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Survivin: A Keystone in Apoptosis and Cancer Pathways

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KEYWORDS

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ABSTRACT:

Survivin, also known as baculoviral inhibitor of apoptosis repeat-containing 5 (BIRC5), is a versatile protein crucial for inhibiting apoptosis, regulating cell division, and promoting angiogenesis. Encoded by the BIRC5 gene in humans, it is the smallest member of the inhibitor of apoptosis (IAP) gene family in mammalian cells. Survivin's baculoviral IAP repeat (BIR) domain allows it to inhibit apoptosis by directly or indirectly interfering with caspase functions, thus negatively regulating programmed cell death. The survivin protein is highly expressed in most human tumors and fetal tissue but is absent in terminally differentiated cells. Its limited expression in normal differentiated tissues makes it an attractive tumor diagnostic and prognostic marker, and a potential biological target for anticancer therapies. Regulated by the cell cycle, survivin is particularly expressed during the G2/M phase, associating with the microtubules of the mitotic spindle. Disruption in this association impairs its ability to inhibit apoptosis and may affect mitosis regulation. Understanding survivin's mechanisms could pave the way for new therapeutic strategies in cancer and other diseases.

1. Introduction

The decision to initiate apoptosis depends on a delicate balance between pro-apoptotic and anti-apoptotic mechanisms. To avoid unnecessary programmed cell death, cells have developed a variety of survival strategies essential for maintaining the balance between life and death. Anti-apoptotic responses are not just the opposite of apoptosis; they act as a regulatory network to prevent unwarranted cell death [1-2].

The Inhibitors of Apoptosis Proteins (IAP) family naturally prevents programmed cell death, or apoptosis. Initially found in the baculovirus genome, these proteins inhibit apoptosis by interacting with and inhibiting mature caspases, the enzymes responsible for cell death. A key feature of all IAPs is the presence of one to three Baculovirus IAP Repeat (BIR) domains, each about 70 amino acids long [3]. The human IAP family includes eight members, with homologs in various organisms. The first IAPs identified were Cp-IAP from Cydia pomonella granulosis virus (CpGV) and OpIAP from Orgyia pseudosugata nuclear polyhedrosis virus (OpNPV). These IAPs compensate for the loss of p35, a baculoviral protein that inhibits caspases, facilitating efficient infection and replication in the host. IAPs inhibit apoptosis triggered by various stimuli, such as death

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receptor activation, growth factor withdrawal, ionizing radiation, viral infections, and genotoxic damage [4-6].
Since the discovery of baculoviral IAPs, numerous cellular homologues have been identified across various species, from Drosophila to vertebrates. The first mammalian IAP, Neuronal Apoptosis Inhibitory Protein (NAIP), was discovered during a positional cloning effort aimed at identifying the gene responsible for Spinal Muscular Atrophy (SMA). Following NAIP (BIRC1), the IAP family expanded to include seven more members: X-linked inhibitor of apoptosis (XIAP/BIRC4), cellular IAP1 (c-IAP1/BIRC2), cellular IAP2 (c-IAP2/BIRC3), Testis-specific IAP (Ts-IAP/BIRC8), BIR-containing ubiquitin-conjugating enzyme (BRUCE/BIRC6), Survivin (BIRC5), and Livin (BIRC7). XIAP, c-IAP1, and c-IAP2 bind to caspase-3, an effector caspase in the apoptosis pathway. However, the precise molecular mechanisms by which IAPs inhibit apoptosis are still unclear [6].

