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Apoptosis in cancer

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ABSTRACT

Apoptosis, also known as programmed cell death, has become a target for treating many diseases, especially cancer. Many factors are influential in the cell's pathway to apoptosis. The defects in these pathways may transform the cell to become malignant, and the organism may face a lethal outcome such as cancer. Understanding apoptosis will provide clues in guiding the pathogenesis of diseases. Two main pathways leading to apoptosis, intrinsic and extrinsic, take an active role. The granzyme B pathway is also considered an apoptotic pathway, and this pathway is activated by enzymes secreted by immune cells such as T and NK. Many caspase molecules have initiator and enforcer roles and are active at critical points in the cell's apoptosis process. In cancer treatments, activating molecules in these pathways and repairing disrupted pathways are among the target approaches. This review discusses target strategies for inhibiting apoptotic pathways and molecules in cancer cells and activating these apoptotic pathways.

Keywords: *Cell death, Apoptosis, Caspases, Bcl-2 family, Cancer*

INTRODUCTION

Cell deaths occur in the organism under physiological and pathological conditions by various stimuli throughout life (Danial et al., 2018). Unexpected increases or decreases in cellular deaths can cause different disorders such as cancer, autoimmune diseases, and immunodeficiency (Tait et al., 2014). Apoptosis, called "programmed cell death," has critical importance essential to organism balance. This balance system is described with various morphological and biochemical mechanisms within the cell (Elmore, 2007), activated by multiple factors. Many pathological conditions such as cancer, metabolic disorder and viral infections can disrupt this balance and activate apoptotic pathways (Kyansakul et al., 2017; Özkaraca et al., 2021). This review, it is aimed to discuss the programmed cell death pathway and the status of molecules, proteins and enzymes involved in this death pathway in cancer cells.

1. APOPTOSIS MECHANISMS

Apoptosis is controlled by extrinsic and intrinsic pathways driven by various cellular signals (Jan and Chaudhry, 2019). The apoptosis mechanism generally occurs through two main processes. These are the mitochondrial pathway and death receptor pathway (Green and Llambi, 2015).

1.1. Extrinsic Pathway

Death receptors (e.g., FAS, TRAIL, TNF) on the apoptotic cell surface have essential roles in forming extrinsic pathways. An exogenous signal that leads to the extrinsic pathway triggers the primary death ligand-receptor proteins interaction. Death receptors (DR) have 80 amino acids motif death domain (DD) on the cell cytoplasmic surface to be later formed in the death-inducing signaling

complex (DISC). DR proteins are classified as tumor necrosis factor (TNF) receptor gene family (Fulda and Debatin, 2006). The TNF receptor 1 (TNFRI), Fas ligand (Fas-L), TNF-related apoptosis-induced ligand-receptor 1 (TRAIL-R1), and TRAIL-R2 are among the best-described death receptors (Fulda and Debatin, 2006). TNF, Fas-L, or TRAIL stimuli are expressed as triple protein structures on the membranes of cytotoxic T or NK cells and bind to their receptors on the membrane of the pathogen-infected cell, leading to the death of the infected cell. Binding death ligands reveal an attachment area to related receptors for the adaptor protein; thus, the DD interaction sites at the cytoplasmic end of the receptors bring together the adapter protein FADD (Fas-Associated Death Domain) procaspase-8 proteins to establish DISC. Procaspase-8 turns into caspase-8 after DISC formation; that is, caspase-8 is activated after several cuts, and then the apoptosis cascade begins with the activation of caspase -3, -6, -7 (Figure 1) (Enari et al., 1998; Stroh and Schulze-Osthoff, 1998; Yamada et al., 1999).

