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Factors Affecting the Inhibition of Survivin Degradation

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ABSTRACT

One family of anti-apoptotic proteins named the inhibitor of apoptosis proteins (IAPs) prevents cell death by blocking the downstream region of the caspase activation pathways. Survivin is a small member of the family of proteins that suppress apoptosis. Survivin performs various tasks that help cancer cells survival, including cytoprotection, preventing cell death, and controlling the cell cycle, particularly during the mitotic process. Cancer cells may survive with the help of survivin, as it is consistently up-regulated in human tumors, connected to poor prognosis, resistance to chemotherapy or radiation therapy, and associated with these treatments. Survivin is often regulated at two levels: the transcriptional level and the post-translational levels. In this review, the different proteins influence the progression of survivin degradation in post-translation adjustment were discussed such as FAT10, Usp22, Csn5; and LNC473. Finding and developing a therapy strategy that can adequately address the range of the aforementioned issues might be aided by understanding regulators and their mechanisms of action.

Keywords: Survivin, Post translational regulation, FAT10, Usp22, Csn5, LNC473

INTRODUCTION

One family of antiapoptotic proteins called the inhibitor of apoptosis proteins (IAPs) prevents cell death partly by blocking the downstream region of the caspase activation pathways [1]. IAPs can block at least two of the primary caspase activation pathways, including the extrinsic and intrinsic apoptosis pathways [1]. Nine family members of the regulatory protein class known as IAPs are melanoma IAP, IAP-like protein 2, X-linked IAP, cIAP1, cIAP2, neural apoptosis inhibitor protein, livin, apollon, and survivin [2-4]. One member of the IAPs family is survivin protein. Survivin is a protein that is encoded by the BIRC5 gene on chromosome 17q25. It has four exons and three introns, totaling 14,796 nucleotides, resulting in transcripts with different functional domains [5]. This protein has multifunctional domains, 142 amino acids (aa) and 16.5 kDa weighs. Survivin has a single BIR domain and a long carboxyl-terminus helix and forms a stable homodimer in solution [6,7]. In the majority of non-proliferating adult tissues, survivin cannot be detected. Additional evidence show that the survivin gene is commonly reactivated in malignancies comes from the fact that survivin is overexpressed in a range of human neoplasms and fetal tissues [8-11]. Currently, the expression analysis of the survivin protein is used as a prognostic indicator in several human neoplasms [11]. In contrast to malignancies that do not produce survivin, high survivin expression by neoplasms is associated with more aggressive behavior, reduced responsiveness to chemotherapeutic treatments, and shorter life spans. Thus, there is a great deal of biological interest in this protein since it has one of the most tumor-specific expression patterns of all gene products [11,12]. In fact, survivin and its alternate splicing variants are participated in critical cellular functions, including cell division and programmed cell death [8]. Survivin is necessary for the proper execution of mitosis and cell division [13]. Like most mitotic genes, its particular expression in G2/M is transcriptionally regulated [14,15]. Survivin connects to the mitotic spindle's microtubules via its carboxy terminal alpha helices during mitosis. Interfering with survivin-microtubule interactions via an antisense-mediated reduction in survivin expression results in the failure of its anti-apoptotic function and an increase in caspase-3 activity which leading to

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apoptosis [11,16]. Survivin dysfunction is associated with the different problems in cell division, such as polyploidy and multinucleation, extra centrosomes, multipolar mitotic spindles, and failure of cytokinesis [17,18]. Hence, studies have provided more evidence of vital role of survivin in mitosis. For example, in knockout mice, the loss of both copies of the survivin gene led to the death of embryos and the null embryos had trouble making microtubules and they couldn't complete cytokinesis [16].

The mechanism by which survivin inhibits apoptosis is still not fully known. Numerous tools are postulated. Some researchers have hypothesised that survivin directly inhibits caspase-3, although survivin lacks the structural elements in other IAPs that permit direct binding to caspase-3 [19]. Additionally, it has been hypothesised that survivin binds to caspase-9 [20]. Another idea is that survivin to bind procaspase 9 and block apoptosis through the intrinsic pathway, as it needs the cofactor hepatitis B X-interacting protein [21]. So, through intermediary proteins, survivin may indirectly inhibit caspases. The proapoptotic protein Smac/DIABLO, which binds to IAPs and stops them from inhibiting caspases, is where survivin interacts [22,23,24]. Researchers show that the regulation of survivin protein occurs in two levels: transcription and post-translation. Transcription level contains promoter regulation and transcription factors. In fact, by increasing or decreasing various factors at the translational or post-translational level causes resistance to survivin degradation. In this review, influential factors in post-translation adjustment were discussed.