Structure of IAP family

The defining structural feature of Inhibitors of Apoptosis Proteins (IAPs) is the presence of at least one baculoviral IAP repeat (BIR) domain at the N-terminal region. This domain, made up of 70–80 amino acids, was first discovered in baculovirus proteins that inhibit apoptosis. IAP family proteins in viruses and animals can have up to three consecutive BIR domains. These domains have a conserved pattern of cysteine and histidine residues (Cx2Cx6Wx3Dx5Hx6C), which likely bind a zinc ion. Additionally, some IAPs, like XIAP, c-IAP1, and c-IAP2, include a RING finger domain capable of coordinating two zinc atoms, characterized by seven cysteine and one histidine residues. Furthermore, specific IAPs such as c-IAP1 and c-IAP2 contain a caspase recruitment domain (CARD) and a ubiquitin-conjugating domain (BRUCE) [6-7].
The primary physiological functions of IAPs are: (1) setting a threshold to keep caspases inactive, and (2) maintaining a reserve of active caspases that can rapidly trigger cell death when released. Additionally, growing evidence suggests that IAP proteins play roles beyond caspase inhibition, such as in protein degradation, cell cycle regulation, and signal transduction [7].

Structure of survivin

Survivin, the smallest member of the IAP family, consists of 142 amino acids and forms a functional homodimer naturally. The human survivin gene is located at the telomeric end of chromosome 17, spans 14.7 kb, and includes four exons and three introns, resulting in a 16.5-kDa protein. Unlike other IAPs, survivin is compact, featuring just a single N-terminal BIR domain and a long C-terminal alpha-helix coiled region, forming a stable dimer in solution. The BIR domain is believed to be essential for its anti-apoptotic activity, while the coiled domain likely interacts with tubulin structures [8-9] (Figure 1).

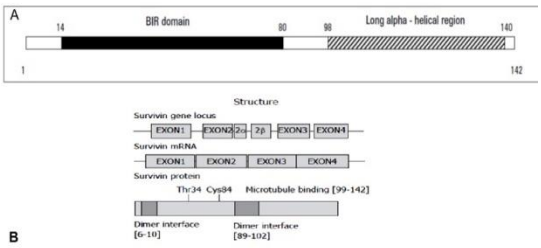

Figure 1: The structure of the survivin protein shows it consists of 142 amino acids, featuring A: BIR domain (represented by a black bar) at its N-terminal region, and an extended alpha-helical section (depicted by a striped bar) at its C-terminal end. B. The structure of the survivin gene, mRNA, and protein: the survivin gene includes exons 1-4, leading to the production of a 16.5-kDa protein.

Isoforms:

The regulation of the survivin gene is complex, involving various transcriptional and post-transcriptional pathways. Located at the end of chromosome 17 (17q25) in humans, the survivin gene undergoes extensive alternative splicing, producing multiple protein isoforms [10]. Its transcription is tightly regulated by the cell cycle, peaking during mitosis.

This single gene can produce five distinct alternatively spliced transcripts [10-11].

1. Survivin features a three-intron, four-exon configuration in both mice and humans.
2. Survivin-2B includes an additional alternative exon 2.
3. Survivin-Delta-Ex-3 lacks exon 3, causing a frameshift that creates a unique carboxyl terminus with potentially new functions, such as

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a nuclear localization signal, and also generates a mitochondrial localization signal.

4. Survivin-3B incorporates an alternative exon 3.
5. Survivin 2α consists of exons 1 and 2 of the survivin gene along with a 197 bp segment from the 3′ end of intron 2 (Figure 2).

In cancer cells, these isoforms are significantly elevated compared to normal tissues. Survivin has a dual role, both in regulating cell death and in driving mitosis.

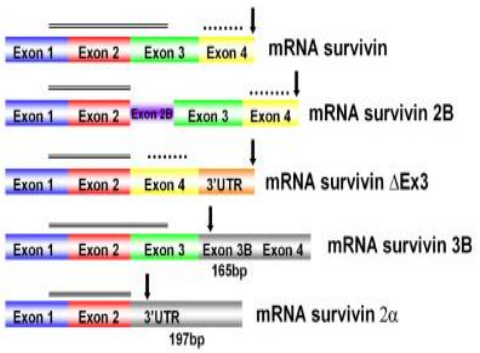

Figure 2: Representative diagram showing the structure of the five known survivin gene splice variants.

