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MECHANISTIC UNDERSTANDINGS AND TREATMENT APPROACHES FOR CANCER THERAPY THAT TARGET ANTI-APOPTOSIS GENES

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ABSTRACT

Cancer, a global health issue, may avoid apoptosis. All cancer cells defy apoptosis and divide and proliferate uncontrollably. Every eukaryotic cell undergoes apoptosis, or cell suicide. Damaged DNA activates apoptosis to kill the cell. Apoptosis is a highly ordered process: cellular membranes are ruptured, chromosomes are damaged, DNA fragments, and immune cells cleanly engulf the dying decreasing cell. This review discusses cancer treatment targets based on apoptotic mechanisms. Evasion of apoptosis leads to uncontrolled cell growth and illnesses like cancer. Developing apoptosis-targeted anticancer medicines is popular because apoptosis generates little inflammation. New techniques to trigger apoptosis in cancer cells have been developed as researchers have learned more about apoptosis and how tumor cells employ it to fight cell death. This review examined the mechanism of apoptosis and the dysregulation of death receptors (DRs) proteins, cellular FLICE inhibitory proteins (c-FLIP), anti-apoptotic Bcl-2 proteins, inhibitors of apoptosis proteins (IAPs), and tumor suppressor (p53) in cancer cells, as well as current clinical approaches to selectively induce apoptosis in cancer cells.

Keywords:*Cancer Therapy, Approaches, Anti-Apoptosis Genes, Treatment Approaches.*

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1. Introduction

Cancer has been one of the primary causes of death in all countries all over the worldfor decades. According to the WHO, there were around 9.6 million deaths due to cancer in 2018 and 70% of such deaths occurred in low- and middle-income countries. Currently, cancer management has multiple treatment strategies available; chemo- and radiotherapy and there is also surgery. Each treatment strategy has its significance and effectiveness in tumor cells which can be assessed by the ability to initiate the apoptosis cascade, thus, manipulate and restore the overexpressed anti-apoptotic proteins levels, and increase the expression of pro-apoptotic molecules could be the new goal of treatment. Recognizing the underlying mechanism of programmed cell death has created a new insight in cancer treatment by obtaining specific molecules that aim for a signal, gene and/or protein in cancer cells to promote its suicidal; meanwhile, non-harmful to the normally developed cells. In this article, we evaluate how apoptosis can be used as targeted therapy in cancer.

1.1.Cancer Therapy: A Battle on Multiple Fronts

Cancer, a complex and heterogeneous disease characterized by uncontrolled cell growth, remains a major global health challenge. Despite significant advancements, treating cancer often presents a multifaceted battle requiring a variety of therapeutic approaches.

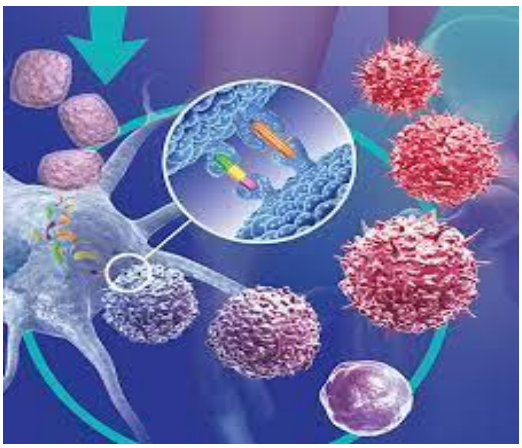

Figure 1: Cancer Therapy

This comprehensive overview delves into the diverse landscape of cancer therapy, highlighting its successes, ongoing challenges, and exciting promises for the future.

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The Arsenal of Weapons

- Surgery
- Radiation Therapy
- Chemotherapy
- Targeted Therapy
- Immunotherapy
- Emerging Therapies

Cancer therapy is a dynamic field undergoing continuous evolution. Despite the challenges, the arsenal of weapons against cancer is expanding, fueled by innovation and a deeper understanding of the disease. The future holds promise for more effective, personalized, and less toxic treatments, offering hope for a future where cancer can be not just controlled, but ultimately conquered.

1.1.Anti-Apoptosis Genes: Shields of Cancer Cell Survival

Programmed cell death, also known as apoptosis, is an essential physiological process ensuring proper development and tissue homeostasis. In healthy cells, a finely tuned network of pro-apoptotic and anti-apoptotic proteins regulates this process.