FAT10

One of the most critical factors associated with increased survivin stability is FAT10 protein which can indirectly inhibit apoptosis. The ubiquitin-like protein (UBL) family member HLA-F locus adjacent transcript 10 (FAT10) has 165 amino acids and two in-tandem ubiquitin-like domains [25,26]. FAT10 is expressed in some immune cells, however it can also be induced in cells of other tissue origins by pro-inflammatory cytokines such as gamma interferon (IFN-γ) and tumor necrosis factor-alpha (TNF-α) [27]. Other research indicates that FAT10 overexpression may accelerate tumorigenesis and function as a new biomarker in various malignancies, including pancreatic ductal adenocarcinoma (PDAC), hepatocellular carcinoma (HCC) and bladder cancer (BC), which have poor prognoses [25,28]. Several evidence show a positive correlation between FAT10 and Survivin expression levels in BC cells which FAT10 stabilizes survivin at the post-translational level (Fig. 1). FAT10's unique strategy for promoting BC cell growth by increasing survivin expression was reduced when FAT10 knocked out. FAT10 overexpression lowers ubiquitin-substrate complex levels while increases FAT10-substrate complex levels because FAT10 and ubiquitin are competed to bind to the substrate to form FAT10- and ubiquitin-

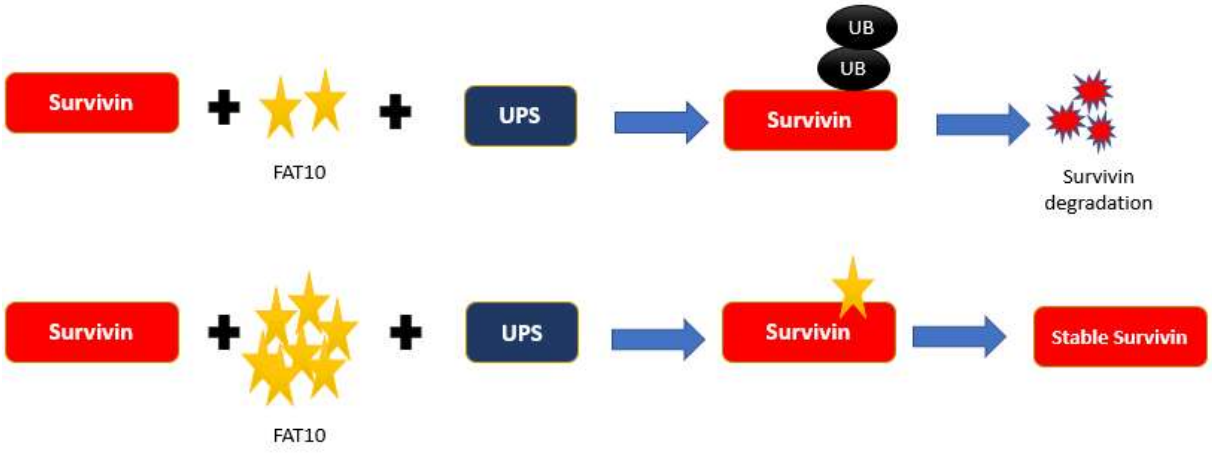

Fig. 1. Increased expression of FAT10 protein causes competition with Ubiqitin molecule as a result Survivin protein is not destroyed by UPS and remains stable.

substrate complexes [25]. Indeed, FAT10 overexpression reduces survivin, which is degraded by ubiquitin proteasome system (UPS) [29]. In other words, the downregulation of FAT10 resulted in a significant increase in ubiquitin-conjugated survivin levels. Hence, increased FAT10 expression lowers the amount of +ubiquitin-Survivin. It seems that FAT10 stabilizes survivin expression by inhibiting survivin ubiquitination in BC. Also, overexpression of FAT10 inhibits the assembly of ubiquitin-Survivin complexes, resulting in an upregulation of survivin expression [30]. It seems that with targeting through changes in survivin expression, FAT10 can open an auxiliary method in tumor therapies.

