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Apoptosis & Anti-Cancer Drugs: A Targeted Therapy

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ABSTRACT
According to the World Health Organisation, cancer is the second leading cause of death worldwide. Although extensive research is being done to find a cure for cancer, we are still years away from it. The most advanced studies done in this field are associated with apoptosis as a target for anticancer drugs which are used currently to treat various types of cancer. One such type of cancer is Leukemia, an umbrella term for cancers related to blood cells. Acute lymphocytic leukemia can arise due to the loss of endogenous microRNAs (miRNAs) which leads to the suppression of BCL-2 gene expression. This membrane protein belongs to the BH-3 family of proteins that further bring about apoptosis of the cancerous cells through the extrinsic or intrinsic pathways. Drugs such as prednisolone, methotrexate, vincristine, among others, are most commonly used to facilitate remission. Plant derivatives such as artemisinin have been found to showcase antitumor activity, inducing cell cycle arrest, inhibiting proliferation of tumor cells, inhibiting tumor cell invasion and metastasis, exerting and inducing cancer cell apoptosis. In the extrinsic pathway or death receptor pathway the expression of the ligands associated with the initiation of the signalling pathway are enhanced by the drugs. They function in a similar way in the intrinsic or mitochondrial pathway of apoptosis. The literature review provides a detailed understanding of the molecular mechanisms associated with the regulation of apoptosis in response to anticancer therapy and provides novel opportunities for pharmaceutical companies to develop targeted therapy.

Keywords- Anticancer Drugs, Apoptosis, Artemisinin, BH-3 proteins, BCL-2 gene, Cancer, Leukemia.

I. INTRODUCTION

The World Health Organisation describes cancer as a large group of diseases that can trigger in any organ or tissue leading to abnormal growth of cells [1]. These abnormal growths of cells sometimes are restricted to the particular organ or tissue called benign, or sometimes they spread to other parts of the body. Treatments for cancer vary depending on the type of cancer and recent studies have shown that inducing apoptosis by drugs could serve as an effective method for treatment. The extrinsic and intrinsic pathways of apoptosis are the target sites for such drugs [2]. Patients suffering from acute lymphocytic leukemia (ALL) typically receive long-term chemotherapy (chemo), but autophagy and apoptosis serve better alternatives as after chemotherapy the cancer is observed to be recurring. In such cases, mitochondria is a favourable target as it is responsible for apoptosis, ROS generation etc. Controlling mitochondrial functions is a treatment strategy that inhibits oxidative phosphorylation and causes the release of proapoptotic proteins such as cytochrome c, the Bcl-2 family and high ratios of these proteins are associated with remission failure in acute leukemia cases. The Bcl-2 / Bax ratio, which is pro-apoptotic proteins, is a critical factor in ALL [3]. The expression of these proteins determines the susceptibility of the cell to undergo apoptosis. Damage to DNA elicits a DNA damage response (DDR) which is a collection of proteins that, upon detection of any DNA damage, stop the cell cycle and initiate repair. Checkpoints in G_1, S, and G_2/M transition can be activated in response to the signals from the DDR[4]. The p53 transcriptional factor is a master regulator of the cell cycle and regulates both these checkpoints (G_1, S, and G_2/M). The induction of p53 is a result of the various stress signals like DNA damage and culminates primarily in cell-cycle arrest and apoptosis [5]. Significant DNA damage leads to p53 induced apoptosis wherein the damaged DNA is prevented from being transferred into daughter cells [6]. Certain drugs like methotrexate and cisplatin target Fas (death receptor 2) which is associated with extrinsic pathways and can cause DNA damage in cancerous cells. Plant-based drugs such as Artemisinin, a compound derived from Artemisia annua L, is observed to have antimalarial properties, while its derivatives have exhibited anti-

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cancer properties through the production of ROS resulting in lysosomal rupture [7]. One such derivative, Dihydroartemisinin (DHA), acts on the cells causing leukemia by increasing ROS production resulting in apoptosis via the intrinsic pathway that is BAK-dependent [8].

II. MATERIAL AND METHODOLOGY:

Databases such as NCBI, PubMed, and Google Scholar were perused for keywords “acute lymphocytic leukemia”, “cancer”, “apoptosis”, “Bcl-2”, “p53”, and “anti-cancer drugs”. The search was conducted independently by all three co-authors in November 2021. Studies from the year 2003 onwards were considered and the search focused on anti-cancer drugs used for the treatment of acute lymphocytic leukemia and the pathways that they target. The outcome of the findings was compiled and the references of each were further scrutinized to find similar studies and research done in that particular field. The data were extracted and presented in a textual format.

III. APOPTOSIS MEDIATED CELL DEATH

Apoptosis is a process of controlled cell death involving distinct biochemical and genetic pathways that are essential for optimal tissue development and homeostasis [9]. These "natural" cell deaths, according to studies, have revealed the first genes dedicated to apoptosis in the nematode C. elegans, are suicides in which the cells engage an intercellular death program, killing themselves in a planned manner - known as programmed cell death [10].

It helps maintain a healthy balance between cell survival and cell death by removing redundant and unwanted cells. Furthermore, this mechanism is not limited to the nervous system, and competition for a limited supply of extracellular survival signals is a widely used general mechanism in animals that regulates cell number [9].

Apoptosis causes distinct morphological changes in cells. They condense and shrink, the cytoskeleton collapses, the nuclear envelope disassembles, and nuclear chromatin breaks up into fragments. The cell surface often blebs and, if the cell is large, it frequently fragments into membrane-enclosed fragments known as apoptotic bodies [10].

