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Recent Advances on Small-Molecule Survivin Inhibitors

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Abstract

Survivin, a member of the inhibitor of apoptosis proteins family, is highly expressed in most human neoplasms, but its expression is very low or undetectable in terminally differentiated normal tissues. Survivin has been shown to inhibit cancer cell apoptosis and promote cell proliferation. The overexpression of survivin closely correlates with tumor progression and drug resistance. Because of its key role in tumor formation and maintenance, survivin is considered as an ideal target for anticancer treatment. However, the development of small-molecule survivin inhibitors has been challenging due to the requirement to disrupt the protein-protein interactions. Currently only a limited number of survivin inhibitors have been developed in recent years, and most of these inhibitors reduce survivin levels by interacting with other biomolecules instead of directly interacting with survivin protein. Despite these challenges, developing potent and selective small-molecule survivin inhibitors will be important in both basic science to better understand survivin biology and in translational research to develop potentially more effective, broad-spectrum anticancer agents. In this review, the functions of survivin and its role in cancer are summarized. Recent developments, challenges, and future direction of small-molecule survivin inhibitors are also discussed in detail.

Keywords

BIRC5 inhibitor; inhibitor of apoptosis proteins; protein-protein interaction inhibitor; small-molecule anticancer agent; survivin and cancer; survivin inhibitor

Introduction

Survivin, an anti-apoptotic protein, was discovered by Grazia Ambrosini and Dario C. Altieri in 1997[1]. Survivin is a member of the inhibitor of apoptosis proteins (IAP) family of which there are eight members: NAIP (NLR family, apoptosis inhibitory protein), c-IAP1, c-IAP2, XIAP (X-linked inhibitor of apoptosis), livin, ILP-2, apollon, and survivin (Figure 1) [2–5]. Each member contains at least a single baculoviral IAP repeat (BIR) domain at the N-terminus region [2]. Survivin is encoded by baculoviral inhibitor of apoptosis repeat-

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Conflict of Interest

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containing 5 (BIRC5), so it is also called BIRC5. Compared with other IAPs that contain multiple domains, survivin is structurally unique because it contains only one single BIR domain. It is the smallest member of the IAP family, has a molecule weight of 16.5 kDa, and contains 142 amino acid residues [6, 7]. Unlike other IAPs that are expressed in both cancerous and normal cells, survivin is expressed only in the vast majority of neoplasms but not in most normal differentiated tissues [8–11]. Survivin also contributes to tumor formation and maintenance because of its functional properties [12, 13]. Therefore, targeting survivin represents a very attractive strategy in cancer drug discovery. However, due to the requirement of efficiently disrupting protein-protein interactions which typically have large interface areas, the development of small-molecule survivin inhibitors has been very challenging. Thus the number of currently available survivin inhibitors is small. In addition, most of these inhibitors target other biomolecules and ultimately reduce the level of survivin, rather than directly interact with survivin protein itself. Despite these challenges and limitations, developing new potent and selective small-molecule survivin inhibitors will be important in both basic science and translational research to develop them into potentially effective, broad-spectrum therapeutic agents. In this review, we first describe the functions of survivin, its role in cancer progression and potential therapy. Then we focus on recently developed small-molecule survivin inhibitors. Challenges for developing survivin inhibitors and future direction will also be covered.

Functions of survivin

The main established functions of survivin are the regulation of cell mitosis and the inhibition of apoptosis as illustrated in Figure 2. Survivin plays an essential role in cell mitosis [14], during which survivin regulates cell division through a multiprotein complex called chromosomal passenger complex (CPC) as shown in Figure 2. In this complex, survivin is associated with other regulators of cytokinesis including aurora kinase B, INCENP, and borealin [15–17]. CPC is essential for accurate chromosome segregation and cytokinesis. Survivin and its molecular partners in the CPC fundamentally control genetic stability of cells [18]. Survivin has also been shown to be associated with regulating microtubule dynamics [19–21]. Survivin stabilizes the microtubules, thereby contributing to the formation of the bipolar spindle [21].