Usp22

One of the most important factors of post-translation adjustment is the large deubiquitinase (DUBs) family. The ubiquitin-specific protease (USP) family of DUBs and its member, ubiquitin-specific peptidase 22 (USP22), have been linked to several physiological and pathological processes. USP22 is abnormally expressed in various malignant tumors, including prostate, lung, liver, and colorectal cancers, indicating that USP22 may be crucial in malignancies [31]. USP22 separates ubiquitin from protein substrates [32], which is a hallmark of cancer stem cells and contributes to carcinogenesis, drug resistance, and cell cycle progression [32,33]. There was a strong correlation between the expression of USP22 and Survivin and malignant behavior, including tumor size, stage, and differentiation. In addition, the histological grade and overexpression of USP22 are related to lymph node metastasis. Importantly, HCC patients' prognoses were poor when USP22 and Survivin expression levels were high. USP22 expression is linked to a weak prognosis in several cancers [34-36]. By deubiquitinating the transcriptional regulator FBP1, USP22 can inhibit the p21 gene from being transcribed, which stimulates cell growth and tumorigenesis [37]. In addition, USP22 can regulate Survivin through deubiquitination (Fig. 2). Following USP22 overexpression or knockdown, the Survivin protein level is modified in cells. There is a positive correlation between USP22 and Survivin protein. Also, studies show that knockdown of USP22 strongly reduces the level of Survivin protein and overexpression of USP22 has the opposite effect and increases the stability of Survivin. However, further research shows that in some special cancer cells, such as renal cell carcinoma (RCC) tissues, USP22 and Survivin levels were considerably more significant than in control tissues. Analysis of protein levels demonstrates that, for example, in RCC tissue, USP22 reduced apoptosis by modifying Survivin stability. Furthermore, overexpression of USP22 significantly increased cell proliferation. According to various analyses, USP22 appears to affect the Survivin protein only at the post-translational level. Both

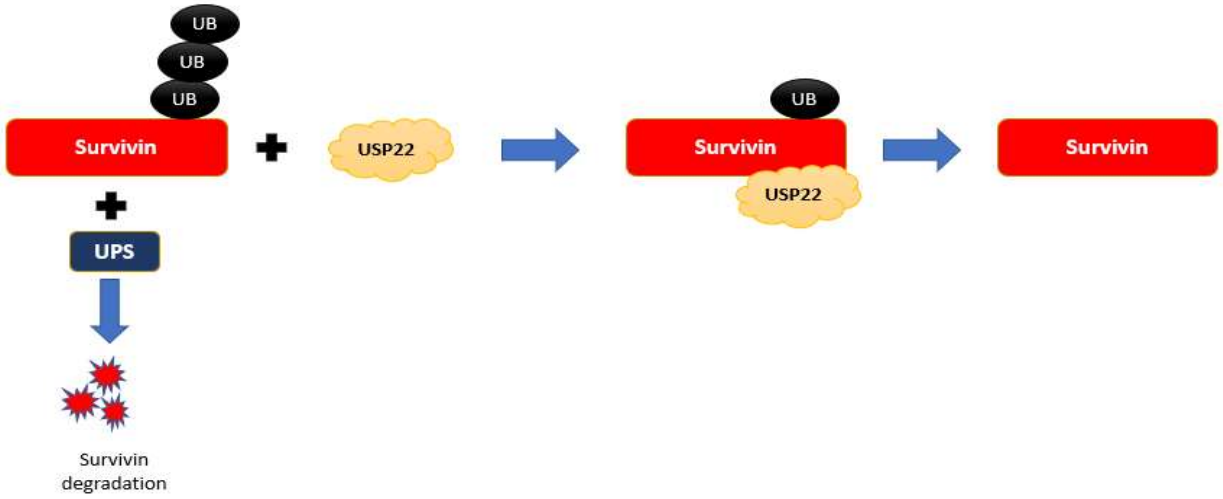

Fig. 2. The ubiquitinated Survivin protein is removed by the USP22 protein, which is a DUBs enzyme, and in this way, the Survivin protein is not exposed to the UPS and is not degraded.

overexpression and knockdown of USP22 did not affect the mRNA level of Survivin in cells [38]. According to the results, USP22 might be exploited as a cutting-edge therapeutic target for people with various cancer cells, namely renal cells [38].