The recognition that several diseases involve either too much (e.g., [neuro]degenerative diseases, Parkinson's, Alzheimer's, spinal muscular atrophy, AIDS) or too little apoptosis has also sparked a lot of interest in apoptosis (e.g., cancer [either by viral infections or by DNA mutations] or autoimmune diseases [Diabetes type I, Encephalomyelitis]). Apoptosis can be triggered by a number of toxins and other cellular stressors (e.g., oxidative stress, alcohol) [11].

This natural cell death mechanism is a promising target for cancer therapy [3].Cancer's hallmarks, such as uncontrolled growth, angiogenesis, and apoptosis evasion, are present in all cancer cells, regardless of the cause or type [12].

The apoptotic pathway can be activated by a wide range of conditions, including DNA damage or uncontrolled proliferation. There are two pathways that lead to apoptosis: intrinsic (or mitochondrial) and extrinsic (or death receptor) pathways that correlate with the type of signal. Intracellular signals include DNA damage, growth factor deprivation, and cytokine deprivation, whereas the most common extracellular signals are death-inducing signals produced by immune system cytotoxic T cells in response to damaged or infected cells. Irrespective of the signal being intracellular or extracellular, the proteins that are engaged in this process are where the pathways converge [3].

Caspases (cysteine aspartyl-specific proteases), a class of cysteine proteins that cleave target proteins, are involved in the signalling process [13].Caspase activity causes apoptotic cells to shrink and undergo plasma membrane changes, signalling the macrophage response [3].

3.1 Bcl-2 Family of proteins

During lymphocyte development, a certain level of expression of FasL, Bcl-XL and Bcl-2 is observed. Bcl-2\Bcl-XL are important antiapoptotic members of the Bcl-2 protein family, in certain lymphomas, the expression of Bcl-2 is under the control of the immunoglobulin heavy chain enhancer gene. It is the first protooncogene discovered to regulate the cell cycle and these genes are conserved over animal evolution; also the addition of new players has been observed [10,14].

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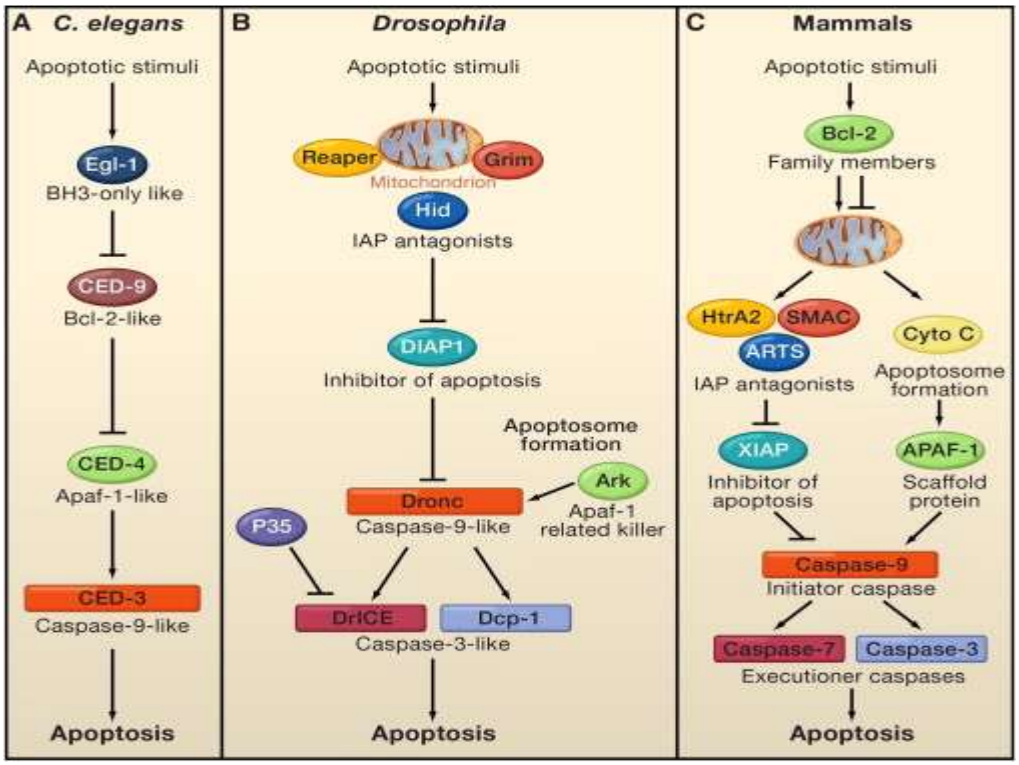

Figure:1Pathways conserved over animal evolution

Retrieved from:Yaron F. &H. StellerProgrammed Cell Death in Animal Development and Disease (vol 147, pg 742, 2011)[cited 2021 Oct 25];
Available on:https://www.researchgate.net/figure/Evolutionary-Conservation-of-the-Core-Apoptotic-Machinery_fig1_279286573

		D.melanogaster		Mammals	
	C.elegans	Intrinsic	Extrinsic	Intrinsic	Extrinsic
Promoter	EGL-1	Debcl	Wengen/Eiger	Bax BH3 only proteins	Fas/FasL TNFR1/TNF DR4,5/TRAIL
Inhibitor	CED-9	Buffy		Bcl-2, Bcl-XL	FLIP
Adaptor	CED-4	Dark	dFADD	Apaf	FADD, TRADD
Initiator Caspase	CED-3	Dronc	Dredd	Caspase-9	Caspase-8
Caspase Inhibitor		Diap-1	Diap-1	IAP	IAP
Effector Caspase	CED-3	Dcp-1, Drice	Dcp-1, Drice	Caspase-3 Caspase-7	Caspase-3 Caspase-7

Table 1: Evolutionary conservation of apoptotic pathways.