Similar to other members in the IAP family, one main function of survivin is the inhibition of apoptosis as shown in Figure 2 [22–25]. Although it has been confirmed that survivin inhibits apoptosis, the exact mechanism of inhibition is still under debate over two major theories. One theory is that survivin directly binds to caspases and subsequently inhibits apoptosis. The interaction between survivin and the effector caspases has been reported by several groups [22, 23]. The second theory is that survivin inhibits caspase activity through indirect mechanisms to inhibit apoptosis [26–28]. One example proposes that survivin binds to XIAP to form a complex that inhibits the activation of caspase-9 [26, 27]. In another example, a survivin-hepatitis B X-interacting protein (HBXIP) complex binds to procaspase-9 to suppress apoptosis [28].

Roles of survivin in cancer

Both the functions of promoting cell proliferation and inhibiting apoptosis contribute to the formation and maintenance of tumors. Because the expression level of survivin in normal cells and malignant cells is largely different, survivin can be used as a tumor biomarker [29–31]. Many studies have confirmed that survivin is overexpressed in a variety of cancers (e.g., lung, breast, pancreatic, and melanoma) [32–35]. Survivin has also been shown to be responsible for multiple types of drug resistance [36–39]. For example, it has been reported that taxol-treated HeLa cells show an increased level of survivin expression, which provides a cell survival pathway to counteract taxol-induced apoptosis [19]. Overexpression of survivin has also been reported in prostate cancer and thyroid cancer cells that are resistant to cisplatin treatment [40, 41]. Because survivin is crucial in the process of carcinogenesis, knockout of survivin impedes the development of cancer. A recent study showed that loss of survivin in the prostate epithelium inhibited the progression of prostatic premalignant lesions to adenocarcinoma in the Pten-deletion mouse model [42]. The study confirms the role of survivin in cancer progression.

Targeting survivin for cancer treatment

Survivin has been proposed as an attractive target for selective cancer treatment because of its unique attributes [43]. The following features are some reasons that targeting survivin is a good strategy. First, the expression of survivin is typically very high in tumor cells but very low or even undetectable in normal adult tissues [8]. This feature is highly significant, because it provides selectivity, a major problem for current cancer drug development. Second, the functions of survivin contribute to the formation and maintenance of tumors [44], so targeting survivin will be very effective for treating cancer. Furthermore, survivin has been shown to be associated with resistance to multiple types of cancer therapies [45–47]. Targeting survivin can help overcome the multidrug resistance which is one of the major reasons many therapeutic agents fail in clinic. However, there are still significant challenges associated with using survivin as a drug target. Small-molecule survivin inhibitors have to disrupt the protein-protein interaction between survivin and other proteins, which could be difficult because most interfaces in protein-protein interactions (PPIs) are not well suitable for effective small molecule binding [48]. Despite the difficulties for small molecules to disrupt protein-protein interactions, there are some successful PPI inhibitors [49], including tirofiban (targeting the integrins) and maraviroc (targeting CCR5–gp120 interactions) which are already on the market [50, 51]. Those successes are probably attributed to the fact that most PPIs have “hot spots” which are small parts of the interface that are essential for high-affinity binding [52]. Small-molecule PPI inhibitors can either interact with those hot spots or bind to allosteric sites to cause conformational change that will prevent protein-ligand binding, which will result in the desired disruption of protein-protein interactions. In the case of developing small-molecule survivin inhibitors, the Ala-Val-Pro-Ile (AVPI) peptide binding region has been proposed as a hot spot for small molecule inhibition [53, 54]. Therefore, targeting survivin is tractable for cancer treatment in spite of the challenges. Many survivin inhibitors have been reported in the literature. These survivin inhibitors are mainly composed of six categories: antisense oligonucleotides, dominant-negative mutant, ribozymes, small interfering RNAs, cancer vaccine, and small-