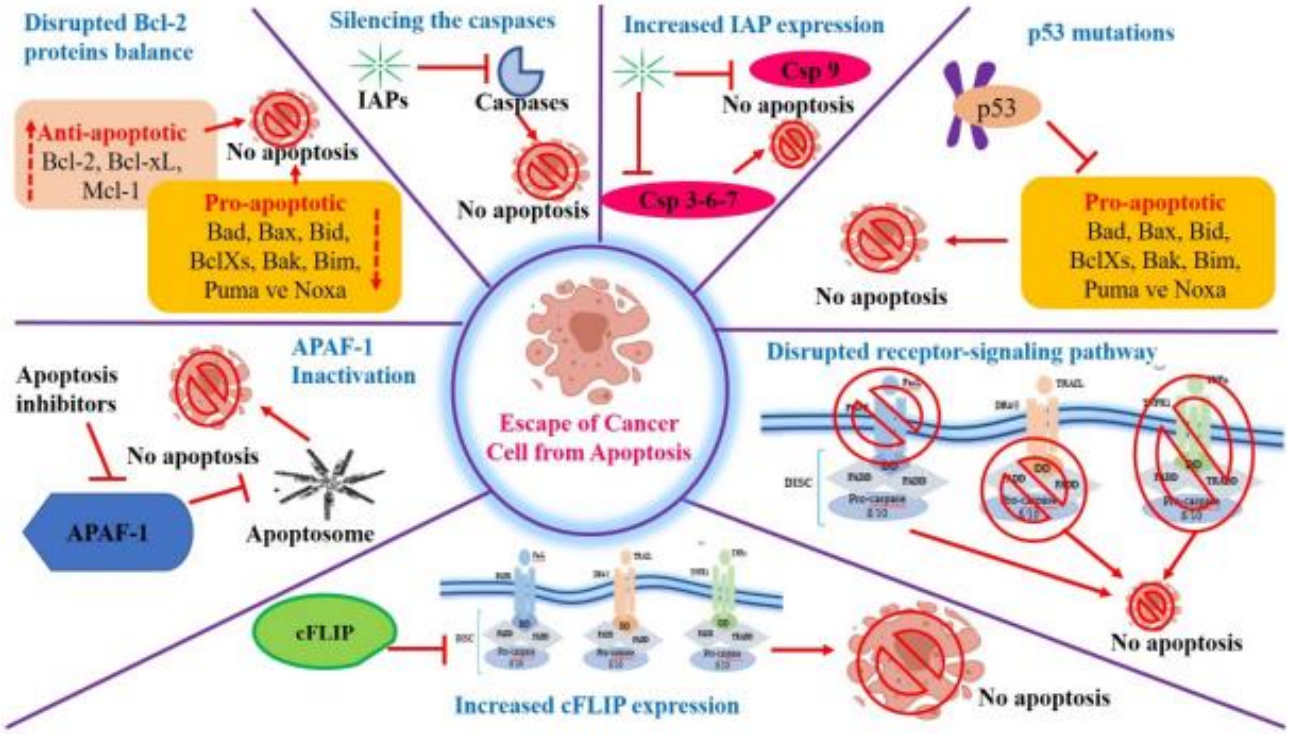

Figure 1. Mechanisms of escape of cancer cells from apoptosis and carcinogenesis.

1.2 Intrinsic Pathway

"Internal stresses" such as an oncoprotein, DNA damage, hypoxia, or infection can prompt the intrinsic pathway. This pathway is promoted by intracellular stimuli such as oxidants, high concentration of intracellular Ca2+, and pH changes resulting in increased mitochondrial permeability and releasing of proapoptotic proteins into the cytoplasm (Radogna et al., 2007). Bcl-2 family proteins have leading regulator roles in apoptotic mechanisms, including proapoptotic (e.g., Bax, Bcl-Xs, Bak, PUMA) and anti-apoptotic proteins (e.g., Bcl-2, Bcl-W, Bcl-XL) (Kannan and Jain, 2000). The p53 protein functions in the intrinsic pathway to increase the level of the proapoptotic Bcl-2 family of proteins. It decreases the release of anti-apoptotic Bcl-2 proteins and causes apoptosis-related death of damaged cells. Moreover, p53 can increase the expression of CD95 and TRAIL receptor 2 (TRAIL-R2/DR5), directing cells to the internal pathway and the external apoptotic pathway (Johnston et al., 2002). Overexpression of proapoptotic proteins on the mitochondrial membrane's outer surface increases the permeability of the inner mitochondrial membrane to ions and solute molecules by opening the pores on the outer membrane. Following the increase in the inner membrane permeability of mitochondria, the flow towards the mitochondrial matrix, swelling of the organelle, and the physical deterioration of the outer membrane result in the expression of Cyt-c within the cytosol (Giorgio et al., 2005). Cyt-c is highly important in mitochondrial ATP production

and carries electrons between the ETS (Electron Transport System) III and ETS IV complexes. However, after being released from the mitochondria, activating factor 1 protein (APAF-1) enters the cytosol and binds to the adapter Cyt-c molecule, leading to the formation of the apoptosome complex required for Cyt-c caspase activation. For the apoptosome to affect effector caspases, it must bind to pro-caspase-9 and activate this caspase. Pro-caspase-9 activates caspase-9, and as a result, it activates effector caspase-3, -6, and -7, causing cell death (Figure 1) (Lopez and Tait, 2015).