Subcellular distribution of survivin:

Survivin is found in different molecular forms and occupies specific subcellular locations. Using methods such as immunohistochemistry and subcellular fractionation, researchers have identified two main pools of survivin: one located in the nucleus and the other in the cytoplasm. Fortugno and colleagues [12], in their study on HeLa cells, determined that the ratio of cytoplasmic to nuclear survivin is roughly 6 to 1. These distinct pools of survivin display immunochemical variations and are independently regulated as the cell cycle progresses.

A new finding has uncovered an extra reserve of survivin located within the mitochondria of cancer cells. When cell death was triggered, this mitochondrial reserve of survivin was released into the cytoplasm, where it was found to prevent apoptosis [13].

Survivin's subcellular localization changes throughout the cell cycle. During interphase, it is linked to the microtubule organizing center. At metaphase, it becomes associated with centrosomes and mitotic spindles. In late telophase, it moves to the midbodies. Likewise, survivin 2a also changes its subcellular position as the cell cycle progresses [14-15].

Nuclear survivin is believed to play a role in regulating cell proliferation, while cytoplasmic survivin is responsible for inhibiting cell death [16].

Function of survivin:

1-Inhibition of apoptosis

Apoptosis is among the most thoroughly studied types of programmed cell death. The word "apoptosis" is derived from the Greek terms "apo," meaning "from," and "ptosis," meaning "falling off," which collectively illustrate the process by which a cell self-destructs using its internal mechanisms when it is beyond repair. The research by Kerr et al. in 1972 [17] is often cited as a pivotal advancement in understanding apoptosis. This process involves two main signaling pathways: the intrinsic and extrinsic pathways. Both pathways culminate in the activation of a family of cysteine proteases called caspases, which function in a proteolytic cascade to methodically dismantle and remove the dying cell [18].

Caspases are typically present in most cell types as inactive precursors called zymogens, which require proteolytic processing to become fully active. These zymogens include several domains: an N-terminal prodomain, a large subunit, and a small subunit. Activation of caspases occurs when the zymogen is cleaved at a specific aspartic acid site between the large and small subunits, with the prodomain being removed. The active enzyme form is a heterodimer composed of one large and one small subunit, and the fully active caspase is a tetramer consisting of two such heterodimers (see Figure 3). As zymogens, caspase activity is primarily regulated post-translationally. There are 14 mammalian caspases, with molecular weights ranging from 32 to 55 kDa, and all except caspases 11 through 13 are found in humans [19].

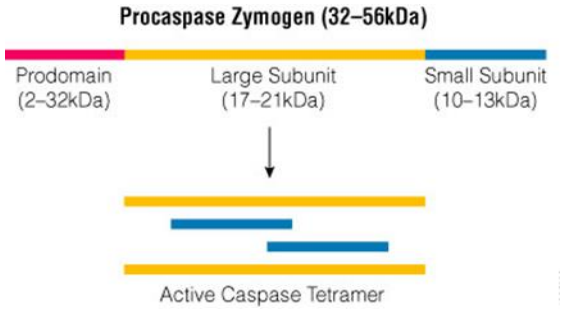

Figure 3: The active caspase enzyme is formed when caspase zymogens are cleaved between their large and

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small subunits, resulting in the removal of the prodomains. The active site consists of a heterodimer composed of one large subunit and one small subunit. Two such heterodimers combine to create the fully active tetramer.

Caspases can be classified in several ways, either by the length of their prodomains or by their substrate specificity. Those with long prodomains, like caspase-2, caspase-8, caspase-9, and caspase-10, are termed initiator caspases and are the first to become active in response to a cell death signal that initiates apoptosis. On the other hand, caspases with short prodomains, such as caspase-3, caspase-6, and caspase-7, are generally activated by initiator caspases. These are known as effector caspases because their activation is believed to lead to irreversible cellular damage, culminating in cell death [19].