molecule inhibitors. Several reviews have been published covering all kinds of survivin inhibitors in general [6, 55, 56], but no review specifically focuses on small-molecule survivin inhibitors, which is the focus of this review. As we discussed earlier, most existing survivin inhibitors do not directly bind and interact with survivin protein itself, instead, they usually target other biomolecules and ultimately reduce survivin expression. Figure 2 shows three representative examples. The first example is YM155 which inhibits survivin by inhibiting survivin gene promoter on the transcriptional level [57]. The second example is represented by cyclin-dependent kinase (CDK) inhibitors. For example, the CDK inhibitor flavopiridol inhibits survivin phosphorylation on Thr34 which leads to progressive loss of survivin expression [58]. The last example shown in Figure 2 for indirect targeting survivin are Hsp90 inhibitors which disrupt the interaction between survivin and Hsp90, destabilize survivin protein and ultimately lead to survivin degradation. In the following sections, we will discuss each reported small-molecule survivin inhibitor (arranged alphabetically) in detail.

Existing small-molecule survivin inhibitors

AICAR (1)

The nonpeptidic, small-molecule 5-aminoimidazole-4-carboxamide-1- β -D-ribofuranoside (AICAR) as a structurally novel inhibitor of Hsp90 was developed through a combined structure- and dynamics-based computational design [59]. AICAR mimics the binding and functional properties of the peptidic antagonist of the survivin-Hsp90 complex, shepherdin. The AICAR/Hsp90 interaction studies revealed that AICAR is involved in direct contacts with Asp93 of Hsp90 through the two hydroxyl groups on position 3 and 5 of the ribose ring, suggesting that replacement of these residues with other polar groups may strengthen the interaction. This is also true for the polar substituents on the imidazole ring. AICAR has been shown to exhibit excellent anti-proliferative activities in multiple cancer cell lines including DU145, JR8 and Hela cells. While AICAR is very potent in inhibiting the growth of tumor cells, it does not affect the proliferation of normal human fibroblasts. AICAR exerts its anticancer activities by inhibiting the chaperone function with destabilization of multiple Hsp90 client proteins, including survivin [59].

Arctigenin (2)

Arctigenin, a ligand isolated from the seeds of *Arctium lappa*, shows anti-proliferative activities against a series of cancers [60, 61]. A study illustrates the mechanism of its anticancer effect [61]. The results showed that arctigenin executed its antitumor effect by inhibiting STAT3 phosphorylation and survivin expression. The level of survivin was significantly reduced in arctigenin-treated ovarian cancer cells. Arctigenin has also been shown to sensitize tumor cells to cisplatin treatment by inhibiting survivin [60].

Cephalochromin (3)

Cephalochromin, a compound isolated from the fermented broth of *Cosmospora vili*or YMJ89051501 [62], is used as an antibacterial agent. It has been reported that cephalochromin can inhibit cell growth and induce apoptosis in human lung cancer cells with IC₅₀ value of 2.8 μ M [62]. Cephalochromin was found to exert its antitumor effect by

downregulating several anti-apoptotic proteins, including survivin. The expression level of survivin was significantly reduced in cephalochromin-treated A549 lung cancer cells compared with untreated cells. Due to the survivin suppression effect, caspases-8, -9, and -3 are activated, which is responsible for the induced apoptosis. The anti-proliferative effect of cephalochromin reveals the therapeutical potential of this antibacterial agent in treating cancer.

FL118 (4)

FL118 was first reported by Ling et al. in 2012 [63]. FL118 was identified through high throughput screening of compound libraries following *in vitro* and *in vivo* analysis. FL118 can inhibit cancer cell growth in a concentration of less than 1 nM. It has shown excellent antitumor activity in a series of cancer cell lines including HCT116 colon cancer cells, A549 lung cancer cells, MCF7 breast cancer cells, and PC-3 prostate cancer cells. Its antitumor activity results from inhibiting survivin promoter activity and survivin gene expression [63]. The study also demonstrated that FL118 can inhibit expression of other cancer-associated IAPs such as Mcl-1, XIAP, and cIAP2, further enhancing its anticancer activity. The *in vivo* studies indicated that FL118 has excellent antitumor efficacy without significant toxicity [63]. The superior anticancer activity of FL118 largely depends on its steric configuration. FL118, which has an *R*-configuration, has much better activity than its analog FL113 with an *S*-configuration. In addition, the free hydroxyl group on position 20 of FL118 is essential for activity. Esterification of the hydroxyl group on position 20 resulted in almost complete loss of activity[64]. The superior efficacy and selectivity hold significant promise for the further clinical development of FL188 and its core structure-derived analogs.