Csn5

The c-Jun co-activator COP9 signalosome subunit 5 (CSN5), also known as JAB1, was first shown to mediate AP-1-dependent gene transcription [39,40]. The Jab1/CSN5 gene in humans is found on chromosome 8, composed of 334 amino acids that make up the human Jab1/CSN5 protein, which has a molecular weight of 38 kDa [40]. CSN5 engages in numerous cellular processes due to its function [41,42]. According to mounting evidence, CSN5 is now known to regulate oncogenes positively and negatively regulate tumor suppressors in a variety of human malignancies [43-45]. Additionally, CSN5 is overexpressed in several malignancies like breast, thyroid, skin, ovarian, lung, and pancreatic cancer, which frequently indicates a poor prognosis [45-47]. Next, CSN5 expression was linked to poor overall and disease-free survival. These results concluded that increased CSN5 expression may act as an oncogene in the emergence of Non-Small Cell Lung Cancer (NSCLC) and may indicate a bad prognosis for NSCLC [46]. Evidence from some cancers, such as NSCLC, shows there is a relationship between CSN5 and the Survivin protein. There is growing evidence that CSN5 has deubiquitination activity. Actually, CSN may operate as a negative regulator of ubiquitin ligase activity by removing NEDD8 from cullin-NEDD8. CSN5 might attach to Survivin and prevent it from becoming ubiquitinated, which would then stabilize it [43]. COP9-associated CSN5 regulates exosomal protein deubiquitination and sorting (Fig. 3). Furthermore, by removing the K-48 linked ubiquitination chains from Survivin, DUBs like CSN5 and Jab1 maintain Survivin and promote the proliferation of NSCLC cells [46,48]. Future NSCLC medicines may target CSN5 as a possible target and utilize it as a prognosis indicator for people with the disease [43].

LNC473

LNCs (long ncRNAs) is one of the factors contributing to cancer progression. Long non-coding RNAs (long ncRNAs, lncRNAs) are RNA types generally defined as transcripts longer than 200 nucleotides that are not translated into proteins. At the 6q27 locus, LINC00473 (LNC473) encodes an intergenic 1,832-bp ncRNA with two identified transcript isoforms. It has three exons and three introns. Recent research discovered that deregulation of LNC473 occurs in a variety of malignancies, including Wilms' tumor, Epithelial-mesenchymal transition (EMT) NSCLC, cervical cancer, and