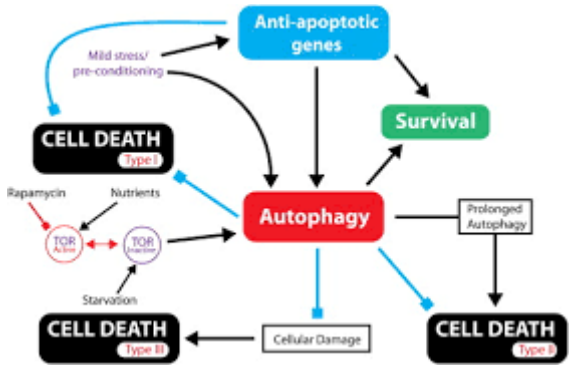

Figure 1: Anti-Apoptosis Genes

However, cancer cells often harbor mutations or dysregulations in these pathways, enabling them to evade apoptosis and proliferate uncontrollably.Several key genes act as guardians, protecting cancer cells from apoptosis. This introduction will delve into some of the most prominent anti-apoptotic gene families:

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- **Bcl-2 Family:** Comprises both pro-apoptotic and anti-apoptotic members. Mutations or overexpression of anti-apoptotic members like Bcl-2 and Bcl-xL allow cancer cells to bypass cell death signals.
- **IAP (Inhibitor of Apoptosis) Family:** Encodes proteins that directly counteract caspases, the crucial executioners of apoptosis. Increased IAP expression contributes to treatment resistance in various cancers.
- **p53 Pathway:** This tumor suppressor pathway triggers apoptosis in response to DNA damage. Mutations in the p53 gene or its downstream regulators render cancer cells less susceptible to cell death.

1.2.Targeting the Guardians: A Therapeutic Arsenal

By understanding the mechanisms of action of anti-apoptosis genes, researchers have developed a diverse arsenal of therapeutic strategies:

- **BH3 Mimetics:** These small molecules mimic the pro-apoptotic BH3 domain, binding to and neutralizing anti-apoptotic Bcl-2 proteins, tipping the balance towards cell death.
- **Smac Mimetics:** These drugs mimic Smac, a naturally occurring protein that binds and inhibits IAPs, reactivating the executioners of apoptosis.
- **FLIP Inhibitors:** These molecules directly target FLIP, preventing its interference with the apoptotic pathway.
- **Gene Therapy Approaches:** Silencing anti-apoptosis genes using siRNA or CRISPR-Cas9 technologies is another promising avenue under exploration.

Anti-apoptosis gene targeting is a potent and comprehensive cancer treatment. Researchers can unleash the potential of this promising avenue in the battle against this dreadful illness by understanding these guardians and creating novel treatment techniques. This approach opens the door to studying the complex processes and possible uses of targeting anti-apoptosis genes in cancer treatment.

2. Literature Review

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Czabotar, Lessene, Strasser, and Adams (2014)provide a thorough analysis of the physiological consequences and therapeutic possibilities of the BCL-2 protein family's regulation of apoptosis. BCL-2 family members control the integrity and permeability of mitochondria, which in turn controls cell destiny, via complex molecular interactions. One essential mechanism for preserving tissue homeostasis and getting rid of unhealthy or superfluous cells is called apoptosis, or programmed cell death. A complex web of proteins controls apoptosis, and the BCL-2 family is one of the main players in this process.

Degterev, Boyce, and Yuan (2003)explore the critical function of the cysteine protease family caspases in controlling apoptotic signaling pathways. Caspases are key players in apoptosis, facilitating the breakdown of cells and the carrying out of predetermined cell death. The review summarizes ten years of research and provides insight into the many roles and regulatory mechanisms of caspases in both healthy and pathological processes.

Fathy et al. (2019) Examine the apoptotic properties of eugenol, a phenolic molecule included in essential oils, and its capacity to make cancer cells more susceptible to traditional therapies like radiation and cisplatin. Their research emphasizes how targeting apoptosis may be used therapeutically to improve the effectiveness of currently available anticancer treatments. The interaction of natural substances with apoptotic pathways offers potential therapeutic approaches for cancer.