Flavopiridol (5)

Flavopiridol is a broad spectrum, cyclin-dependent kinase (CDK) inhibitor. In the study by Nathan *et al.*, flavopiridol caused progressive loss of survivin expression by inhibiting survivin phosphorylation on Thr34 when incubated with HeLa cells [58]. Thr34 phosphorylation of survivin is a critical requirement for survivin function [65]. Sequential treatment with flavopiridol and other anticancer agents enhanced anticancer activity both in breast carcinoma MCF-7 cells and SCID/bg mice bearing MCF-7 xenograft tumors [58]. A recent study showed that flavopiridol inhibited human uterine leiomyoma growth both *in vitro* and in a xenograft model [66]. Flavopiridol is now in Phase II clinical trial [67, 68]. In one phase II clinical trial of flavopiridol, the combination of flavopiridol and cisplatin treatment showed clinical activity in platin resistant and sensitive ovarian/primary peritoneal cancers [68].

ICG-001 (6)

ICG-001 is a small-molecule inhibitor of β -catenin/T cell factor (TCF)-mediated transcription [69]. It has been shown that the survivin gene is mediated by TCF/ β -catenin. The treatment of SW480 and HCT116 colon cancer cells with ICG-001 clearly showed the inhibition of survivin gene transcription. The survivin inhibition effect was also observed in the SW620 xenograft tumors in the ICG-001-treated group. The inhibition of survivin expression results in induction of apoptosis, which causes tumor growth inhibition. Because survivin is upregulated in most cancer cells but not in normal tissues, ICG-001 increases

caspase activity in colon carcinoma cell lines (SW480 or HCT116) but not in normal colonic epithelial cells [69]. The specificity and strong potency of ICG-001 promise it to be a new anticancer therapeutic agent.

KPT-185 (7)

KPT-185, a selective inhibitor of nuclear export, has been shown to be effective in several cancers including pancreatic cancer, acute myeloid leukemia, mantle cell lymphoma, and nonsmall cell lung cancer (NSCLC) [70–73]. KPT-185 can significantly induce growth inhibition and apoptosis of tumor cells. A recent study showed that the survivin level is downregulated in KPT-185-treated NSCLC cell lines. The survivin level was also suppressed in an NSCLC H1975 xenografted model when treated with KPT-185 [73]. The survivin inhibition effect of KPT-185 contributes to its antitumor efficacy. Although KPT-185 has strong cytotoxicity, it is not suitable for *in vivo* use due to poor PK properties, while its analog KPT-330 which attaches a 2-pyrazinylhydrazinyl group to the carbonyl group and replaces the methoxy substitution on the phenyl ring with a trifluoromethyl group compared with the structure of KPT-185, has comparable potency as KPT-185 and optimal PK properties [74].

Lapatinib (8)

Lapatinib, a potent small-molecule inhibitor of ErbB1 and ErbB2 tyrosine kinases, has been shown to markedly suppress survivin expression and subsequently induce apoptosis when treated in ErbB2-overexpressing breast cancer cell lines, such as BT 474 [75]. The inhibition of survivin by lapatinib is primarily posttranslational through the promoted ubiquitin-proteasome degradation of the survivin protein. The observation that the protein levels of His-tagged survivin, which are under the transcriptional control of a heterologous promoter and endogenous survivin are equally downregulated in response to lapatinib provides evidence for a posttranslational mechanism by which lapatinib regulates survivin. Lapatinib causes synergistic effects when used with other cytotoxic agents such as sorafenib [76]. Lapatinib is now in Phase 3 clinical trial [77, 78].