Retrieved from: Alfons L Apoptosis - an introduction. BioEssays [Internet]. 2003 Sept [cited 2021 Oct 25];
Available from: Programmed Cell Death in Animal Development and Disease (vol 147, pg 742, 2011)
https://onlinelibrary.wiley.com/doi/abs/10.1002/bies.10329

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3.2 Extrinsic/Receptor-mediated pathway of cell death

The extrinsic pathway or receptor-mediated pathway for apoptosis is dependent on an extrinsic signal for its initiation. Any external stress can initiate this pathway with the introduction of a promoter ligand that binds to its receptor, hence triggering downstream processes. These receptors are present inside the plasma membrane with their receptor binding sites on the surface and anchoring sites inside the cytosol which are basically death domains (DD). They are also called death receptors and could be of the type- Fas (CD95), TNFR (tumor necrosis factor receptor) family, etc. The enzymes governing the series of reactions that take place are called caspases (Cysteine Aspartic acid Proteases). The pathway leads to the recruitment of caspase-8/10 which is induced by binding of ligands to the receptor forming a ligand-receptor complex. Once this is done the pro-initiator caspases bind to the ligand-receptor complex forming the death induced signalling complex (DISC). This then gives rise to an active form of caspase that further engages the executioner caspases who recruit nucleases and proteases which destroy the cell machinery and eventually form apoptotic bodies which are then phagocytosed [3,10,11].

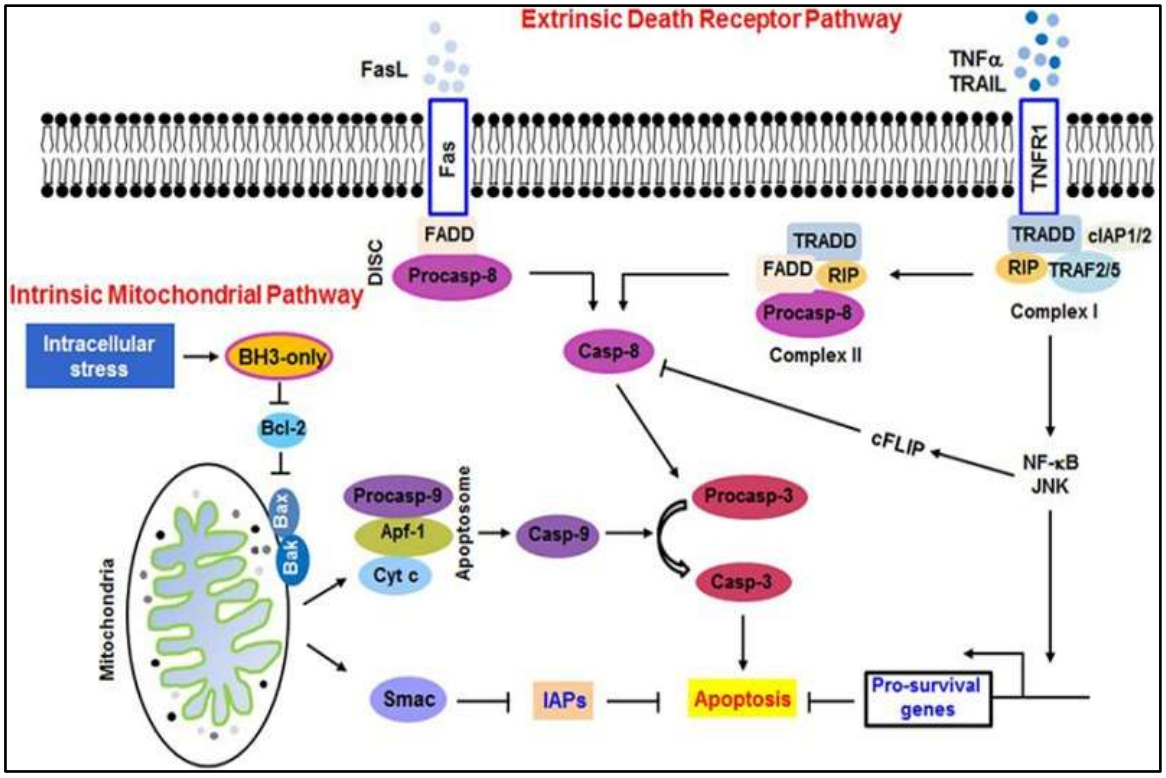

Figure 2: Extrinsic & Intrinsic Pathways of Apoptosis
Retrieved from Chapter 9, Apoptosis in Polycystic Kidney Disease: From Pathogenesis to Treatment
https://www.ncbi.nlm.nih.gov/books/NBK373375/figure/fig9_1/

3.3 Intrinsic/ mitochondrial pathway of cell death

The intrinsic pathway is governed by stress that is generated inside the cell; it does not require any external stress or signal for its initiation and is regulated by the BH-3 family of proteins. Certain apoptotic and anti-apoptotic proteins regulate this process. Bcl-2 protein expression is inhibited by BH-3 only proteins and the activation of Bax and Bak proteins that are pro-apoptosis generate a downstream cascade that acts on the outer mitochondrial membrane causing it to rupture. Cytochrome c complex which is a part of the electron transport chain comes out into the cytoplasm causing internal stress and activating caspase 9 which, along with cytochrome c and Apaf-1 (apoptosis promoting factor) together called the apoptosome, activates procaspase 3 to caspase 3, eventually forming apoptotic bodies [3,10,11].