Fuchs and Steller (2011)provide a thorough explanation of the many functions that programmed cell death plays in shaping tissues during embryogenesis and preserving tissue homeostasis in maturity, as well as its implications for animal development and illness. The review highlights the importance of programmed cell death in healthy and pathological circumstances by emphasizing the complex interactions between apoptotic pathways and cellular differentiation. Precisely controlling tissue morphogenesis and pathogenesis, programmed cell death becomes evident in the framework of developmental biology and disease.

Green and Kroemer (2004) Examine the pathophysiology of mitochondrial cell death and clarify the complex processes that control the release of apoptogenic substances and the permeabilization of the mitochondrial outer membrane (MOMP). Known as the "powerhouse" of the cell, mitochondria are essential components in apoptotic signaling pathways. The review

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sheds light on how mitochondria function to combine several apoptotic signals and plan cellular death in response to both internal and external stimuli.

3. Apoptosis

The Greek roots of the English word "apoptosis" indicate "dropping off"—the process by which leaves fall off trees during the fall. In contrast to necrosis, it is used to characterize a cell's active pursuit of death in response to certain stimuli. One of the most studied processes in biologic study since its description by Kerr et al. in the 1970s is apoptosis. Apoptosis plays a crucial role in both healthy and unhealthy states because to its great selectivity.

3.1 Morphological changes in apoptosis

The nuclear and cytoplasmic morphological changes associated with apoptotic cell death are strikingly conserved across a wide variety of cell types and animal species. Typically, it takes a few hours for cells to die and then for them to finally break apart. The amount of time required, however, is conditional on the apoptotic pathway, the cell type, and the stimuli. Chromatin condensation and nuclear fragmentation are the morphological hallmarks of nucleus apoptosis. Other characteristics include cell rounding, loss in cellular volume (pyknosis), and retraction of pseudopodes. A crescent or ring-shaped structure, chromatin condensation begins near the nuclear membrane's edge.

The process of chromatin condensation continues until it fragments inside a cell that still has its membrane intact; this phenomenon is called karyorrhexis. During the whole procedure, the plasma membrane remains undamaged. Melanomas, ultrastructural changes to cytoplasmic organelles, and blebbing membranes are among of the morphological hallmarks of late-stage apoptosis.

Prior to the formation of apoptotic bodies, phagocytic cells typically consume dying cells. This is why apoptosis was only found in 1972, a relatively late year in the field of cell biology, and why, under certain circumstances, apoptotic bodies might be seen in vitro. Secondary necrosis is the breakdown of apoptotic cell remains that mimics necrosis when phagocytosis is not possible, as in an artificial cell culture environment.

3.2 Biochemical changes in apoptosis

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In apoptosis, there are three primary kinds of biochemical changes:

1) activation of caspases,
2) DNA and protein breakdown and
3) membrane changes and recognition by phagocytic cells.

Phosphoserine (PS), which has been "flipped out" from the inner layers of the cell membrane, is expressed in the outer layers of the membrane early in the process of apoptosis. This enables macrophages to phagocytose dead cells without secreting proinflammatory biological components, thanks to their early detection of these cells. Following this, DNA undergoes its typical fragmentation into huge fragments ranging from 50 to 300 kilobases in size. Subsequently, endonucleases cause DNA to undergo internucleosomal cleavage, resulting in oligonucleosomes with 180–200 base pairs. The usual DNA ladder in agarose gel electrophoresis is seen in necrotic cells as well, therefore this feature is neither specific nor diagnostic of apoptosis.

The caspase family of cysteine proteases is activated during apoptosis, which is another hallmark of the cell death process. A cysteine protease is what the "c" in caspase means, and the "aspase" is the enzyme's special ability to break after aspartic acid residues. The nuclear scaffold and cytoskeleton are disrupted and several essential cellular proteins are cleaved by activated caspases.

In addition, they trigger DNAase, which proceeds to further break down nuclear DNA. Biochemical studies of DNA fragmentation or caspase activation should not be used to define apoptosis, as apoptosis can happen without oligonucleosomal DNA fragmentation and can be caspase-independent; however, these changes do help to explain some of the morphological changes in apoptosis. There is no clear-cut equivalence between ultrastructural changes and biochemical cell death characteristics, thus the Nomenclature Committee on Cell Death (NCCD) has suggested that morphological criteria alone should be used to classify cell death modalities. Despite this, many biochemical assays and experiments have been employed to detect apoptosis.