MK-2206 (9)

MK-2206, a novel allosteric inhibitor of Akt [79, 80], has strong anticancer efficacy in a series of cancer cells [79, 80]. It has been shown that Akt phosphorylation is associated with the formation of survivin/XIAP complex. Deactivating Akt phosphorylation can lead to downregulation of survivin [81]. As an Akt inhibitor, MK-2206 suppresses survivin. In a study, the level of survivin was reduced both in GEO cancer cells and GEO cell xenografted model when treated with MK-2206, which led to increased cancer cell death via apoptosis [82]. MK-2206 is now actively evaluated as a new anticancer agent and is now in Phase II clinical trial.

NU6140 (10)

NU6140, (4-(6-cyclohexylmethoxy-9Hpurin-2-ylamino)-N, N-diethyl-benzamide) is a novel CDK inhibitor developed by Davies *et al.* in 2002 through structure-based design [83]. Structure-activity relationships for this compound indicate that a cyclic hydrophobic

substituent at O⁶-position such as cyclohexylmethyl is optimal and the extended groups at N²-position increased potency and selectivity. It has been shown that CDK1-mediated phosphorylation of survivin on Thr34 is essential for the cytoprotective function of survivin [65]. As a CDK inhibitor, NU6140 induced a concentration-dependent decrease in the level of survivin protein when treated in HeLa Cells. In addition, the level of the active, Thr34-phosphorylated form of survivin was reduced in a concentration-dependent manner after HeLa cells were treated with NU6140 [84]. Because the CDK inhibitor NU6140 can inhibit the expression and phosphorylation of survivin, a combination treatment of taxol and NU6140 in HeLa cells causes a synergistic effect on tumor growth inhibition.[84]

Panepoxydone (11)

Panepoxydone, a secondary metabolite isolated from an edible mushroom, has long been known for its antibacterial effect. Studies have shown that panepoxydone interferes with NF- κ B, which can lead to tumor inhibition [85, 86]. Panepoxydone caused significant growth inhibition in MCF-7 and TNBC cell lines MDA-MB-231, MDA-MB-468, and MDA-MB-453 [86]. The induction of apoptosis is one main factor contributing to tumor cell growth inhibition. Mechanism of action studies showed that the survivin level in the panepoxydone-treated cells was reduced, which was responsible for inducing apoptosis. The strong antitumor effect of panepoxydone promises its further development.

Piperine (12)

Piperine, an alkaloid from black pepper, inhibits the growth of several colon cancer cell lines [87]. The mechanism of action studies showed that the survivin protein levels in piperine-treated HT-29 colon carcinoma cell were reduced compared with untreated cells. The survivin inhibition effect of piperine may account for the inhibition of apoptosis and cell growth observed in piperine-treated cancer cells. Piperine can also sensitize cancer cells to other chemotherapeutic agents due to its survivin inhibition effect [88, 89].

Purvalanol A (13)

Purvalanol A is p34^{cdc2}-specific CDK inhibitor. Studies have shown that elevated p34^{cdc2} kinase activity can lead to increased survivin expression [19]. Purvalanol A as a p34^{cdc2}-specific inhibitor not only inhibits Cdc2 activity, but also suppresses survivin expression [90]. Purvalanol A can inhibit the mitotic phosphorylation of survivin on Thr34, which causes protein destruction of survivin and blockage of its function. The hyperphosphorylation of survivin on Thr34 has been found to be associated with the drug resistance of taxol in tumor cells [91]. Co-administration of taxol with purvalanol A suppressed the hyperactivity of survivin imposed by taxol, which helped overcome the taxol drug resistance [19]. Purvalanol A can also inhibit ABCB1 transporter and cause synergistic effects when used in combination with other anticancer drugs that are ABCB1 substrates [92].