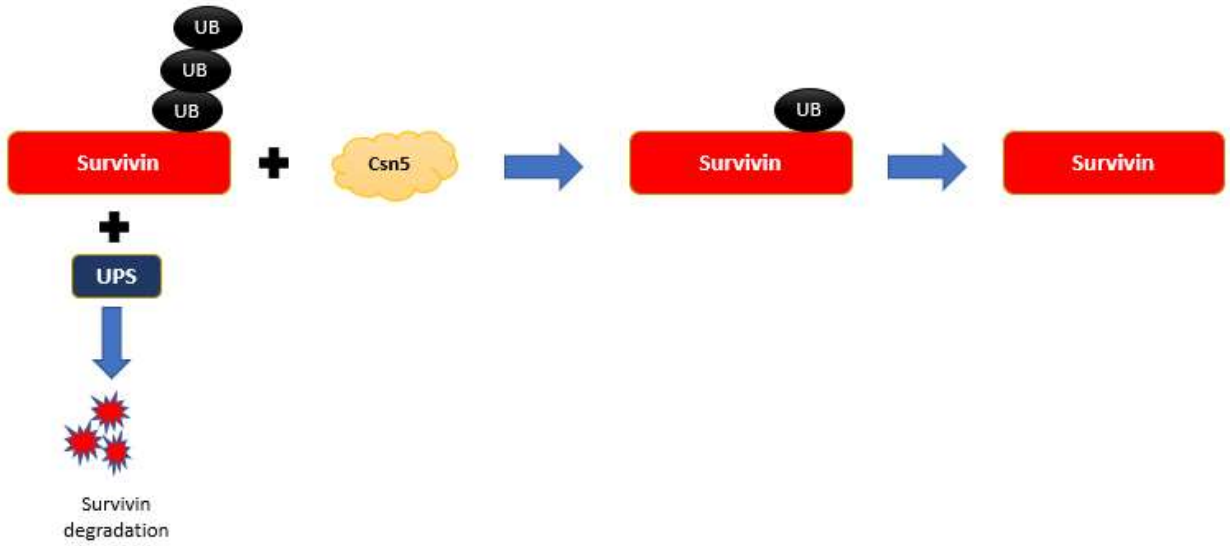

Fig. 3. The ubiquitinated Survivin protein is removed by the Csn5 protein as a result, the half-life of Survivin increases.

HCC [49,50]. Moreover, high levels of LNC473 expression have been linked to malignancy and late detection of HCC cancer, as well as greater tumor size (it is also suggested that overexpressing LNC473 increased cell proliferation and pushed advanchccement over the G1/S transition, whereas LNC473 knockdown caused cell cycle arrest at the G0/G1 phase.

More research shows a positive correlation between LNC473 and Survivin. Indeed Survivin's protein level was drastically reduced by LNC473 knockdown but not its mRNA level. LNC 473 expression has a significant impact on Survivin protein stability. LNC473 facilitated Survivin protein stability through USP9X-mediated deubiquitination of Survivin proteins, which increased cell proliferation, invasion and EMT (Fig. 4). Since LNC473 stimulates cell cycle progression and inhibits cell apoptosis to increase cell proliferation, the investigation results suggest that LNC473 acts as an oncogene in cancer cells such as HCC cells and may represent a suitable therapeutic target [50].

DISCUSSION AND CONCLUSION

Survivin is a member of the IAPs family. It promotes cell survival through interference with multiple cell cycle-related proteins such as INCENP and Aurora B kinase. Survivin also inhibits cell death through interference with both caspase-dependent and -independent cell apoptosis [51,52]. Undoubtedly the main clinical interest in survivin is in cancer. It is the fourth most upregulated mRNA in the human cancer transcriptome. Its expression has been correlated with increased tumor resistance to a broad range of chemotherapy agents, radiation insensitivity and poor patient prognosis [53,57]. In addition to cancer, survivin has been implicated in rheumatoid arthritis and multiple sclerosis. In autoimmune disorders, survivin is secreted, and its cytokine-dependent expression correlates with reduced apoptosis and inflammation [58-59]. Survivin protein expression is regulated at two levels, transcription and translation [60]. Understanding the importance of survivin as an essential factor in cancer diagnosis and resistance to treatment in cancers with high protein expression, it seems necessary to know the regulation mechanisms [61]. Considering the different regulations of survivin in two levels of transcription and translation, identifying and classifying the mechanism of action of each of the groups can help to know the standard treatment strategies in each pathway. Regulation at the transcription level is mainly made by signaling pathways and transcription factors caused by phosphorylation changes. Regulation at the translation level is often made by DUBs or factors that compete with the ubiquitin molecule in connection with Survivin[62].