3.3 Mechanisms of apoptosis

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The etiology of diseases caused by abnormal apoptosis may be better understood with a firm grasp of the processes behind this process. Because of this, it's possible that medications targeting certain apoptotic genes or pathways will be easier to create. Because they are involved in both the start and finish of cell death, caspases play a pivotal role in the apoptotic process. In order to activate caspases, one of three mechanisms must be satisfied. The intrinsic (or mitochondrial) and extrinsic (or death receptor) routes are the two most often mentioned mechanisms in which apoptosis might begin. At the end of the day, both routes end up at the same place: the execution phase of cell death. The intrinsic endoplasmic reticulum route is the third and last recognized starting pathway.

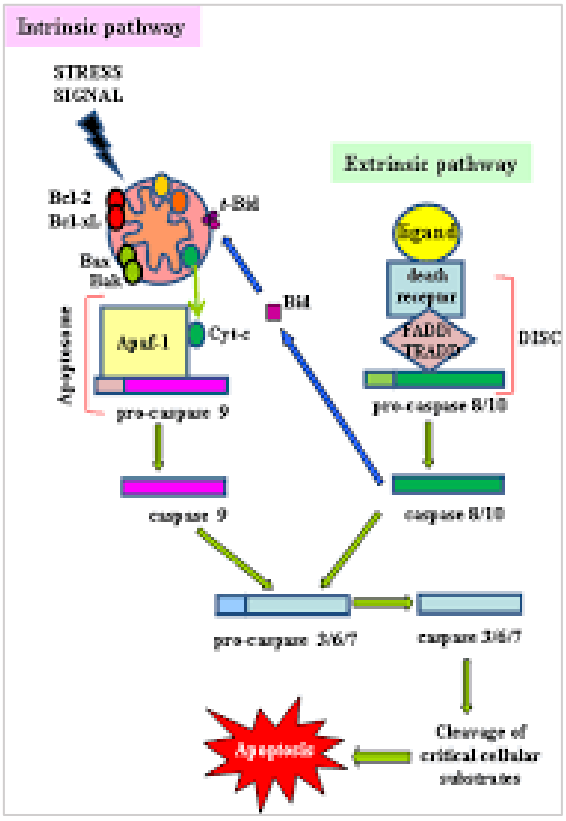

Figure 2: The intrinsic and extrinsic pathways of apoptosis.

3.3.1 The extrinsic death receptor pathway

The binding of death ligands to death receptors initiates the extrinsic death receptor pathway. Despite the fact that other death receptors have been identified, the most well-known ones are type 1 TNF receptor (TNFR1), Fas (CD95), and TNF and Fas ligand (FasL), respectively. The intracellular death domain of these death receptors is responsible for bringing in adaptor

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proteins like TRADD and FADD, and cysteine proteases like caspase 8. The death-inducing signalling complex (DISC) is the whole complex consisting of the death ligand, the death receptor, the adaptor protein, and the binding site for the adaptor protein. Pro-caspase 8 assembly and activation are subsequently initiated by DISC. Caspase 8, in its active state, is an initiator caspase that cleaves other caspases, either downstream or executioner, to start the cell death process.

3.3.2 The intrinsic mitochondrial pathway

The intrinsic route begins within the cell, as its name suggests. Some internal cues that initiate the intrinsic mitochondrial pathway include hypoxia, excessively high concentrations of cytosolic Ca2+, severe oxidative stress, permanent genetic damage, and other similar conditions. The route is always triggered by increased mitochondrial permeability and the release of pro-apoptotic chemicals into the cytoplasm, such as cytochrome-c, regardless of the stimulus. A family of proteins called Bcl-2, which is named after the BCL2 gene that was first found at the chromosomal breakpoint of the translocation of chromosome 18 to 14 in follicular non-Hodgkin lymphoma, tightly regulates this pathway. The Bcl-2 proteins may be broadly classified into two groups: those that promote cell death (such as Bax, Bak, Bad, Bcl-Xs, Bid, Bik, Bim, and Hrk) and those that inhibit cell death (such as Bcl-2, Bcl-XL, Bcl-W, Bfl-1, and Mcl-1).

In order to control cell death, anti-apoptotic proteins prevent mitochondrial cytochrome-c release, while pro-apoptotic proteins promote this release. The equilibrium between pro- and anti-apoptotic proteins, rather than their absolute number, dictates whether or not apoptosis will be triggered.

