a stable complex. Inhibition of JAK/STAT signaling by TG101209 is associated with a decrease in Survivin gene expression; furthermore, in murine models of lung cancer xenografts, treatment with TG101209 sensitized the cancer cells to radiotherapy [131,132]. In Burkitt lymphoma, TG101209 inhibited cell growth and induced apoptosis, particularly during cell differentiation toward the mature B phenotype. Additionally, when TG101209 was associated with Doxorubicin, a chemotherapeutic agent, a synergistic effect was observed [133]. In T cell acute lymphoblastic leukemia (T-ALL), TG101209 inhibited proliferation and induced apoptosis in a dose-dependent manner [134]. SD-1029 is a molecule identified from a library of bioactive molecules. SD-1029 is reported to inhibit translocation of STAT into the nucleus by

compromising autophosphorylation of JAK2. Autophosphorylation of JAK2 is a crucial step for transducing signals through the JAK/STAT pathway. SD-1029 acts as a modulator of the JAK/STAT pathway, influencing downstream gene expression, particularly inhibition of Survivin in the context of disrupting cancer cell survival mechanisms [135]. SD-1029 induces apoptosis by compromising STAT3 phosphorylation. This action leads to downregulation of BCL2 like 1 and Survivin. SD-1029 may have therapeutic potential in ovarian cancer by influencing key molecular pathways associated with cell survival and apoptosis. Targeting proteins like BCL2 like 1 and Survivin could be a strategy to promote cancer cells death in ovarian cancer [136], and in chordoma also a reduced of cell growth rate could be observed [137].

12. Inhibition of protein activity

Apart from inhibiting Survivin gene expression, there are other approaches aimed at impairing Survivin protein activity. These alternative strategies focus on influencing the protein itself rather than its production at the genetic level. The approaches include destabilizing its structure, inhibiting the formation of dimers and decreasing its half-life. Shepherdin, a peptide antagonist of the Hsp90-Survivin complex, interacts with the ATP-binding motif of the Hsp90 protein, destabilizing and degrading Survivin. Shepherdin has shown an antitumor effect both *in vitro* and *in vivo*; in cervical cancer it drastically reduces cell viability, inhibited colony formation and induced apoptosis [138,139]. Systemic treatment of glioblastoma U87 cell line xenografted mice suppressed tumor growth and prolonged the animal's survival [140]. In a xenograft model of AML it inhibited tumor growth [141] as well as for gallbladder carcinoma [142].

5-Aminoimidazole-4-carboxamide ribonucleotide (AICAR) is a natural intermediate of purine biosynthesis detected in all organisms. The molecule interacts with the amino-terminal domain of the Hsp90 protein inducing destabilization in its interactors, including Survivin, which are ubiquitinated and degraded by proteasome [143]. Through regulation of the AMPK/mTOR pathway, the molecule inhibited cell growth in prostate cancer, induced apoptosis and inhibited epithelium-mesenchyme transition (EMT). Furthermore, it also shows no adverse effects in non-cancerous cells [144]. In osteosarcoma cells it inhibited cell growth and both *in vitro* and *in vivo* stimulated apoptosis [145]. In acute lymphoblastic leukemia (ALL) it reduced expression of Immediate Early Genes (IEGs), involved in survival, proliferation and adaptation of cancer [146].

13. Other molecules that impair the function of the Survivin protein

UC112, an indole-based analog, specifically interacts with Survivin's BIR domain, destabilizing the protein, which is degraded *via* proteasome [147]. Abbott-8 was identified among a number of synthetic molecules in the Abbott laboratories; in particular, for Survivin/Abbott-8 complex a new binding site was identified at the interface of the two Survivin monomers [148]. LLP3 and LLP9 molecules, designed on Abbott-8 basis, are effective in inhibiting Survivin dimers [149]. *In silico* prediction experiments suggested that Survivin Antagonist-S12 molecule inhibited Survivin dimerization localizing close to the interface involved in the Survivin dimerization as established by mutagenesis experiments of substitution of the Phe86 and Val89 residues. Further experiments established its efficacy in inhibiting the functionality of the protein [150]. Inhibition of the phosphorylation of the amino acid residue Thr34 in Survivin by CDKs through treatment with Flavopyridol reduced its half-life [151]. Overall, many experimental evidences demonstrate the proven antitumor capacity of the aforementioned Survivin inhibitors in various cancers [152–155]. The chemical name of the compounds cited are depicted in Table 3.

Table 3
IUPAC nomenclature for the chemical compounds discussed in the text.