1.3 Morphological Changes in Apoptosis

The cell is seen to shrinkage and pycnosis in the early stage of apoptosis (Elmore, 2007). While shrinkage forms, the nucleus shrinks, condensation occurs, and nucleus fragmentation is observed (karyorrhexis). The fragmentation separates the apoptotic cell from the neighboring cells, protrusions form (Saraste and Pulkki, 2000), and cell organelles divide into membrane-covered apoptotic bodies without fragmentation (Kerr et al., 1994). Membranes and mitochondria protect the unity in the body (Saraste and Pulkki, 2000). The phagocytic cells, such as macrophages and dendritic cells, recognize cell membrane changes and engulf apoptotic cells. These changes arise from the migration of the phosphatidylserine molecule inside the cell membrane to the outer wall of the cell membrane, which occurs by the activity of the aminophospholipid transferase enzyme (Saraste and Pulkki, 2000). Signals on cell surfaces signal phagocytic cells for phagocytosis, which eliminates the apoptotic cell. The DNase-II enzyme in phagocytic cells insists on DNA degradation of apoptotic cells resulting in broken into pieces into 50kb pieces and then disrupting the nuclear units (Nagata et al., 2003).

2. APOPTOSIS AND CARCINOGENESIS

The idea that apoptosis may affect the malignant phenotype was raised in the 1970s. It has been shown that apoptosis contributes to decreasing malignant cells, tumor progress and inhibiting hyperplasia. Conversely, cancer cells also avoid and reduce apoptosis (Kerr et al., 1972; Wyllie et al., 1980). Apoptosis is formerly accepted as a physiological death mechanism, nonimmunogenic, or even telogenic. However, late apoptotic cells enter the immunological process by being specifically identified with phagocytic cells by the "eat me" signals they display on their surface. Immunogenic apoptosis termed immunogenic cell death (ICD), is described by its capability to alert the immune system and respond. In tumor cells, apoptosis is induced by multiple signal stimuli, serving tumor-specific neoantigens on the cell surface creating dangerous signals to immune system cells. Although carcinogenesis events such as the conversion of proto-oncogenes to oncogenes, taking continuous growth signal to cell, invasion, and metastasis activates apoptotic pathways, inversely malignant cells suppress apoptotic processes in various ways. These pathways called the apoptosis escape mechanisms of cancer cells, contain the imbalance of pro-apoptotic and anti-apoptotic proteins, decreased caspase function, and deterioration of the death signal mechanism (Figure 1) (Wong, 2011).

2.1. BCL-2 Family Proteins

The Bcl-2 protein family consists of proapoptotic proteins (e.g., Bak, Bax, Bcl-Xs, Bim, Bid, Hrk/DP5, Bim/Bod, Bmf, Noxa, Puma/Bbc-3, etc.) and antiapoptotic proteins (Bcl- 2, Bcl-W, Bcl-XL, Mcl-1, Bfl-1, etc.). Anti-apoptotic Bcl-2 members enable cancer formation and development by promoting mutated or transformed cells (Akl et al., 2014). They preserve mitochondrial functions and prevent mitochondrial degradation. By protecting the mitochondria membrane integrity, cyt-c, which enables initiation of the intrinsic apoptosis pathway, is prevented from being released into the cytoplasm. Bcl-XL, one of the anti-apoptotic proteins, can inhibit cancer treatment by activating oxidative phosphorylation inhibitors (OXPHOS) when apoptotic stimuli reach the cell (Neil et al., 2004). Together with this inhibition, they inhibit the apoptotic pathway. Levels of Mcl-1 and Bfl-1 anti-apoptotic proteins occur in reply to cell death alerts (Campbell and Tait, 2018). Bcl-2 and Bcl-XL are stable proteins in the cell, but other anti-apoptotic proteins are formed by polyubiquitination and proteasomal degradation. The increase of miRNAs such as micl-195, miR-24-2, and miR-365-2 along with Bcl-2 has been mentioned in cancer cells (Pandey et al., 2016), and also Bcl-2 caused an increase in AKT and IKK by acting NF-Kβ pathway (Mortenson et al., 2007; Kumar et al., 2008; Tucker et al., 2008).