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IV. CANCER

Cancer, also known as neoplasm or malignant tumor, is a generic term for a group of diseases that can affect any part of the body. With an estimated 10 million deaths in 2020 [15], cancer, according to many biologists, is an evolutionary legacy. Thus, in addition to environmental factors, genetic factors shaped by evolution, that is, cells of multicellular organisms harbouring both oncogenes and tumor-suppressor genes, play a critical role in cancer development [16].

In the process of carcinogenesis [17], cancer cells proliferate and form tumors giving rise to different types of cancers [18]. Cancer can be a result of a series of genetic changes or abnormal proliferations that transform a normal cell into a malignant one, with evasion of cell death being one of the critical changes in a cell that causes this malignant transformation [19]. Men are more likely to develop prostate, lung colorectal, and liver cancer whereas women are susceptible to breast, lung, cervical, and thyroid cancers [15]. Cancer cells can leave the primary site of establishment and invade other organs of the body after a period of time and this phenomenon is known as metastasis and makes it difficult to treat [18].

Cancerous tumors are also known as malignant tumors[20] which, as opposed to benign tumours, develop metastasis that is caused in part by the down-regulation of cell adhesion receptors required for tissue-specific cell to cell attachment and the up-regulation of receptors that promote cell motility [17]. On the other hand, benign or non-cancerous tumors do not invade and spread into nearby tissues and in some instances grow to be quite large. When benign tumors are removed, they usually do not recur, whereas malignant tumors occasionally do. Many cancers form solid tumors, but blood cancers, such as leukemias, do not form tumors[20].

Because each cancer type necessitates a unique treatment regimen, an accurate cancer diagnosis is critical for appropriate and effective treatment [15]. One of the main goals of cancer experiments is to control the cell cycle by inducing cell death via cell cycle arrest or apoptosis activation and the regulation of cell cycle is governed by a variety of proteins. The interaction of cyclins with specific cyclin-dependent kinases (CDKs) allow cells to progress from one phase to the next [18]. Controlling or possibly terminating the uncontrolled growth of cancer cells is one method of treating cancer. Additionally, the most effective non-surgical treatment is one that targets apoptosis as apoptosis evasion is one of the hallmarks of cancer and is not specific to the cause or type of cancer hence, targeting apoptosis is effective for all types of cancer [3]

4.1 Types of cancer

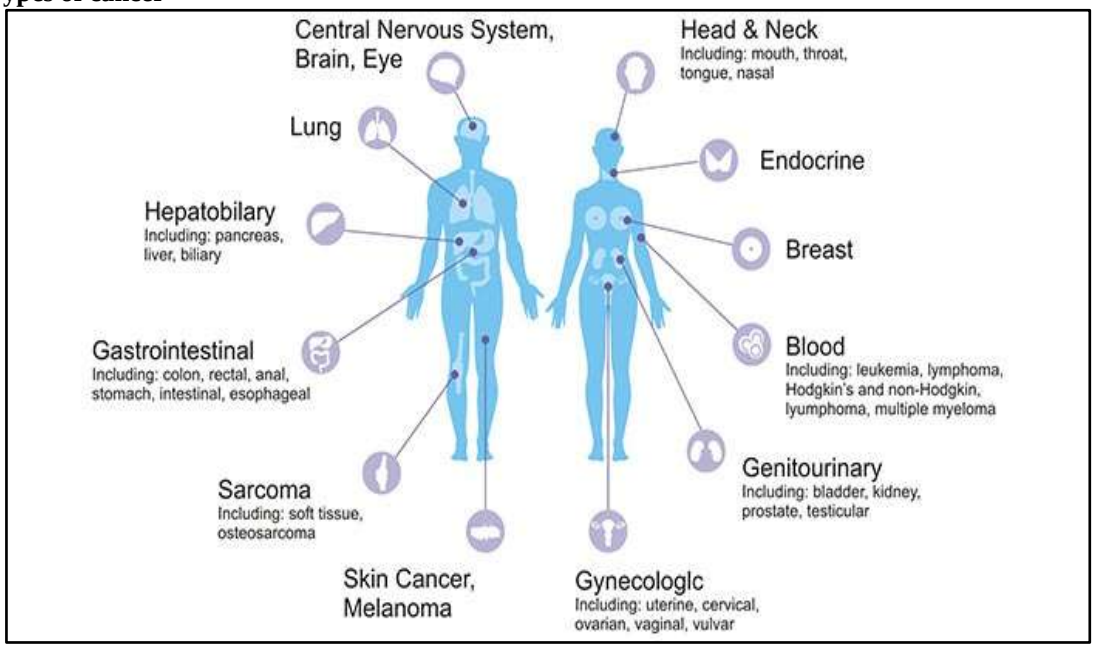

Figure 3: Types of Cancer

Retrieved from: https://www.cusabio.com/cancer.html

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4.1.1 Acute Lymphocytic Leukemia

Leukemia is a type of cancer that begins in cells that may proliferate into different cell types. Although most leukemias originate from white blood cells, acute lymphocytic leukemia (ALL), also known as acute lymphoblastic leukemia, begins in other types of blood cells. The term "acute" refers to the fact that leukemia can progress quickly and, if not treated, will most likely be life-threatening within a few months [21].