Intrinsic Pathway: As implied by the name, the intrinsic pathway is triggered internally within the cell, often as a response to cellular signals arising from DNA damage, a malfunctioning cell cycle, detachment from the extracellular matrix, hypoxia, the absence of survival factors, or various other forms of cellular stress. The intrinsic pathway is initiated by factors such as genetic damage, the overexpression or activation of Bcl-2-associated protein X (Bax), and cell death processes dependent on mitochondria. Bax undergoes a structural transformation, forms oligomers, and moves to the mitochondria, where it creates or opens pores, facilitating the release of mitochondrial factors that trigger effector caspases. These factors include cytochrome c, apoptosis-inducing factor (AIF), second mitochondrial activator of caspases (Smac), direct IAP binding protein with low pI (DIABLO), and endonuclease G into the cytosol. Once released, cytochrome c combines with apoptosis protein-activating factor-1 (Apaf-1) and caspase-9 to form an apoptosome, which activates caspase-9 in an ATP-dependent process. The activated caspase-9 then stimulates caspase-3, resulting in cell death. Consequently, mitochondria have become a focus for anticancer chemotherapy, as many conventional and experimental drugs aim to permeabilize the mitochondrial membrane in cancer cells to release apoptosis-inducing proteins. This strategy may help address the defective apoptosis regulation seen in cancer cells. Interestingly, several potential cancer-preventive agents can also trigger apoptosis in transformed, premalignant, or malignant cells in vitro by permeabilizing mitochondrial membranes [19-21].

Extrinsic Pathway: This pathway is initiated outside the cell when death receptors on the plasma membrane are engaged by their specific ligands, also known as death activators. These activators include [22]:

- Tumor necrosis factor-alpha (TNF-α), which binds to the TNF receptor 1 (TNF-R1);
- Lymphotoxin (also referred to as TNF-β), which also binds to the TNF receptor;
- Fas ligand (FasL), a molecule that attaches to a cell-surface receptor known as Fas (or CD95);
- TNF-related apoptosis-inducing ligand, which connects with TNF-related apoptosis-inducing ligand receptors 1 and 2, TRAIL-R1 and TRAIL-R2 (also known as death receptors 4 and 5, DR4 and DR5).

When extracellular ligands bind to these receptors, their intracellular regions, known as 'death domains' (thus giving rise to the term death receptor pathway), engage with the adaptor protein Fas-associated death domain (FADD). This engagement results in the assembly of the death-inducing signaling complex (DISC). As a result, multiple procaspase-8 molecules are brought into close proximity, enabling them to activate one another through autoproteolysis. The activity of caspase-8 subsequently triggers the activation of effector caspase-3, which leads to the caspase-mediated degradation of protein substrates. This sequence initiates the mechanisms required for apoptotic cell death, culminating in DNA fragmentation and chromatin condensation [23,24].

Damage to specific organelles can activate alternative pathways for caspase activation. Increasing evidence indicates that stress on the endoplasmic reticulum can specifically activate caspase-12 through calpains. Furthermore, mitochondria can trigger a type of apoptosis that relies on the organelle itself but does not depend on caspases, through the release of an apoptosis-inducing factor (AIF). AIF mainly impacts the nucleus, leading to DNA condensation without fragmentation. Despite this, the main apoptotic pathways identified so far primarily involve the activation of caspases, which play a critical role in cell death [25].

Research on cellular apoptotic mechanisms has shifted towards pinpointing specific inhibitors of cell death.

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Numerous natural inhibitors are known to suppress caspase activity. Among these, the viral and mammalian inhibitors of apoptosis protein (IAP) are well-studied and have been the subject of extensive reviews recently. Additionally, several lesser-known factors also effectively inhibit caspases. These include caspase-specific decoy molecules, calpains, phosphoinositides, B-cell lymphoma 2 (Bcl-2) proteins, heat shock proteins (Hsp), and proteases [26].