Pro-apoptotic Bcl-2 proteins possess 9-16 amino acid homology domains (BH3). These BH3 domains are necessary to bind to anti-apoptotic proteins and induce apoptosis. These proteins become active precursors of apoptosis during

cellular stress (Bouillet and Strasser, 2002). The X protein associated with Bak and Bcl-2, namely the BAX protein, can inhibit Bcl-2 with these two pro-apoptotic proteins and promote mitochondrial outer membrane permeabilization (MOMP) (Elkholi et al., 2011). Decreased expression in pro-apoptotic genes containing only the encoded BH3 region promotes apoptosis deficiency and tumor formation (Lomonosova and Chinnadurai, 2008). The Bim pro-apoptotic protein is involved in Myc-induced apoptosis, and the observation of Bim deficiency suggests prolonging the survival process in Myc tumors. Cytokine deficiency is also reported in the tumors with Bim deficiency. The overexpression of Bid pro-apoptotic protein works as a tumor suppressor in cells of myeloid origin cancer types such as prostate, ovarian, colon, and brain cancer. Puma pro-apoptotic protein does not cause tumors by itself, but it triggers survival in many cancer cells and increases apoptotic resistance in some cancer types (Vo and Letai, 2013).

2.2. Increasing Flip Expression and Expression of Apoptosis Inhibitors

FLIP is an anti-apoptotic protein called FLICE-like inhibitory protein, overexpressed in cancer cells and associated with poor prognosis (Humphreys et al., 2018). FLIP is located in the exogenous apoptotic pathway in the cell. Celular-FLIP (c-FLIP) is expressed in two forms, long-FLIP (l-FLIP) and short-FLIP (s-FLIP) in cells, it binds to FADD, caspase-8, caspase-10, or death receptor TRAIL-5. FLIP provides immortality in a cancer cell by inhibiting caspases that would be activated after apoptotic signals (Hyer et al., 2006). Both s-FLIP and l-FLIP of FLIP bind to FADD in the DISC domain and prevent caspase-8 and caspase-10 from activating. Some cancer types have been associated with c-FLIP expression, and resistance to chemotherapy and TRAIL-induced apoptosis was reported (Piras et al., 2011). It has been shown to repair apoptosis pathways by cytokine and chemotherapeutic agents after downregulation or silence of c-FLIP. Thus c-FLIP is a crucial target protein in cancer therapy**.**

2.3.Expression of Apoptosis Inhibitor Proteins

Apoptosis inhibitory proteins (IAP) mainly inhibit apoptosis, and XIAP is the most functionally important member of this gene family. XIAP is generally found in the apoptosome structure and regulates the apoptosome structure. The expression of apoptosis inhibitor proteins in the cell prevents the binding of caspase-9 to apoptosome after the apoptotic signals are received and inhibit the apoptotic pathway. XIAP can also directly link and restrict the effector caspases. Inhibition of caspase-9 inhibits effector caspases, and cell death does not occur (Berthelet and Dubrez, 2013). Survivin, one of the apoptosis inhibitor proteins, is a member of the IAP family, and can directly stop the death pathway by inhibiting caspase-3. Survivin expressed during fetal development and carcinogenesis rarely existent in normal adult cells. It acts as an oncogene, and its overexpression promotes tumor growth in many ways in cancer cells. İmpairment of the apoptosis mechanism, caspase inhibition, resistance to antitumor drugs, and survival of cancer stem cells may be promoted by survivin. The expression level of the survivin may be used as a biomarker in apoptotic resistance in cancer treatments (Garg et al., 2016). The increasing survivin in the cell results in cancer development and drug resistance, whereas reduced expression results in apoptosis in susceptibility to chemotherapy. It has been reported that a survivin inhibitor YM155 triggers cell death in some cancer types (Xie et al., 2016). Apoptosis inhibitor proteins, IAPs, function as negative regulators of caspases and cell death mechanisms. In addition to their apoptotic functions, IAPs regulate the release of genes essential for inflammation, immunity, cell migration through ubiquitin. Signaling pathways regulated by IAPs are degraded in cancer cells. SMAC mimetics target inhibitors of apoptosis proteins (Silke and Meier, 2013).