Chemical compounds	IUPAC name
YM155	1-(2-Methoxyethyl)-2-methyl-3-(pyrazin-2-ylmethyl)benzo[*f*]benzimidazol-3-ium-4,9-dione;bromide
Deguelin	(1*S*,14*S*)-17,18-Dimethoxy-7,7-dimethyl-2,8,21-trioxapentacyclo[12.8.0.03,12.04,9.015,20]docosa-3(12),4(9),5,10,15,17,19-heptaen-13-one
Gemcitabine	4-Amino-1-[(2*R*,4*R*,5*R*)-3,3-difluoro-4-hydroxy-5-(hydroxymethyl)oxolan-2-yl]pyrimidin-2-one
Wogonin	5,7-Dihydroxy-8-methoxy-2-phenylchromen-4-one
Paclitaxel	[(1*S*,2*S*,3*R*,4*S*,7*R*,9*S*,10*S*,12*R*,15*S*)-4,12-Diacetyloxy-15-[(2*R*,3*S*)-3-benzamido-2-hydroxy-3-phenylpropanoyl]oxy-1,9-dihydroxy-10,14,17,17-tetramethyl-11-oxo-6-oxatetracyclo[11.3.1.03,10.04,7]heptadec-13-en-2-yl] benzoate
Cisplatin	Azane; dichloroplatinum
Tamoxifen	2-[4-[(Z)-1,2-Diphenylbut-1-enyl]phenoxy]-*N*,*N*-dimethylethanamine
Doxorubicin	(7*S*,9*S*)-7-[(2*R*,4*S*,5*S*,6*S*)-4-Amino-5-hydroxy-6-methyloxan-2-yl]oxy-6,9,11-trihydroxy-9-(2-hydroxyacetyl)-4-methoxy-8,10-dihydro-7H-tetracene-5,12-dione
LLP3	4-[3,5-bis(Phenylmethoxy)phenyl]-6-(5-chloro-2-hydroxyphenyl)-2-oxo-1H-pyridine-3-carbonitrile
Flavopyridol	2-(2-Chlorophenyl)-5,7-dihydroxy-8-[(4*R*)-3-hydroxy-1-methylpiperidin-4-yl]chromen-4-one

14. Conclusion and future prospects

Survivin is the first member discovered within the IAP family. This polypeptide, later named Inhibitor of Apoptosis Protein, IAP, exhibits a unique structure with a single BIR domain and α-helical folding in the C-terminal region when compared to other IAP family members. While virtually absent in adult tissues, Survivin plays a crucial role in ASCs, particularly in maintaining their undifferentiated state. In cellular physiology, Survivin plays essential roles in cell cycle progression, chromosomal segregation, and apoptosis. In contrast, in cancer, Survivin shows a distinct functional pattern: specifically, its expression decreases in almost all phases of the cell cycle and increases in the G2/M phase. Moreover, Survivin is overexpressed in numerous tumor forms and, in cancer stem cells, its overexpression correlates with self-renewal capacity. For nearly two decades, Survivin has been proposed as a potential anticancer target. Survivin isoforms, documented in the literature, exhibit structural variations, affecting the BIR domain or the C-terminal structure when compared to the *wild type*. The expression pattern of Survivin isoforms appears dysregulated in several tumors, suggesting that structural variations may exert a negative trans-dominant effect, compromising the *wild type* dimer functionality. In cervical cancer, the ΔEx3 isoform inhibits tumor growth and clonogenic potential when overexpressed: this result contradicts the role of Survivin isoforms and deserves further investigation, in various forms of cancer. Survivin is a key player in complex molecular mechanisms involving numerous protein-protein interactions. Future perspectives may focus on a deeper understanding of the functionality of different dimeric products in terms of protein-protein interactions to identify potential targets involved in tumorigenesis. Survivin is generally modulated by cancer pro-survival cell signaling pathways, such as MAPK, JNK, PI3K/AKT, and JAK/STAT, in several cancer contexts. Experimental evidences report that some inhibitors not only modulate expression of these signaling pathways but also downstream Survivin expression. Examples include CI-1040 and PD0435901 for MAPK signaling, Bentamapimod for the JNK pathway, Trastuzumab for PI3K/AKT, and TG101209 for JaK/STAT signaling. These molecules have provided valuable results regarding inhibition of tumor growth *in vitro* or *in vivo* models. The presence of SNPs in Survivin is also known, both in the coding and non-coding sequences; those examined in this article generally correlate with a risk of tumorigenesis. Performing comprehensive functional studies to investigate the role of specific SNPs in Survivin, within *in vitro* tumor models, by employing SNP-correction through the CRISPR/Cas9

method, holds significant scientific interest. We have discussed impairment of Survivin in various tumor models, not only through silencing of canonical signaling pathways that regulate Survivin expression but also through multiple regulatory mechanisms, from epigenomic to translational. Apigenin, despite demonstrating significant anticancer properties, does not seem to be specific in silencing Survivin; instead, it inhibits expression of all IAP members. The CRISPR/Cas9 method to silence Survivin has not entered clinical trials. It is worth considering that knowledge regarding the function of Survivin is not yet fully understood, and the presence of potential off-targets inherent in the method could affect the exclusive gene targeting. The inhibition of transcription by the drug YM155 has been studied in various tumor forms, both *in vitro* and in different clinical trials. However, despite achieving a high safety profile, the drug has not shown a substantial improvement in the response rate in advanced NSCLC. Messenger RNA translation has been inhibited by the oligonucleotide LY2181308, and in various tumor models of lung, colon, pancreas, liver, breast, prostate, ovary, cervix, skin, and brain, it has demonstrated its efficacy. Other molecules have been designed to destabilize the protein, and many experimental evidences have demonstrated their proven effectiveness in combating tumorigenesis. Overall, it can be asserted that, despite the considerable knowledge about the function of Survivin, there is undoubtedly room for expansion through basic research. In conclusion, several Survivin inhibition strategies seem to compromise tumor development.

CRediT authorship contribution statement

Giuseppe Siragusa: Conceptualization, Writing – original draft, Writing – review & editing. **Laura Tomasello:** Data curation, Investigation, Validation. **Carla Giordano:** Conceptualization, Funding acquisition, Writing – review & editing. **Giuseppe Pizzolanti:** Data curation, Supervision, Validation, Writing – review & editing.

Declaration of competing interest

The authors have no conflicts of interest to declare. All co-authors have seen and agree with the contents of the manuscript and there is no financial interest to report.

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