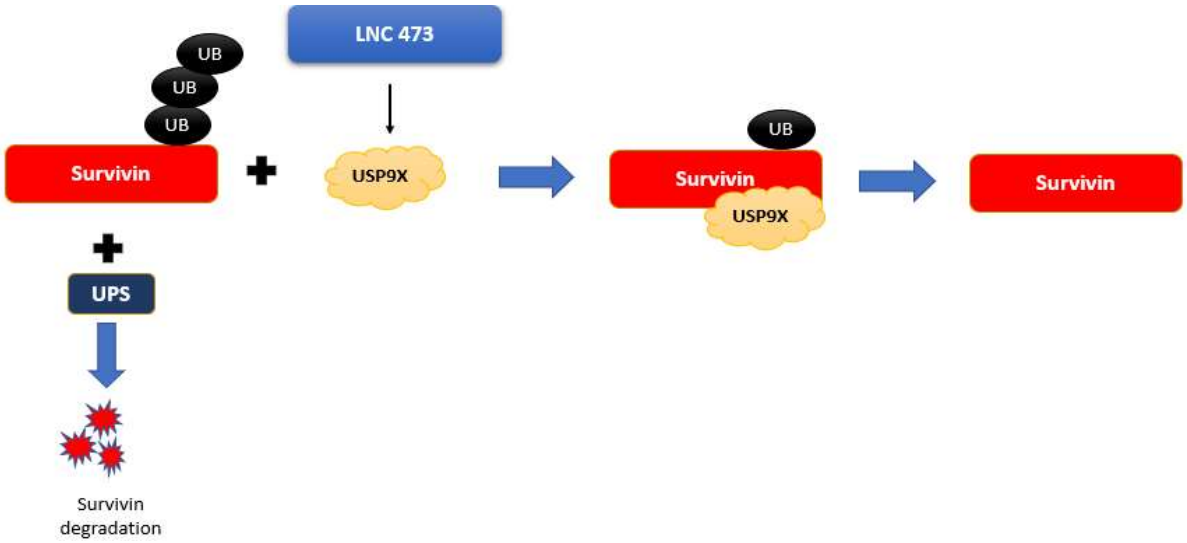

Fig. 4. LNC473 is one of the effective factors in the stability of Survivin protein. This non-coding RNA helps to increase the stability of Survivin by increasing the expression of DUBs USP9x and removing the Ubiquitin molecule.

Table 1. Abundance of Proteins Affecting Survivin Stability in Cancers

Protein	Variety of malignancies	Ref.
FAT10	Pancreatic ductal adenocarcinoma	D. Dong *et al.* [26]
	Bladder cancer hepatocellular carcinoma	A. Canaan *et al.* [25]
	Prostate, lung, liver, and colorectal cancers, breast	X. -Y. Zhang *et al.* [34]
Usp22		B. Tang *et al.* [36]
		Y. Lin *et al.* [38]
	Breast, thyroid, skin, ovarian, lung, and pancreatic	T. J. Shackleford *et al.* [40]
Csn5		Y. H. Lee *et al.* [43]
		M. A. Kouvaraki *et al.* [44]
	Wilms' tumor, non-small-cell lung cancer, cervical cancer, and hepatic cellular	H. Wu *et al.* [49]
LNC473	carcinoma	H. Chen *et al.* [17]
		C. H. A. Cheung *et al.* [51]
		C. -Y. Lin *et al.* [38]

In this review, the most effective post-translational regulators in increasing the stability of Survivin have been mentioned, while there are other factors such as XAF1 which will cause the destruction of Survivin and thereby cause the half-life of Survivin to decrease in some types of cancer. These counter settings can be divided into two groups; the first group consists of proteins that inhibit Survivin degradation directly by competing with or removing the ubiquitin molecule, such as USP22, FAT10, and CSN5; and the second group, such as LNC473 alters the expression of an intermediate protein, causing Survivin to be destroyed indirectly (Table 2).The factors described in this review all inhibited the degradation of Survivin and thereby increased the half-life of this protein. Increased stability of survivin as a result of various factors in some cancers will cause resistance to treatment [63].

Due to the many factors in increasing the stability of survivin and the unpredictable changes in the expression of proteins in cancer cells, the most suitable treatment method is downstream control. Because inhibition of any mentioned factors can be compensated in the cell by changing the expression profile of the cell. And virtually no significant change in survivin protein expression can be observed Also, due to the generality of the proteasome system, its inhibition cannot be considered a comprehensive method. One of the methods of control and treatment is to target Survivin, the main factor of inhibiting apoptosis in research. Based on the research, different methods can be used to reduce the expression of Survivin. Status of survivin cancer therapeutics, which is classified into five classes which contain: (i) survivin-partner protein interaction inhibitors, (ii) survivin homodimerization inhibitors, (iii) survivin gene transcription inhibitors, (iv) survivin mRNA inhibitors and (v) survivin immunotherapy. Of course, each of the mentioned methods has its advantages and disadvantages [64].

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