Apoptosis inducing factor (AIF), second mitochondria-derived activator of caspase (Smac), direct IAP Binding protein with Low pI (DIABLO), and Omi/high temperature requirement protein A (HtrA2) are among the other apoptotic factors that are released into the cytoplasm from the mitochondrial intermembrane space. The development of the apoptosome, which consists of cytochrome c, Apaf-1, and caspase 9, is the mechanism by which cytoplasmic release of cytochrome c activates caspase 3. In contrast, Smac/DIABLO and Omi/HtrA2 reduce inhibitor of apoptosis protein (IAP) interactions with caspase-3 and caspase-9, which activates caspases.

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3.3.3 The common pathway

The activation of caspases is a crucial step in the execution phase of cell death. Caspases 8 and 9 are the upstream caspases of the extrinsic and intrinsic pathways, respectively. There are two mechanisms that lead to caspase 3, one internal and one external. To trigger nuclear apoptosis, caspase 3 cleaves the inhibitor of caspase-activated deoxyribonuclease. Furthermore, protein kinases, cytoskeletal proteins, DNA repair proteins, and inhibitory components of the endonuclease's family are all cleaved by caspases that are downstream. In addition to influencing the cytoskeleton, cell cycle, and signaling pathways, these factors work in tandem to cause the characteristic morphological alterations seen after cell death.

3.3.4 The intrinsic endoplasmic reticulum pathway

Not as well-known is the third route, which involves the intrinsic endoplasmic reticulum (ER). It is thought to be mitochondria-independent and caspase 12-dependent. A protein called TNF receptor associated factor 2 (TRAF2) separates from procaspase-12, which activates the latter, when the endoplasmic reticulum (ER) is damaged by cellular stresses such as hypoxia, free radicals, or glucose starvation. This leads to protein unfolding and decreased protein synthesis in the cell.

4. Targeting Apoptosis in Cancer Treatment

On the one hand, any flaw or anomaly along the apoptotic pathways might potentially be a promising target for cancer therapy on the other. Cancer cells rely on these abnormalities to survive; hence, the elimination of these cells may be possible using drugs or therapy methods that bring the apoptotic signaling pathways back to normalcy. New avenues for the development of anticancer medication classes have been uncovered by a plethora of significant discoveries in recent years. Here we focus on novel therapeutic approaches that aim to address some of the apoptotic abnormalities discussed in Section 3. Here is a rundown of the medications and therapy methods that are available.

4.1 Targeting the Bcl-2 family of proteins

Using therapeutic drugs to inhibit the Bcl-2 family of anti-apoptotic proteins or silencing the elevated anti-apoptotic proteins or genes implicated are some possible therapy techniques that target the Bcl-2 family of proteins.

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4.1.1Agents that target

A protein family known as Bcl-2 Oblmersen sodium, the first Bcl-2 targeting agent to enter clinical development, is an excellent example of one of these drugs; it is a Bcl-2 antisense oblimer. When used in conjunction with standard anticancer medications, the medicine has been shown to increase survival rates in individuals with chronic myeloid leukemia by making them more sensitive to chemotherapy. Small molecule inhibitors of the Bcl-2 family of proteins are another example that falls within this category. One may further classify them as follows:

1) The chemicals that influence the expression of genes or proteins and
2) Those interacting with the proteins directly.

The first category contains compounds such as sodium butyrate, depsipetide, fenretinide, and flavipirodol; the second category includes compounds such as gossypol, ABT-737, ABT-263, GX15-070, and HA14-1. This new class of medicines includes a few of these tiny compounds; they're dubbed BH3 mimetics because they resemble the binding of BH3-only proteins to the hydrophobic groove of Bcl-2 family anti-apoptotic proteins.

Inhibiting anti-apoptotic proteins including Bcl-2, Bcl-xL, and Bcl-W is one function of ABT-737, a BH3 mimic. Cytotoxicity was shown in lymphoma, small cell lung cancer, and primary patient-derived cell lines, and it induced tumor regression and a high rate of cure in animal models. There have been reports of other BH3 mimetics binding to and inhibiting Mcl-1, including ATF4, ATF3, and NOXA.