Acute leukemia is the most common type of cancer in children, accounting for 30% of all childhood (pediatric) malignancies [22].

ALL arises from the early stages of lymphocytes, a type of white blood cell, which are the primary cells that make up the lymph tissue. They are an important component of the immune system that develops from lymphoblasts into mature, infection-fighting cells.

ALL begins in the bone marrow and mainly affects the blood and bone marrow, lymphomas mainly affect the lymph nodes or other organs. Since these leukemia cells invade the body pretty quickly [21], Acute lymphoblastic leukemia (ALL) occurs 5 times more frequently than acute myeloid leukemia (AML). The global incidence of ALL in the population was estimated to be between 0.4 and 2 per 100,000 in the year 2020, with a prevalence rate ranging from 0.37 to 1.6 per 100,000. Although the majority of ALL cases are seen in children between 2 to 5 years of age, 60% of cases occur prior to the age of 20 [23].

In ALL, an excessive number of stem cells differentiate into lymphoblasts and lymphocytes and these cells are also referred to as leukemia cells [22].

Lymphocytes are classified into two types:

B lymphocytes (or B cells) protect the body by producing proteins known as antibodies and account for 80-85% of cells. Antibodies bind to pathogens like bacteria, viruses, and fungi in the body, allowing the immune system to destroy them.

T lymphocytes (or T cells) are classified into several types, each with a specific function and account for over 20-25% of the cells. Some T cells can directly destroy germs, while others help to boost or slow the activity of other immune system cells [21, 23].

These leukemia cells are not very good at fighting infection and as the number of leukemia cells in the blood and bone marrow increases, there is less space for healthy white blood cells, red blood cells, and platelets [22].

V. TREATMENT

Adults with acute lymphocytic leukemia (ALL) typically receive long-term chemotherapy (chemo), however, other medications may be required to help prevent or treat these side effects. ALL can sometimes spread to the area around the brain and the spinal cord too [4]. The common symptoms of ALL include bleeding gums, frequent fevers, bone pain and recurring infections [24].

Treatment is usually divided into three stages (lasting two years):

- Induction (remission induction)

The purpose of induction chemotherapy is to put leukemia into remission (complete remission). This means that leukemia cells are no longer detected in bone marrow samples (via a bone marrow biopsy), normal marrow cells are restored, and blood counts return to normal levels.

Induction chemotherapy usually lasts about a month and various chemo drug combinations, such as vincristine and prednisone, may be used. Treatment is intensive for the first month as leukemia cells may still be present in the body, necessitating additional treatment.

- Consolidation (intensification)

If the leukemia goes into remission, the next stage usually consists of another relatively short course of chemo with many of the same drugs used for induction therapy. This usually lasts a few months. Typically, the drugs are administered in high doses to ensure that the treatment remains fairly intense.

Some remission patients, such as those with specific ALL subtypes or other poor prognostic factors, are still at high risk of the leukemia relapsing (coming back). Doctors may recommend an allogeneic stem cell transplant (SCT) instead of standard chemo at this time.

- Maintenance

Following consolidation, the patient is usually placed on a maintenance chemotherapy regimen. The maintenance stage is the most time-consuming of the three.

In about 10-20% of cases, acute leukemia can be refractory or relapsing [25]. When cancer returns in this way, it is referred to as a relapse or recurrence. That is, after complete remission, blast cells are still present in the bone marrow. Relapse occurs in approximately 15-20% of childhood ALL patients. As a result, understanding how to effectively detect minimal residual disease (MRD) is critical for ALL prognosis and is determined by examining remission bone marrow samples. MRD

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can be assessed using a variety of techniques, including polymerase chain reaction, flow cytometry, and next-generation sequencing.

Aside from detecting MRD, apoptosis and autophagy are extremely important molecular factors in treating ALL relapses. Apoptosis regulation is known to be abnormal in relapsed ALL and the decrease in the Bax/Bcl-2 ratio with loss of spontaneous caspase-3 processing is associated with relapse in childhood ALL. The Bcl-2 family is a key regulator in the intrinsic apoptosis pathway and its overexpression is one of the chemo-resistance mechanisms.

Apoptosis is the primary mechanism by which tumour-inhibiting effects can be exerted through the mitochondrial pathway, the production of reactive oxygen species (ROS), and the induction of cell death. Mitochondria are vital organelles that regulate numerous cellular pathways in mammalian cells. As a result, anticancer treatment focuses on mitochondria.

Controlling mitochondrial functions is a therapeutic strategy that inhibits oxidative phosphorylation and causes the release of proapoptotic proteins such as cytochrome c, the Bcl-2 family, Bak, and Bax. High Bcl-2 / Bax ratios are associated with remission failure in acute leukemia cases. Hence, Bcl-2 / Bax ratio is a critical factor in ALL [23].

The relative expression of pro-apoptotic (Bax, Bcl-10, Bak, Bid, Bad, Bim, Bik, and Blk) and anti-apoptotic (Bax, Bcl-10, Bak, Bid, Bad, Bim, Bik, and Blk) molecules determines cell apoptosis susceptibility (Bcl-2, Bcl-x, Bcl-XL, Bcl-XS, Bcl-w, BAG, MCL-1) [26].

