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Nanoparticle-mediated inhibition of survivin to overcome drug resistance in cancer therapy

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ABSTRACT

The acquired resistance of human cancer cells to apoptosis is one of the defining hallmarks of cancer. Upregulated expression of inhibitors of apoptosis proteins (IAP) has been implicated in drug resistance in several cancers. Survivin (encoded by BIRC5), the smallest member of the IAP family, has been correlated with both the control of cell apoptosis and regulation of cell mitosis in cancer. Owing to its critical role in regulation of cell survival and development of cancer resistance, as well as its distinguishingly high level of expression in many types of cancer, survivin has long been regarded as a promising therapeutic target for cancer therapy. This review first presents an overview of the mechanism by which survivin regulates cell function, followed by a discussion of the current state of survivin-targeted therapies. We focus on the application of nanoparticulate systems to deliver survivin inhibitors, co-delivery of survivin inhibitors with chemotherapeutic agents, synchronous targeting of survivin, other drug resistant molecules, and survivin regulators. We conclude by highlighting the current limitations associated with survivin-targeted therapies and speculating on the future strategies to surmount these impediments.

1. Introduction

Evasion of cell death is a hallmark of human cancers and represents a crucial cause of resistance to current treatment strategies including chemotherapy and radiotherapy [1,2]. Therefore, reactivation of cell death programmes, especially apoptosis, in therapy-resistant cancer cells is a logical strategy to overcome cancer resistance. Inhibitor of apoptosis proteins (IAPs) are a group of conserved proteins that act as endogenous apoptosis inhibitors by inhibiting caspases [3]. Upregulation of IAP expression has been correlated with drug resistance in several cancers [4]. Survivin (encoded by BIRC5), the smallest member of the IAPs family, has been associated with both the control of cell apoptosis and regulation of cell mitosis in cancer [5]. Owing to its preferential expression in tumor *versus* normal tissues [6], survivin has long been considered a prime cancer-specific drug target. Indeed, downregulation of survivin has been reported to sensitize cancer cells to various chemotherapeutic agents.

However, survivin-targeted therapy has only met with limited success in clinical trials, purportedly undermined by inefficient delivery and poor bioavailability of the synthetic inhibitors and/or interfering RNAs [5,7]. Moreover, many normal cell types also express survivin, including vascular endothelial cells (ECs), primitive hematopoietic cells and T lymphocytes [8]. Therefore, to improve the tissue- and cell-specificity of survivin inhibition, nanomedicine comes into the picture. This review begins with a comprehensive overview of the mechanism of cell function regulation involving survivin and the current progress in survivin-targeted therapies. It will be followed by a coverage of the recent and important achievement of survivin inhibition by nanoparticulate systems in four categories: (i) targeted delivery of survivin inhibitors; (ii) co-delivery of survivin inhibitors with chemotherapeutic agents; (iii) synchronous targeting of survivin and other drug resistant molecules; and (iv) targeting of survivin regulators. The review will end by highlighting the limitations of the current strategies and discussing the potential solutions.

2. The multifaceted role of survivin in cancer

2.1. Multiple functions of survivin

Survivin belongs to the IAP family, of which eight members have been identified, namely X-linked inhibitor of apoptosis (XIAP), ILP2, NAIP (NLR family, apoptosis inhibitory protein), livin, BRUCE, c-IAP1, c-IAP2 and survivin [9]. As the smallest member of the mammalian IAP family,

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survivin (16.5 kDa) contains only one baculovirus IAP repeat (BIR) and lacks a carboxy-terminal RING finger or other identifiable domain [6]. Not being a kinase, an enzyme or a typical scaffold protein, survivin is widely expressed in various human cancers and functions as a promoter or inhibitor in various intracellular events in cancer cells *via* interactions with other protein molecules [10]. Survivin is a nodal protein that interferes with the process of apoptosis regardless of which pathways the apoptosis is initiated [11]. However, survivin does not directly bind caspases [12], it interacts with XIAP to inhibit the caspase-dependent apoptotic pathway [13]. Survivin also possibly exerts its anti-apoptotic function by binding to Smac/DIABLO, which is a known proapoptotic protein that counteracts the interactions of XIAP with caspase-9 and -3 [12].

In addition to regulation of cell death, survivin is likely essential for cell division. Localized at the microtubules of the mitotic spindle [14], survivin shows a cell cycle-regulated expression manner in the G2/M phase of the cell cycle [15]. Survivin is one of the four members of the chromosomal passenger complex (CPC), together with Borealin, Aurora B and INCENP, that regulates chromosome-microtubule attachment, activation of the spindle assembly checkpoint, and cytokinesis at cell division [16]. Survivin can be also characterized as a metastatic factor. It enhances cancer cell motility by supporting Akt activation and integrin α5 upregulation [17], and survivin-XIAP complex can activate NF-κB (nuclear factor kappa B), which in turn upregulates cell invasion and migration-related genes to promote motility and metastatic potential of cancer cells [18,19].

2.2. Role of survivin in cancer drug resistance

In retrospective studies, patients whose tumors expressing survivin are associated with a reduced overall survival, a resistance to chemotherapy, and an increase of recurrence rate [20]. Survivin is overexpressed almost 40-fold in tumors, rendering cancer cells resistant to both chemotherapy and radiotherapy [5,6]. Survivin can inhibit cell apoptotic function through both caspase-dependent and caspase-independent pathways [5]. It interferes with mitochondrial apoptosis-inducing factor (AIF) to block caspase-independent DNA fragmentation [21]. Survivin also promotes drug resistance by stabilizing microtubule organization [22], as overexpression of survivin leads to the development of resistance toward different microtubule destabilizers [23,24]. In that context, the combination of a microtubule-destabilizing agent BPR0L075 with survivin siRNA could prove synergistic in treating chemoresistant cancers [24]. Nuclear survivin interacts with the components of DNA-double-strand break (DSB) repair machinery and enhances the repair process [25,26]. In addition, growing evidence suggests that transient induction of survivin expression by vascular endothelial growth factor (VEGF) or basic fibroblast growth factor (bEGF) in ECs could promote tumor angiogenesis and tumor resistance against chemotherapeutic agents [8,27].