4.1.2 Silencing the anti-apoptotic proteins/genes

Instead,than using medications or medicinal treatments to block the anti-apoptotic Bcl-2 proteins, some research has shown that increasing apoptosis might be accomplished by reducing gene expression for these proteins. One example is the anti-proliferative and pro-apoptotic effects shown in pancreatic cancer cells when Bcl-2 specific siRNA was used. These effects were detected both in vitro and in vivo. In contrast, Wu et al. showed that doxorubicin increased apoptotic cell numbers in vitro and in vivo after Bmi-1 silencing MCF breast cancer cells, which in turn decreased pAkt and Bcl-2 expression.

4.2 Targeting p53

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There have been several cancer therapeutic options that have been studied that target p53. These may often be grouped into three main types:

1) Gene therapy,
2) Drug therapy and
3) Immunotherapy.

4.2.1 p53-based gene therapy

It was shown in the first publication of p53 gene therapy in 1996 that p53-based gene therapy might be possible by injecting tumor cells of non-small cell lung cancer generated from patients with a retroviral vector expressing a wild-type p53 gene. Subsequent research has explored the possibility of combining p53 gene therapy with other anticancer tactics, as p53 gene therapy on its own proved unable to eradicate all tumor cells. Head and neck, colorectal, prostate, and glioma tumor cells are made more sensitive to ionizing radiation when the wildtype p53 gene is introduced. So yet, the FDA has not given its final clearance, even though several research have progressed to phase III clinical trials. Using modified viruses to eradicate p53-deficient cells was another intriguing p53 gene-based approach. An example of this is the use of ONYX-015, a genetically modified oncolytic adenovirus. This virus can specifically target tumor cells lacking p53 and lyse them since the E1B-55 kDa gene has been removed.

4.2.2 p53-based drug therapy

Several medicines have been studied for their potential to target p53 via various pathways. Small compounds that can revert mutant p53 to its wild-type activities constitute one class of medicines. For instance, it has been shown that the tiny molecule Phikan083, a carbazole derivative, may bind to mutant p53 and restore its function. To restore unstable p53 mutants, another tiny chemical called CP-31398 intercalates with DNA and changes and destabilizes the DNA-p53 core domain complex.

In addition to tenovins, nutlins, and MI-219, other medicines have been used to target p53. In contrast to MI-219, which was found to inhibit cell proliferation, selectively induce apoptosis in tumor cells, and completely inhibit tumor growth, Nutlins, which are analogues of cis-imidazoline, inhibit the MSM2-p53 interaction, stabilize p53, and selectively induce

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senescence in cancer cells. Comparatively, tenovins are small molecule p53 activators that reduce tumor development in vivo.

4.2.3 p53-based immunotherapy

The p53 vaccination has been the subject of many clinical studies. Kuball et al. conducted a clinical experiment where a vaccination comprising a recombinant replication-defective adenoviral vector with human wild-type p53 was administered to six patients with advanced-stage cancer.

At the three-month follow-up after vaccination, four of the six patients remained disease-free. But from the seventh month forward, only one patient showed disease stability. Vaccines based on dendritic cells have also been tested in clinical trials, in addition to those based on viruses. In their phase I clinical study, Svane et al. investigated the efficacy of p53 peptide pulsed dendritic cells. They found that p53-specific T cell responses occurred in three of the six patients and a clinical response in two of the six patients overall. Long peptide-based vaccinations and short peptide-based vaccines are among the other vaccines that have been used.

4.3 Targeting the IAPs

4.3.1 Targeting XIAP

The IAPs are promising molecular targets for the development of new cancer medications. It has been shown that out of all the IAPs, XIAP inhibits apoptosis the most effectively. It binds to caspase-9 upstream and inhibits caspases-3 and -7 downstream, thereby blocking both the intrinsic and extrinsic routes of apoptosis. Antisense techniques and small interfering RNA (siRNA) molecules are two examples of new therapies that target XIAP. It has been shown that inhibiting XIAP via the antisense method improves in vivo tumor control with radiation. Lung cancer cells were shown to have improved chemotherapeutic activity in vitro and in vivo when XIAP antisense oligonucleotides were administered in conjunction with anticancer medicines. Meanwhile, Ohnishi et al. found that XIAP siRNA targeting increased radiation sensitivity in human cancer cells regardless of TP53 status, and Yamaguchi et al. found that hepatoma cells are more susceptible to death receptor- and chemotherapeutic agent-induced cell death when siRNA targeting XIAP or Survivin is used.