Mechanism of Inhibition of apoptosis by survivin

Numerous studies conducted both in vitro and in vivo studies have shown that survivin plays a crucial role in inhibiting cell death, particularly apoptosis. In vitro experiments have demonstrated that survivin can counteract various triggers of apoptosis, including the withdrawal of IL-3, activation of the FAS receptor, exposure to TRAIL, overexpression of proteins such as BAX and p53, activation of caspases-3, -7, and -8 [27]. in vivo studies have confirmed survivin's capability to inhibit apoptosis [28,29]. By neutralizing apoptotic signals, survivin promotes cell survival, which supports the proliferation of cells, including mutant ones. This uncontrolled cell proliferation can lead to the development of cancer. Furthermore, the inhibition of apoptosis by survivin makes cancer cells more resistant to various therapies, including chemotherapy and radiotherapy [30].

While there is significant evidence suggesting that survivin can inhibit apoptosis, the exact mechanisms remain somewhat ambiguous. Survivin, similar to other members of the Inhibitor of Apoptosis Protein (IAP) family, has been observed to interact with both initiator and effector caspases. Research has highlighted its association with caspase-3 at pericentriolar locations. Some studies propose that this interaction may inhibit the activities of caspase-3 and caspase-7, either directly or indirectly, via survivin's BIR domain [30-31]. However, other studies indicate that survivin does not inhibit caspase-3 even at elevated concentrations [32]. Thus, the consensus suggests that most IAPs, including survivin, inhibit apoptosis through mechanisms other than the direct inhibition of effector caspases. Instead, survivin is believed to prevent cell death upstream of the effector caspases, potentially by inhibiting caspase-9 in certain situations [33].

Survivin also hinders apoptosis by inhibiting the mitochondrial release of the proapoptotic protein SMAC/Diablo [34]. In addition, it interacts with the aryl hydrocarbon receptor binding protein, which stabilizes survivin and enhances its antiapoptotic properties, thereby elevating the cell's antiapoptotic threshold [35]. The antiapoptotic activity of survivin is intricately tied to its function in facilitating mitosis. By associating with mitotic spindle microtubules, survivin prevents the default initiation of cell death during mitosis. This expression of survivin in cancer cells plays a crucial role in enabling these cells to resist both intrinsic and extrinsic apoptotic signals [15].

The imbalance between cell proliferation and apoptosis is a critical feature of malignant tumors, highlighting the importance of proteins that regulate the cell cycle and apoptosis in tumorigenesis. Research suggests that the different isoforms and phosphorylation status of survivin play a significant role in determining its subcellular localization and function. As such, it is vital to understand survivin's unique position within the cell, acting as a bridge between cell death and division. Given that both apoptosis and cell proliferation pathways are often disrupted in cancer, targeting components from these pathways presents a potential strategy for developing anticancer therapies [36].

2- Cellular proliferation (Regulation of cytokinesis)

Survivin is typically absent during interphase but becomes present during the G2-M phase. In the mitosis stage, survivin integrates into a multi-protein complex known as the chromosomal passenger complex (CPC) [37]. This complex plays a critical role in cell division by ensuring accurate sister chromatid segregation and by stabilizing microtubules during the later stages of mitosis. Additionally, survivin may facilitate mitosis by acting as a connection between the centromere/central spindle and the CPC. Its presence is essential for the successful progression through various stages of cell division, including centrosome functions and accurate kinetochore attachment [36-38].

3- Angiogenesis

In addition to its roles in apoptosis and cell proliferation, survivin is also associated with angiogenesis. The evidence supporting the connection between survivin and angiogenesis includes:

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- An increase in survivin expression in endothelial cells stimulated by angiogenesis, compared to inactive cells [39].
- Elevated survivin levels in cultured vascular endothelial cells after being exposed to angiogenic factors like vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (FGF) [40].
- Mice with a heterozygous deficiency in the survivin gene showed reduced blood vessel density after occlusion of the middle cerebral artery [41].
- Reducing survivin expression using either antisense methods or dominant negative mutants led to a decrease in both tumor growth and angiogenesis in gastric cancer [42].
- Introducing a phosphorylation-deficient version of survivin into endothelial cells resulted in the inhibition of angiogenesis [43].