There are also reported correlations between survivin and other drug-resistant molecules. P-glycoprotein (P-gp) and survivin are always co-overexpressed in drug-resistant cancer cells [28], and survivin transcription is associated with P-gp overexpression [29]. Patients with acute myeloid leukemia (AML) who exhibit an upregulation in the transcription of MDR1 and survivin mRNA also show poor therapeutic response and survival [30]. Another study suggests a relation between expression of survivin and mutant p53 in renal cell carcinoma, but there is no correlation between P-gp and survivin in conferring drug resistance to renal cancer cells [31]. Additionally, survivin can also diminish p53-mediated NF-κB (p50) inhibition, which leads to the upregulation of drug transporter breast cancer resistance protein (BCRP) [32].

2.3. Survivin-targeted therapies

2.3.1. Antisense oligonucleotide and RNA interference

One of the most successful molecules in phase II clinical trials for targeting survivin is an antisense oligonucleotide, designated as LY2181308 [33]. It suppresses survivin at both the mRNA and protein levels, and produces strong antitumor activity in preclinical studies. In phase I trials, LY2181308 showed a favorable toxicity profile with evidence of survivin inhibition [34,35]. However, in a randomized phase II study that included 154 castration-resistant prostate cancer (CRPC) patients who received the combination of LY2181308 and docletaxel/prednisone, the results were less promising [36]. No difference in efficacy between the combination group and chemotherapy group was observed. On the other hand, a locked nucleic acid (LNA) antisense oligonucleotide targeting survivin, namely SPC3042, appears promising [37]. SPC3042 could induce cell cycle arrest, promote cellular apoptosis, downregulate Bcl-2 and sensitize prostate cancer cells to Taxol treatment *in vitro* and *in vivo*. A phase I clinical trial with SPC3042 also showed excellent safety results [38], suggesting that further investigation would be warranted.

RNA interference and hammerhead ribozymes are also used as molecular survivin antagonists [39]. Chemically synthesized small interfering RNA (siRNA) and plasmid/viral vectors encoding short hairpin RNAs (shRNAs) mediating survivin knockdown have been shown to induce caspase-dependent cell apoptosis in a variety of human cancers [40]. Knockdown of survivin using RNA interference is a promising strategy to overcome drug resistance due to the overexpression of survivin in resistant cancer cells [41–43]. It proves effective in sensitizing patient-derived acute lymphoblastic leukemia (ALL) drug-resistant cells to chemotherapeutic regimens with survivin shRNA [44]. Although the delivery of survivin-silencing RNAs *in vivo* remains suboptimal, the continuing innovations in nanocarrier development will likely realize the full potential of this therapeutic strategy in the future.

2.3.2. Synthetic survivin inhibitors

YM155 is the first small chemical molecule discovered to inhibit survivin expression by high-throughput screening (HTS) from in-house chemical compound libraries designed by *Astellas Pharma* in 2007 [45]. Using an artificial reporter system encompassing the survivin promoter, Nakahara and colleagues reported that the imidazolium-based compound YM155 specifically repressed survivin promoter activity with an IC_{50} of 0.54 nM. Moreover, the inhibitory ability of YM155 against survivin appears highly selective, with no activity against other IAP family proteins like cIAP2, XIAP [45] or cIAP1 [46] at concentrations up to 100 nM. In 2008, a phase I study involving 41 patients suffering from advanced solid malignancies or lymphoma established a maximum-tolerated dose (MTD) of YM155 (30 mg of YM155 in 3 mL lactic acid-based buffer, pH 3.6) treatment at 4.8 mg/m^2/day by continuous intravenous infusion (CIVI) [47]. However, a multicenter phase II study testing YM155 in 34 chemotherapy naive subjects with unresectable stage III or IV melanoma appeared less positive [48]. After YM155 treatment (4.8 mg/m^2/day CIVI for 7 days followed by a 14-day rest period) for up to 6 cycles, the objective tumor response rate (ORR) of patients to YM155 treatment was only about 3%. Another phase II study reported that YM155 (at similar dosage to the abovementioned study) exhibited only modest single-agent activity in stage IIIb/IV NSCLC patients, with an ORR of approximately 5.4% [49].

FL118 [50] and GDP566 [51] are another two survivin selective inhibitors discovered by HTS that exhibit potent anti-tumor activity *in vitro* and *in vivo*. Since survivin inhibitors show only limited antitumor efficacy in clinical trials, it may be fruitful to combine these agents with conventional chemotherapeutic agents in future clinical trials [52]. Indeed, combination therapy of YM155 with chemotherapeutics such as doxorubicin (DOX) [53], cisplatin [54], rapamycin [55], and erlotinib [56], has shown potential in reversing cancer drug resistance in animal studies.

2.3.3. Natural product-derived survivin inhibitors

Until now, >100 compounds have been reported to downregulate survivin expression based on their action against expression of survivin or downstream effector targets [57]. Most of these agents are small molecules, with the majority of them extracted from plants. However, unlike