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4.3.2 Targeting Survivin

The possibility of targeting Survivin for cancer intervention has been the subject of several investigations. The usage of oligonucleotides that produce antisense is one example. The antisense method was first shown to work in human melanoma cells by Grossman et al. Researchers demonstrated that YUSAC-2 and LOX malignant melanoma cells induced spontaneous apoptosis when transfected with anti-sense Survivin. Applying the anti-sense strategy to medullary thyroid cancer cells inhibited their growth and proliferation, and it was also discovered to trigger apoptosis in head and neck squamous cell carcinoma cells, making them more sensitive to chemotherapy.

Use of small interfering RNAs (siRNAs) is another strategy for targeting Survivin. These RNAs have several effects, such as reducing radio resistance in pancreatic cancer cells, suppressing Survivin expression, inhibiting cell proliferation, and enhancing apoptosis in SKOV3/DDP ovarian cancer cells, and increasing radiosensitivity in human non-small cell lung cancer cells. In addition, gene therapy, small molecule Survivin antagonists including cyclin-dependent kinase inhibitors and Hsp90 inhibitors, and other cancer treatments have all explored targeting Survivin.

4.3.3 Other IAP antagonists

Additional small compounds that inhibit IAP include those that are peptidic and those that are non-peptidic. Two of the several instances were 2 and 3, which are cyclopeptidic Smac mimetics; they mimic the actions of caspases 9 and 3/-7 that XIAP inhibits by binding to XIAP and cIAP-1/2. However, by simultaneously targeting XIAP and cIAP1, the non-peptidic IAP inhibitor SM-164 was shown to significantly boost TRAIL activity.

4.4 Targeting caspases

4.4.1 Caspase-based drug therapy

It is possible to synthetically activate caspases using a number of medications. Apoptin, a caspase-inducing chemical first isolated from chicken anaemia virus, selectively triggers cell death in cancer cells while leaving normal cells alone. There is another group of medications called small molecule caspase activators. The arginin-glycine-aspartate motif is present in these peptides. Their capacity to directly stimulate procaspase 3 auto-activation makes them pro-

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apoptotic. In addition to increasing cancer cells' susceptibility to drugs, they have the ability to either activate caspase or decrease its activation threshold.

4.4.2 Caspase-based gene therapy

Caspases have been the subject of both pharmacological and genetic treatments in various investigations. Genomic transfer of constitutively active caspase-3 into HuH7 human hepatoma cells selectively induced apoptosis in these cells; for example, AH130 liver tumor model researchers discovered that extensive apoptosis and reduced tumor volume were outcomes of human caspase-3 gene therapy in conjunction with etoposide treatment. Additionally, anti-cancer effects in hepatocellular carcinoma have been shown in vitro and in vivo by use of a recombinant adenovirus that carries immunocaspase 3.

4.5 Molecules targeting apoptosis in clinical trials

There has been a recent influx of novel apoptosis-targeting agents into different phases of clinical trials. There is a plethora of findings returned by (a registration and results database of clinical studies financed by the federal government and private organizations worldwide). Multiple apoptotic proteins are the targets of these compounds. Among these are those that target the Bcl-2 protein family and those that act as antagonists to IAPs.

5. Conclusions

The literature strongly suggests that apoptotic pathway aberrations are essential to carcinogenesis and that multiple innovative apoptosis-targeted therapies are feasible and might be employed to treat various malignancies. Several of these studies have entered preclinical or human clinical trials. These innovative chemicals or treatment methods may enhance anticancer therapy when paired with established drugs, according to many clinical trials. However, numerous questions remain, such as whether these treatment techniques may cause tumor resistance and kill many benign cells. Given the catastrophic side effects and tumor resistance of standard anticancer drugs, this is cause for concern. If these apoptosis-targeting drugs preferentially targeted a protein or pathway, they may be therapeutic. Many Bcl family protein inhibitors and a few pan-IAP inhibitors work on many targets and enter clinical studies. Thus, evidence-based innovative cancer therapy must be followed for lengthy periods of time,

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and researchers should continue to find techniques to target cancer cells for apoptosis rather than normal cells.

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Author's Declaration

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