Shepherdin (14)

Shepherdin, a novel antagonist of the survivin-Hsp90 complex, was discovered by Janet *et al.* in 2005 [93]. Shepherdin is actually the survivin sequence K79-L87 (KHSSGCAFL). It

was named shepherdin because it binds to the “shepherding” chaperone Hsp90. Binding assay results revealed that shepherdin was bound to the N domain of Hsp90, while no specific binding of shepherdin to the C domain of Hsp90 was observed. Shepherdin disrupts the interaction between survivin and Hsp90 through the ATP binding pocket of Hsp90. Shepherdin can also destabilize survivin and several other client proteins of Hsp90, such as Akt, CDK6, and telomerase, which cause cancer cell death via apoptotic and nonapoptotic mechanisms. Shepherdin has very good selectivity, because it does not affect normal cells while maintaining excellent antitumor activity [93]. Shepherdin can sensitize tumor cells to different cytotoxic drugs because of its survivin suppression effect. For example, shepherdin sensitized imatinib mesylate-resistant chronic myelogenous leukemia cells to hydroxyurea or doxorubicin in a recent study [88]. Current clinical development is through the Rapid Access to Intervention Development (RAID) program at the National Cancer Institute.

Terameprocol (15)

Terameprocol, meso-tetra-O-methyl nordihydroguaiaretic acid, also known as M4N, has been reported to inhibit HIV transactivation [94]. Terameprocol was made based on 3'-O-methylnordihydroguaiaretic acid, which was isolated from *Larrea tridentata*. Subsequent studies showed that terameprocol as a transcription inhibitor can inhibit tumor growth by inhibiting expression of Cdc2 and survivin [95, 96]. In the study of Chang *et al.* [96], terameprocol-treated C3 cells showed downregulation of Cdc2 and survivin expression. The observation that C3 cells transfected with Cdc2 and survivin were resistant to terameprocol-induced cell arrest or death confirmed the tumor growth inhibition mechanisms of terameprocol. Terameprocol significantly enhanced the sensitivity of nonsmall-cell lung carcinoma cells to radiation therapy in the study of Sun *et al.* [97]. Now terameprocol is in Phase I clinical trial [98, 99]. The clinical results have shown that this agent has an excellent safety profile in cervical intraepithelial neoplasia, making it a promising candidate for anticancer treatment [98].

UC112 (16)

UC112 was recently reported by our group as a potent and selective survivin inhibitor [53]. It was identified through a similarity-based virtual screening in which the three-dimensional shape of the AVPI peptide in the survivin-Smac crystal complex was used as the template for searching hit structures, followed by biological validation. UC112 showed broad anti-proliferative activities as indicated by NCI-60 cell line screening and preliminary *in vivo* studies in an A375 melanoma tumor model. Interestingly, preliminary studies showed that UC112 selectively downregulated survivin level with minimal effects on other members of IAPs. [53] This compound may represent a unique scaffold for the development of new selective survivin inhibitors. Further modifications of this compound are currently being carried out.

YM155 (17)

YM155, 1-(2-Methoxyethyl)-2-methyl-4, 9-dioxo-3-(pyrazin-2-ylmethyl)-4, 9-dihydro-1*H*-naphtho [2, 3-*d*] imidazolium bromide, a small-molecule survivin inhibitor, was first discovered by Astellas Pharma in 2007 [57]. It suppresses survivin gene promoter in PC-3 and PPC-1 human HRPC cell lines at 10 nmol/L in cell based proliferation assay. It also

shows very good selectivity of survivin over other IAPs. In the study of Nakahara *et al.*, YM155 suppressed survivin expression but had little effect on the expression of other IAPs even up to 100 nmol/L. YM155 induced tumor regression in PC-3 xenografted tumor model [57]. YM155 can help overcome drug resistance in tumors when used with other chemotherapeutic agents. For example, YM155 reversed rapamycin resistance in rapamycin-resistant renal cell carcinoma [100], and the combination of YM155 and cisplatin induced apoptosis and tumor regression in cisplatin-resistant ovarian cancer cells [101]. YM155 is now in Phase II clinical trial [102, 103]. Recent studies have shown that YM155 is a substrate of the P-glycoprotein [104], suggesting that it may suffer from multidrug resistance in its later clinical use.