2.4. Silencing the P53

The p53 protein encoded by the TP53 gene functions as a tumor suppressor protein in the cell. DNA damage is critical in protecting cells from stresses, including oncogene activation. Cellular stress may lead to the accumulation of p53. Mutations in the TP53 gene encode the p53 protein are seen in about 50% of cancers. These mutations increase cells' survival and reduce cancer prognosis (Zhu et al., 2013). The TP53 gene mutations result in approximately 10-15% of the p53 protein's inability to function. Silencing of p53 modifications usually occurs in a small gene region between exons of the TP53 gene encoding the p53-DNA binding domain (Perri, Pisconti, and Scarpati, 2016). A point mutation (R337H) was defined in a study on the COOH-terminal region of p53. This mutant p53 forms a tetramer similar to wild-type p53, but its activity has been shown to

be much lower than wild-type p53. A new p53 mutation was detected in human neuroblastomas (p53ΔC). The results have shown that mutant p53 may have low pro-apoptotic impacts (Ozaki and Nakagawara, 2011).

2.5. APAF-1 Inactivation

Apaf-1 protein is a pro-apoptotic protein that enables caspase-9 activation by interacting with cyt-C released from mitochondria. Inactivation of Apaf-1 in cancer cells can inhibit p53 mediated apoptotic pathways. The Apaf-1 absence caused by p53 mutation has been demonstrated by much research and is associated with tumor development. The increase of Apaf-1 expression is no obligation for the apoptotic pathway, but its' presence is essential for the death signaling in the intrinsic apoptotic pathway (Soengas et al., 2001). Inhibition of Apaf-1 has been described in advanced-stage melanoma cells and the allelic losses of Apaf-1 in melanoma cells with loss of expression. Using 5-aza-2p-dioxide in treatment, Apaf-1 may have a function, and Apaf-1 related apoptotic defects can be eliminated (Soengas et al., 2001).

2.6. Silencing the Caspases

Caspases have significant effects on apoptosis pathways. Caspase activity maintains the balance between aggressiveness and death in cancer cells. It is a biomarker in apoptosis research (Kurmyshkina et al., 2015). Lacking expression of caspase-8, an initiating caspase in apoptotic pathways, increases malignancy in NCI-H82 (lung cancer model) cells. The functional loss of caspase-8 resulted in resistance against the exogenous way initiated by death ligands such as TNF, TRAIL, and CD95 after receiving the signal (Hensley et al., 2013). Loss of function mutations in the CASP10 gene encoding the caspase-10 protein cause impairment of the function of FAS (CD95), one of the death receptors that activate the exogenous pathway. As a result, autoimmune diseases may occur (Clemente et al., 2015). Palmerini et al. (2001), in a study on colon cancer, showed that caspase-7 fell below its average level and had less apoptotic activity. The apoptotic proteins in treatments are very promising. The caspase function losses in human cancers affected cancer development and had a poor prognosis (Soung et al., 2003). Like caspase-3, -7, caspase-6 is also one of the effector caspases. Studies have suggested that both low and high expression of caspase-6 may promote tumor development. However, it has been demonstrated that the mutant form of caspase-6 reduces intrinsic pathway activity in cancer cells. Although the number of studies on caspase-6 is insufficient, its effects are a matter of debate (Dagbay et al., 2017).

2.7. Loss of Death Receptors

Resistance to apoptosis has been demonstrated to be related to death receptors in many cancer types (Ivanov et al., 2003). Allele losses in loci of chromosomes (10q24 and 8p21-22) gene encoding FAS and TRAIL-R2 have been identified in breast cancer. These mutations in death receptors also result in metastatic effects in cancer cells. For example, mutations in the FAS gene have been defined in metastatic cells in a patient with T-cell leukemia (Shin et al., 2001). It has been shown that TRAIL-mediated apoptosis inhibits pancreatic cancer, melanoma, and neuroblastomas (Piras et al., 2011). DR4 polymorphisms were defined in human ovarian cancer (SKOV3) and bladder cancer. In this polymorphism, A1322G nucleotide change of the DR4 gene was. This polymorphism resulted in the replacement of lysine with arginine from amino acids in the DD region of the DR4 protein. Polymorphic DR4 develops resistance to apoptosis in cancer types such as lung and head and neck cancer. Different DR4 polymorphisms have also been identified in recent studies (Zhang and Fang, 2005). The C626G nucleotide change was T209R, while the G422A nucleotide change caused the R141H shift. The R141H polymorphism in the ligand-binding region of DR4 results in suppressing apoptosis (Zhang and Fang, 2005). Mutations in the DR5 gene, one of the death receptors, were described in head and neck, lung, breast, and non-Hodgkin lymphomas. These mutations are in the DD region and block TRAIL-induced apoptosis. At the same time, due to mutations in the DR5 gene, FADD and caspase-8 could not interact with DD regions, and apoptotic cell death pathways were also inhibited (Zhang and Fang, 2005). Mutations in the gene of another death receptor, the FAS ligand, have been reported in lymphatic and epithelial cancer types (Takakuwa et al., 2002). The mice's CD8 + cells were detected to abolish their cells. Another study reported FAS ligand deletions in patients with ALPS (congenital immune lymphoproliferative syndrome). At the same time, these mutations in the FAS gene lead to the inhibition of FAS-mediated apoptosis (Maeda et al., 1999).