Survivin likely enhances angiogenesis by preventing apoptosis in endothelial cells, thus boosting their survival.

Expression characteristics

Survivin expression is tissue-specific and varies with the cell cycle. It is prominently found in embryonic tissues and common adult solid tumors, including those in the lung, breast, colon, brain, stomach, esophagus, pancreas, liver, prostate, uterus, and ovaries. Conversely, survivin is almost absent in fully differentiated tissues, with exceptions such as thymocytes, endothelial cells, colonic mucosa, placenta, bone marrow, and the basal layer keratinocytes of the skin. Additionally, survivin has been observed in melanocytes, testes, and ovaries. Stem cell factor and human chorionic gonadotropin can stimulate survivin expression in the testes and ovarian granulosa cells, suggesting a possible role in regulating spermatogenesis and oogenesis. These findings indicate that survivin's function in cell division and its role in preventing apoptosis are crucial, not only during early development but also in the progression of cancer. In proliferating cells, survivin expression is regulated by the cell cycle, being nearly undetectable during the G1 and S phases, and reaching peak levels in the G2/M phase [37,44].

Regulation by p53

p53 inhibits survivin expression at the transcriptional level

Wild-type p53 has been shown to reduce survivin expression at the mRNA level. Normally, p53 governs genes that manage apoptosis. Since survivin is known to inhibit apoptosis, it can be concluded that p53's suppression of survivin aids in promoting apoptosis in response to apoptotic signals or triggers. This suggests that p53's downregulation of survivin is essential for the p53-driven apoptotic pathway to successfully induce cell death. It is widely recognized that a common characteristic of many tumors is the overexpression of survivin alongside the total loss of wild-type p53 [45].

Why survivin is an attractive target for anti-cancer therapy

Survivin has several appealing characteristics as a potential new target for cancer treatment, including:

*1- **Low expression in most normal cells and increased expression in cancerous tissue***: As previously noted, survivin is rarely present in normal differentiated tissues but is markedly elevated in most cancerous tissues. Initial statistical analyses in genetic epidemiology recognized survivin as one of the top four 'transcriptomes' in several common human cancers. These early findings have been extensively confirmed through immunohistochemistry and RT-PCR [46]. The heightened expression of survivin in cancer cells is thought to stem from enhanced gene transcription rather than protein stabilization. Indeed, various tumor-related signaling proteins, including c-myc and STAT-3 [47], have been shown to boost survivin expression, whereas tumor suppressor genes like p5345 have been found to decrease its expression [45].

***2- Survivin as a Central Regulatory Protein**:* Survivin acts as a central regulatory protein involved in numerous signaling pathways crucial for tumor sustainability. As noted, survivin boosts cell proliferation and confers resistance to apoptosis, both of which are essential for cancer growth and progression. Therapies targeting these regulatory proteins might offer benefits over those that focus on single molecules, potentially minimizing the

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risk of resistance by impacting multiple cellular pathways [34].

*3- **Inhibiting survivin could impede both angiogenesis and tumor cell growth*:** Angiogenesis, the formation of new blood vessels, is crucial for tumor development and the proliferation of cancerous cells [48]. Therefore, targeting survivin could effectively hinder tumor progression by promoting tumor cell death and blocking angiogenesis [43].

Survivin plays a role in developing resistance to different anticancer treatments. Most anticancer therapies work by inducing apoptosis to shrink tumors, but when apoptosis is not effectively triggered, resistance to these treatments can occur. Many studies support this notion, showing that increased levels of survivin in tumor cells are associated with resistance to various anticancer drugs. Furthermore, these studies demonstrate that blocking survivin's activity can enhance the efficacy of conventional cancer therapies. Additionally, elevated survivin expression has been linked to resistance to radiation therapy [49].