Challenges for development of survivin inhibitors

Although survivin is a very promising target for cancer treatment and many studies have been carried out to develop survivin inhibitors, the pool of existing survivin inhibitors is still relatively small. Several problems limit the development of effective survivin inhibitors. Unlike an enzyme or a receptor molecule located on the cell surface, survivin is not a traditional target. Survivin is a nodal protein involved in multiple processes of cancer cell proliferation, including mitosis, apoptosis and autophagy. It also interferes with various molecules such as Hsp90, Borealin, INCENP, aurora B kinase and caspases. Therefore, it is a significant challenge and is very critical to unambiguously confirm that the drug action is resulted from survivin-specific inhibition. Because of such challenges, currently it is difficult to evaluate the effectiveness and target specificity of survivin inhibitors accurately via high throughput assays. The lack of suitable assays to identify survivin inhibition by high throughput screenings is one main factor to impede the development of potent and selective survivin inhibitors. Moreover, recent studies have shown that survivin exists in certain types of normal cells, mainly hematopoietic and immune systems [105]. Potential side effects will be a concern for those normal cells. Although clinical studies of survivin inhibitors to date have shown that targeting survivin does not cause toxic side effects, the prolonged use of survivin inhibitors should still be carefully studied because of the emerging role of survivin in regulating functions in normal cells.

Conclusion remarks and future directions

The results from studies in the past fifteen years provide convincing evidence that survivin is a promising target for cancer therapy treatment. As discussed in this review, survivin distinguishes itself by its unique functional properties, preferentially expressed in most human cancer cells, and involves in a myriad of cellular functions. Survivin contributes to tumor formation and progression which makes it a promising cancer drug target. Although there are significant challenges in developing effective survivin inhibitors and the number of small-molecule survivin inhibitors is still very limited, several potent survivin inhibitors have entered clinical trials, including flavopiridol, lapatinib, terameprocol, MK-2206 and YM155. Most of them have shown positive initial results, suggesting it is feasible to develop small-molecule inhibitors as efficacious anticancer drugs. Lapatinib is the most promising one among them, which is now in phase 3 clinical trials. Currently the lack of a survivin-specific assay is limiting the development of novel small-molecule survivin inhibitors.

Developing optimized assays will greatly accelerate research in this field. In addition, further investigations of differential mechanisms regulating survivin expression and functions in tumor and normal cells will be critical to develop novel strategies for selective survivin inhibition by small molecules. Finally, it is well recognized that the efficacy of any single agent including a survivin inhibitor may be limited due to high heterogeneity and plasticity in tumor cells. Not surprisingly, the combination of survivin inhibitors and other traditional chemotherapeutical agents have been evaluated and shown enhanced clinical efficacy, indicating the inhibition of survivin can enhance the efficacy of other agents. Thus the next direction will be developing the best combinations of survivin inhibitors with other existing chemotherapeutical agents for the most efficacious strategy.

List of Abbreviations

AICAR	5-aminoimidazole-4-carboxamide-1- β -D-ribofuranoside
BIR	baculoviral IAP repeat
BIRC5	baculoviral IAP repeat-containing 5
CDK	cyclin-dependent kinase
CPC	chromosomal passenger complex
HBXIP	hepatitis B X-interacting protein
IAP	inhibitor of apoptosis proteins
M4N	meso-tetra-O-methyl nordihydroguaiaretic acid
NAIP	NLR family, apoptosis inhibitory protein
NSCLC	nonsmall-cell lung cancer
PPI	protein-protein interaction
RAID	Rapid Access to Intervention Development
TCF	T cell factor
XIAP	X-linked inhibitor of apoptosis

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Figure 1.
Schematic diagram of human IAPs

Figure 2.
Functions of survivin and targets of survivin inhibitors

Figure 3.
Chemical structures of recently developed small-molecule survivin inhibitors.