3. APOPTOSIS IN CURRENT CANCER TREATMENT STRATEGIES

The many therapies are promising to destroy cancer cells with ICD by stimulating apoptotic mechanisms in cells without damaging the healthy cells.

Chemotherapy has been used for many years to treat cancer. Chemotherapeutic agents function by inhibiting proliferation in cancer cells and disrupting the genetic content of these cells (Johnstone et al., 2002). The chemotherapy targets inhibition of DNA synthesis, cell cycle arrest, and activation of multiple cell death pathways (Seitz et al., 2010; Pan et al., 2016;). Generally, chemotherapeutic agents activate apoptotic cell death pathways destroyed by anti-inflammatory phagocytes with tolerogenic signals (Elliott et al., 2009; Yoon et al., 2015). As an example of this event, it is seen that apoptotic pathways are activated after the application of paclitaxel in lymphoma cells. The chemotherapeutic agent cisplatin, which causes DNA damage, and doxycycline, which inhibits enzymes involved in protein synthesis, activate both intrinsic and extrinsic apoptotic pathways (Wang et al., 2004; Onoda et al., 2006; Kim et al., 2008;). Mutations in the receptors that recognize damage-associated molecular patterns (DAMPs) on the dendritic cell have been proven to cause breast cancer and it has been seen that these patients cause early relapse after chemotherapy (Kim et al., 2016).

In the treatment with radiotherapy, also known as ionizing radiation, the structure of DNA is disrupted by high-energy radio waves, which causes the activation of apoptotic cell death pathways. At the same time, the stress created by the radiation that the cell is exposed to can activate death pathways other than apoptotic death pathways (Ogura et al., 2009; Sia et al., 2020). At the same time, it was observed that as the height of the radio waves given to the patient increased, it became active in necrosis, except for apoptotic death pathways. After this necrosis, a high level of HMGB1 release occurs. In addition, a study showed that the RIP-kinase pathway was inactivated after radiotherapy-induced necrosis, resulting in raised survival in non-small cell lung cancer patients (Wang et al., 2016; Wang et al., 2018).

The gene therapy applied to cancer patients is to prevent anti-apoptotic and pro-apoptotic genes, disruptions in cell death, and escape of cancerous cells from the immune system. Genes related to apoptosis (e.g., Caspases and BCL-2 family, etc.) can also act on cancer cells independent of apoptotic cell death (Lebedeva et al., 2003; Jia et al., 2012). One of the critical initiatives of gene therapy is to be administered to cancerous cells to restore cell cycle regulating and tumor suppressor proteins such as p53, Rb (retinoblastoma), p16INK/CDKN2, PTEN (Vogelstein et al., 2000; Shanker et al., 2011). Gene therapy has long been studied for use in cancer cells. One of the oldest studies was the study conducted in 1996 to control non-small cell lung cancer with a viral vector expressing the p53 gene linked to the actin promoter (Roth et al., 1996). In addition, in a study to stop the growth of melanoma cancer cells, antisense oligonucleotides were used to target the c-Myc gene, and cancer growth in melanoma cells was slowed down with this gene therapy (Putney et al., 1999). In addition, tumor growth was suppressed by using antisense RNAs for mutations in the RAS gene family that are ordinary in colon cancers (Fleming et al., 2005; Krens et al., 2010;).