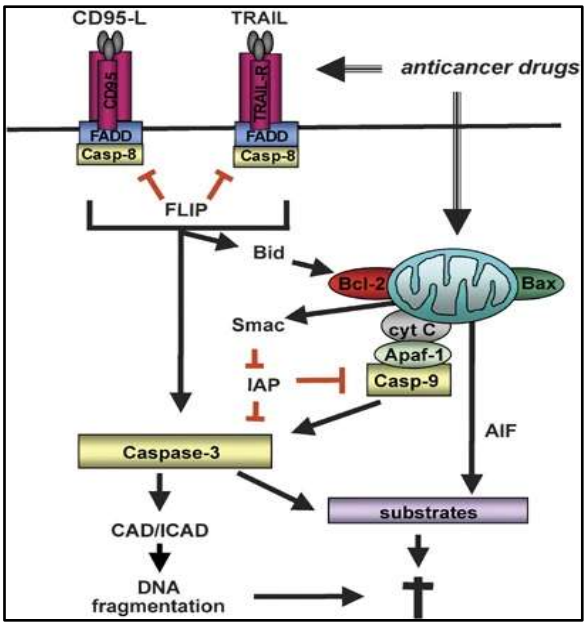

Figure 4: Action of Anticancer drugs.

S.Fulda et.al(2006), Extrinsic versus intrinsic apoptosis pathways in anticancer chemotherapy, Nature.
https://www.nature.com/articles/1209608#Abs1

Reliability of polymorphism in Bcl-2 promoter region is higher as compared to that observed in the Bax promoter region during the estimation of ALL patient survival time, when compared to healthy individuals.

According to Meng et al 21, paediatric ALL patients in the drug-resistance group had significantly higher Bcl-2 mRNA expression than those in the chemotherapy-sensitive group .

Recent in vitro research studies on chemotherapeutic resistance have refocused attention on the role of apoptosis pathways in risk stratification and treatment of leukemia patients. Cancer chemotherapeutic agents are thought to work primarily by inducing cancer cell death via the activation of various apoptosis signalling pathways. Apoptosis occurs in leukemias both spontaneously and as a result of anti-tumor therapies [23, 26].

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VI. ANTI-CANCER DRUGS TARGETING APOPTOSIS:

In recent years it has been observed that cancerous cells have started developing resistance to chemo-therapy and traditional anticancer treatments. Toxicity of these therapies towards self and cancerous cells have also been observed, therefore, a safer alternative is needed [3]. Therapies targeting apoptotic pathways have emerged as a safer and a non-toxic solution to resistant cancerous cells. Specific drugs can be designed to target either the intrinsic or extrinsic pathways of apoptosis and bring about programmed cell death in the targeted cancer cells [27].

In the case of ALL, there are chances of recurrence due to the presence of remnant cancerous cells that may have escaped previous treatment. Apoptosis is an important phenomenon in the treatment and regulation of cancer and drugs are available that specifically target this process.

6.1 Targeting extrinsic pathway: Death receptors

Drugs such as methotrexate and cisplatin target Fas (death receptor 2) and cause DNA damage in cancerous cells. Further, TRAIL-R1 (death receptor 4) and TRAIL-R2 (death receptor 5) are expressed when etoposide, Ara-C, and camptosar (CPT-11) are administered. Induction of apoptosis has also been observed as a result of antibodies that target TRAIL-R1 and R2, especially at a higher magnitude in solid tumours. TRAIL receptors have shown the capability to bring about cell death in cancerous cells, therefore formulation of antagonistic antibodies showcased apoptotic behaviour in many cancerous cells [23]. Another drug, doxorubicin, targets the extrinsic pathway of apoptosis by overexpression of death receptors. It has also been known to promote p53 expression which leads to apoptosis via both intrinsic and extrinsic pathways [28]. Cisplatin is another such drug that is part of the conventional chemotherapeutic drug treatment that targets Fas (death receptor 2) leading to DNA damage and eventually resulting in apoptotic behaviour [27].

6.2 Targeting intrinsic pathway: Bcl-2 family of proteins

Prednisolone is a synthetic glucocorticoid used to control the immune system and also treat many inflammatory and autoimmune diseases including ALL. Its function is to initiate a caspase action which ultimately results in apoptotic behaviour by upregulating BAX protein expression and suppressing Bcl-2 expression. In a study conducted by Ganbarjeddi et al 2020, revealed that methylation on Bax and Bcl-2 promoters was observed in CCRF-CEM cells (T-lymphoblastoid cell line) when prednisolone was administered after 24 and 48 hours. The results showed an upregulation in BAX and downregulation in BCL-2 after conducting a western blot. An increase in BAX protein and a decrease in BCL-2 protein was also observed after 24 and 48 hours. The study concluded that prednisolone caused an apoptotic effect through different pathways from promoter methylation of BAX and BCL-2 genes in the CCRF-CEM cell line [29].