Targeted Therapy:

Survivin's selective expression in cancer cells and its importance in prognosis render it a promising target for therapeutic strategies. Present research is dedicated to creating survivin inhibitors for clinical use, aiming both to enhance spontaneous apoptosis to reduce tumor growth and to increase the sensitivity of tumor cells to treatments that induce apoptosis. A range of survivin molecular antagonists is under investigation, such as antisense oligonucleotides, ribozymes, small interfering RNAs (siRNAs), and cancer vaccines [9].

Antisense Oligonucleotides

A therapeutic approach to suppress survivin involves the use of antisense oligonucleotides (ASONDs), which reduce survivin mRNA and thus lower its protein levels. ASONDs work by forming duplexes with the natural mRNA inside cells, disrupting ribosome assembly and hindering protein translation [50].

Ribozyme Approach for Inhibiting Survivin (RNA Enzyme)

As an alternative method to inhibit survivin, ribozymes targeting various segments of survivin mRNA have been created. These ribozymes are small RNA molecules with specific endonucleolytic activity, enabling them to catalyze the hydrolysis of particular phosphodiester bonds, thereby cleaving the RNA target sequences [51].

Survivin RNA Interference Strategy

RNA interference (RNAi) technology serves as a potent method to suppress gene expression in mammals for functional studies [52]. RNAi involves a highly precise post-translational silencing of gene expression triggered by introducing double-stranded RNA into a cell. Various studies using experimental human tumor models have shown the practicality of this technology for inhibiting cancer-associated genes, including surviving [53-54].

Survivin-derived cancer immunotherapy

Immunotherapy is emerging as a viable strategy for treating tumors that express survivin. Studies indicate that tumors from various origins are capable of presenting the same set of peptide epitopes derived from survivin. In patients with chronic lymphocytic leukemia, melanoma, and breast cancer, a spontaneous cytotoxic T lymphocyte response to surviving restricted by the major histocompatibility complex class I has been observed. Additionally, inducing cytolytic T-cells in vitro against a survivin epitope has resulted in cytolytic activity against a diverse range of human tumors [55]. Therefore, survivin is considered a universal tumor antigen, making immunotherapy a promising approach for treating survivin-positive tumors .

Vaccination based on survivin has been found to be safe, with no significant side effects, and is frequently linked to antigen-specific immune responses [56-57].

Others therapies

There are numerous other therapies targeting survivin, including the dominant negative (DN) mutant approach and strategies using small organic compounds or other small antagonists like peptides. Potential small chemical molecules include those that inhibit survivin expression either transcriptionally or post-transcriptionally or disrupt survivin function, such as interfering with survivin-caspase interactions. For instance, tetra-O-methyl nordihydroguaiaretic acid has been shown to directly suppress Sp1-dependent survivin gene expression, leading to the activation of mitochondrial apoptosis in tumor cells [58]. Several small-molecule antagonists indirectly impact survivin levels, such as cyclin-dependent kinase inhibitors, T-cell factor antagonists [59], and Hsp90 inhibitors [60]. These

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compounds reduce survivin levels through various mechanisms. Initially, molecules targeting survivin will be utilized as single agents or in combination with low-dose chemotherapy for patients with relapsed or refractory conditions. As more experience is gained, these targeted therapies will be integrated into standard chemotherapy regimens for initial treatment. In the future, as more small molecules are developed to modulate the apoptosis cascade, they will be used together to address different molecular defects simultaneously.

Conclusion

Survivin is a powerful inhibitor of caspases, but it also prevents cell death by affecting cell cycle progression, cell division, and signal transduction pathways. The significant difference in survivin expression between normal tissues and cancer cells highlights its potential as a key molecule in studying the biology of tumor development and as a foundation for creating targeted therapies to eliminate cancer cells. Since its discovery in 1997, survivin has garnered significant interest across various areas of biochemical science. The fundamental insights into survivin's structure and function are now being applied in clinical settings. Tumors expressing survivin tend to be more aggressive and less responsive to chemotherapy, making survivin an independent negative prognostic factor in cancer. Additionally, survivin presents a promising target for developing new anti-cancer treatments.

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