6.3 Plant-based compounds inducing apoptosis

Plant-based medicine offers a safer and non-toxic alternative to conventional cancer treatments while providing a solution against the rising resistance to standard therapies. Inhibition of Bcl-2 proteins and upregulation of BAX leading to apoptosis has been a signature of Graviola. This fruit-bearing tree is known for its anti-cancer properties and harmlessness towards healthy cells. Apples, containing the compound Quercetin, have the ability to trigger caspase activity resulting in apoptosis. Another widely used ingredient in many cuisines and Ayurvedic medicine is turmeric, with its active principle curcumin. It is widely known that curcumin possesses anti-carcinogenic properties among many other benefits. Curcumin has been observed to interact with as many as 33 different proteins which aid in its involvement in activating various pathways that lead to tumour suppression. In the case of apoptosis, curcumin targets both the intrinsic and extrinsic pathways upregulating BAX and BAK expression while suppressing Bcl-2 and XIAP expression. An increase in mitochondrial permeability is another effect of curcumin interaction which leads to greater levels of cytochrome c being released. The end result is apoptosis and cell death via caspase activation [3].

In traditional Chinese herbal medicine, a sequestered compound called matrine could initiate reactive oxygen species (ROS) which is regulated by the mitochondria. Apoptosis induction due to the surplus of ROS is a possibility and this is another approach for treating leukemia. Matrine has been reported to cause elevated levels of Bax/Bcl-2 in ALL B-lymphocytes and finally result in cell death via apoptosis [23].

Artemisinin, a compound derived from Artemisia annua L., has been studied to showcase antimalarial properties. However, its derivatives have exhibited anti-cancer properties through the

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production of ROS resulting in lysosomal rupture [7]. One such derivative, Dihydroartemisinin (DHA), acts on leukemia cells by increasing ROS production resulting in apoptosis via the intrinsic pathway that is BAK-dependent [8].

VII. RESULTS & CONCLUSION

A large amount of advancement in the field of cancer has been observed over the years, yet some questions remain unanswered. Anticancer chemotherapy is one such treatment that changed the perspective of treatment plans for cancer. This method is highly effective since it induces apoptosis through the intrinsic or extrinsic pathways. Similarly, recent studies have discovered various drugs that perform a similar function without being invasive like chemotherapy. In the case of ALL which is observed to be recurring and resistant to chemotherapy, autophagy and apoptosis are used as a target. In vitro studies suggest that functional defects in apoptosis signalling molecules or insufficient activation of apoptosis pathways are to blame for chemotherapy resistance and treatment failure in acute leukemia.

The rising resistance of cancerous cells against traditional forms of chemotherapeutic treatments has led to the need for alternative therapy. Chemotherapeutic treatments have been observed to be toxic hence safer substitutes are required which can be in the forms of anticancer drugs targeting apoptotic mechanisms. However, the exact pathways that some of these drugs target is unknown and further research needs to be done to elucidate these comprehensive pathways. Further, the molecules participating in these processes need to be identified to increase the efficiency of these drugs. Plant-based anticancer therapy is an interesting avenue that must be explored while developing future treatments as they offer safer and non-toxic solutions while also battling the growing resistance of cancerous cells against traditional anticancer therapies.

From this, we can conclude that the ongoing research studies on the use of apoptotic markers in predicting the clinical characteristics or prognostic outcome of ALL patients along with the use of anticancer drugs either chemical or plant-based have shown promising results. However, the variations in the results of different studies published worldwide, due to differences in ethnicity, sample size, follow up data, as well as techniques used to study apoptosis, there is a further need to search for newer more-specific molecular markers to study this area of molecular oncology and chemotherapy resistance.

REFERENCES

[1]. Cancer [Internet]. World Health Organisation: Health Topics [cited 2021 Oct 25]. Available from https://www.who.int/health-topics/cancer#tab=tab_1

[2]. Fulda, S., Debatin, KM. Extrinsic versus intrinsic apoptosis pathways in anticancer chemotherapy. Oncogene 25, 4798–4811 (2006). https://doi.org/10.1038/sj.onc.1209608

[3]. Pfeffer, C. M., & Singh, A. (2018). Apoptosis: A Target for Anticancer Therapy. International journal of molecular sciences, 19(2), 448. https://doi.org/10.3390/ijms19020448

[4]. Visconti, Roberta, et al. "Cell cycle checkpoint in cancer: a therapeutically targetable double-edged sword." Journal of Experimental & Clinical Cancer Research, vol. 35, no. 153, 2016. https://jeccr.biomedcentral.com/articles/10.1186/s13046-016-0433-9. [Accessed 29th October 2021.]

[5]. Chen, Jiandong. "The Cell-Cycle Arrest and Apoptotic Functions of p53 in Tumor Initiation and Progression." Cold Spring Harbor Perspectives in Medicine, vol. 6, no. 3, 2016, p. a026104. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4772082/. [Accessed 29th October 2021.]

[6]. Okzaki, Toshinori, and Akira Nakagawara. "Role of p53 in Cell Death and Human Cancers." Cancers, vol. 3, no. 1, 2011, pp. 994-1013. PMC, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3756401/. [Accessed 30th October 2021.]

[7]. Drenberg, C. D., Buaboonnam, J., Orwick, S. J., Hu, S., Li, L., Fan, Y., Shelat, A. A., Guy, R. K., Rubnitz, J., & Baker, S. D. (2016). Evaluation of artemisinins for the treatment of acute myeloid leukemia. Cancer chemotherapy and pharmacology, 77(6), 1231–1243. https://doi.org/10.1007/s00280-016-3038-2

[8]. Xiaohua Lu, Thomas Efferth, Repurposing of artemisinin-type drugs for the treatment of acute leukemia, Seminars in Cancer Biology, Volume 68, 2021, Pages 291-312,

ISSN 1044-579X, https://doi.org/10.1016/j.semcancer.2020.05.016.

[9]. Yaron Fuchs, Hermann Steller. Programmed Cell Death in Animal Development and Disease. Cell, Volume 147, Issue 4 (2011) Pages 742-758, ISSN 0092-8674. https://doi.org/10.1016/j.cell.2011.10.033.

[10]. Alberts, Bruce, et al. Molecular Biology of the Cell. Fifth ed., Jackie Harbor, 2008. [Assessed on 2nd November 2021]

[11]. Alfons L Apoptosis - an introduction. BioEssays [Internet]. 2003 Sept [cited 2021 Oct 25]; Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/bies.10329

[12]. Lopez, J., & Tait, S. W. (2015). Mitochondrial apoptosis: killing cancer using the enemy within. British journal of cancer, 112(6), 957–962. https://doi.org/10.1038/bjc.2015.85

[13]. Zaman, S., Wang, R., & Gandhi, V. (2014). Targeting the apoptosis pathway in hematologic malignancies. Leukemia& lymphoma, 55(9), 1980–1992. https://doi.org/10.3109/10428194.2013.855307

[14]. Yip, K., Reed, J. Bcl-2 family proteins and cancer. Oncogene 27, 6398–6406 (2008). https://doi.org/10.1038/onc.2008.307

[15]. Cancer [Internet]. World Health Organization: Cancer. 2021 Sept. [Assessed on 15/12/2021 (10:30 pm)] https://www.who.int/news-room/fact-sheets/detail/cancer

[16]. Shen, L., Shi, Q., & Wang, W. (2018). Double agents: genes with both oncogenic and tumor-suppressor functions. Oncogenesis, 7(3), 25. https://doi.org/10.1038/s41389-018-0034-x

[17]. Sarkar, S., Horn, G., Moulton, K., Oza, A., Byler, S., Kokolus, S., & Longacre, M. (2013). Cancer development, progression, and therapy: an epigenetic overview. International journal of molecular sciences, 14(10), 21087–21113. https://doi.org/10.3390/ijms141021087

[18]. Ngabire, D., Seong, Y., Patil, M., Niyonizigiye, I., Seo, Y., & Kim, G. (2018). Induction of apoptosis and G1 phase cell cycle arrest by Aster incisus in AGS gastric adenocarcinoma cells. International Journal of Oncology, 53, 2300-2308. https://doi.org/10.3892/ijo.2018.4547

[19]. Wong R. S. (2011). Apoptosis in cancer: from pathogenesis to treatment. Journal of experimental & clinical cancer research : CR, 30(1), 87. https://doi.org/10.1186/1756-9966-30-87

[20]. National Cancer Institute: Understanding Cancer. [Assessed on 15/12/2021 (10:34 pm)] https://www.cancer.gov/about-cancer/understanding/what-is-cancer

[21]. ALL [Internet] American Cancer Society: What is Acute Lymphocytic Leukemia. [Assessed on 17/12/2021 (1:52 pm)] https://www.cancer.org/cancer/acute-lymphocytic-leukemia/about/what-is-all.html

[22]. ALL [Internet] National Cancer Institute: Adult Acute Lymphoblastic Leukemia Treatment. [Assessed on 17/12/2021 (2:01pm)] https://www.cancer.gov/types/leukemia/patient/adult-all-treatment-pdq

[23]. Huang, F. L., Yu, S. J., & Li, C. L. (2021). Role of Autophagy and Apoptosis in Acute Lymphoblastic Leukemia. Cancer control : journal of the Moffitt Cancer Center, 28, 10732748211019138. https://doi.org/10.1177/10732748211019138

[24]. Symptoms of ALL [Internet] Mayo Clinic: Acute Lymphocytic Leukemia. [Assessed on 17/12/2021 (4:14pm)] https://www.mayoclinic.org/diseases-conditions/acute-lymphocytic-leukemia/symptoms-causes/syc-20369077

[25]. Treatment of ALL [Internet] American Cancer Society: Typical Treatment of Acute Lymphocytic Leukemia [ALL]. [Assessed on 17/12/2021 (4:17pm)] https://www.cancer.org/cancer/acute-lymphocytic-leukemia/treating/typical-treatment.html

[26]. Kapoor, G., & Singh, N. (2018). Role of apoptotic markers in paediatric acute lymphoblastic leukemia. The Indian journal of medical research, 147(3), 225–227. https://doi.org/10.4103/ijmr.IJMR_906_17

[27]. Jan, R., & Chaudhry, G. E. (2019). Understanding Apoptosis and Apoptotic Pathways Targeted Cancer Therapeutics. Advanced pharmaceutical bulletin, 9(2), 205–218. https://doi.org/10.15171/apb.2019.024

[28]. Christidi, E., &Brunham, L. R. (2021). Regulated cell death pathways in doxorubicin-induced cardiotoxicity. Cell

death & disease, 12(4), 339. https://doi.org/10.1038/s41419-021-03614-x

[29]. Ganbarjeddi, S., Azimi, A., ZadiHeydarabad, M., Hemmatzadeh, M., Mohammadi, S., Mousavi Ardehaie, R., Zamani, M., Baharaghdam, S., Esmaeili, S., &Ghasemi, A. (2020). Apoptosis Induced by Prednisolone Occurs without Altering the Promoter Methylation of BAX and BCL-2 Genes in Acute Lymphoblastic Leukemia Cells CCRF-CEM. Asian Pacific journal of cancer prevention : APJCP, 21(2), 523–529. https://doi.org/10.31557/APJCP.2020.21.2.523