Immunotherapy stimulates a host's natural immune response mechanisms to attack cancer. Monoclonal or recombinant antibodies are the most commonly used ligand in immunotherapy. They bind to the specific and overexpressed antigen specified to the cancer cell surface, thereby enhancing the recognition of the cancer cell to the cells of the immune system and preventing proliferation and metastasis. The most commonly used antibodies in this way for therapeutic purposes are those that bind to HER2 (human epidermal growth factor receptor 2), EGFR (epidermal growth factor receptor), TfR (transferrin receptor), and PSMA (prostate-specific membrane antigen) (Sharkey and Goldenberg 2009). In another immunotherapeutic method called adaptive cellular therapy, T cells isolated from patients are cured ex vivo and reintroduced to the patient (Rosenberg et al., 2008). Chimeric antigen receptor (CAR)-T cell therapy specifically recognizes the antigens of cancer cells by modifying target T cells to express the CAR receptor. CRISPR/Cas9 technology, another popular method, and techniques such as plasmid DNA and mRNA transfer are used in designing CAR receptors. (McCune, 2018; Miliotou and Papadopoulou, 2018).

Oncolytic virotherapy is tumor immunotherapy mimicking viral infection using an oncolytic virus that targets cancer cells and kills them. Oncolytic

viruses can enter cancer and healthy cells, induce cell signaling pathways and activate stress in cancer cells. It stimulates the ICD in tumor cells and occurs as an effective immune reaction instead of cancer cells' aim as the primary mechanism. Concurrently, apoptotic pathways are activated by ER stress aggravation in the cancer cell, leading to its death. Human herpes simplex virus-1 (HSV-1) has been proven its' recombinant forms oncolytic capable. HSV-1 RH2 can impel squamous cell carcinoma cells to apoptosis by HMGB1 and ATP releasing and the exposure of CRT (Donnelly et al., 2013). Cell death of glioma cells has developed following NDV infection with CRT translocation, HMGB1 releasing, and rising antigen expression (Takasu et al., 2016). It has been shown that HSV-2 causes DAMPs in murine mammary gland cancer cells (Workenhe et al., 2014). Coxsackievirus B3-infected human non-small cell lung cancer cells also similarly leaded apoptosis (Donnelly et al., 2013).

3.1. Breaking Apoptosis Resistance in Cancer Treatment

The one of most critical difficulty in cancer treatments is resistance to treatment. Today, the combined applications of targeted therapies aim to break the resistance mechanisms (Mohammad et al., 2015).

3.1.1. The Activation of P53

The p53 gene is the most studied in cancer research due to mutations in approximately 50% of cancer types. Some studies have focused on drug-like small molecules targeting the p53 system (Kogan and Carpizo, 2019). Small molecules that activate both mutant and wild-type p53 were studied in cell-based treatments to induce apoptosis. MDM2 is an oncogene that can interact with p53, resulting in the inactivation of p53 in many cancer types. Small molecules are discovered to target blocking the MDM2-p53 protein-protein interaction. A molecule called MI-219 inhibits the MDM2-p53 interaction by phosphating, and thus p53 pathways can be activated in normal cells (Suzuki and Matsubara, 2011). Nutlin 3a is another small molecule that inhibits p53 and E3 ligase MDM2 interaction.

Many cancer types have been associated with mutant p53 and metastatic phenotype. Mutated p53 aggravates proliferation and metastasis of cancer cells by connecting to transcription factors such as NF-Y, E2Fs, NFkBp65, NfkBp50, SREBP, YAP, and VDR, or NRF2. As a result, raised proliferation causes autophagic cell death and inhibition of DNA repair mechanisms, ROS accumulation, and cell survival (Blandino and Agostino, 2018). Small molecules explicitly targeting the mutant p53 were investigated and triggered apoptosis in cancer cells by using them. The PRIMA-1 and MIRA-1 molecules have been researched in p53-targeted therapies. MIRA-1, one of these molecules, revealed to its toxicity rate was high. Conversely, it is shown that PRIMA-1 and PRIMA-1MET can reactivate mutated p53 proteins and their transcriptional activity and transform to wild-type p53, resulting in increased expression of Puma, Bax, and Noxa in cells (Blandino and Agostino, 2018). Tenovin is another small molecule that can act as an activator of p53 and increase the level of p53 protein. It targets SIRT-1 and SIRT-2 proteins influent to cell proliferation, repressing the cell growth and inducing apoptosis in the cell. It has been displayed that it inhibits tumor cell survival in mice. Another molecule, RITA, binds and reactivates the p53 molecule, leading cancer cells to apoptosis (Suzuki and Matsubara, 2011).

3.1.2. The Activation of Caspases

The death pathway is targeted by anti-cancer drugs that trigger caspase activation and is frequently preferred in cancer treatments (Fulda and Debatin, 2000-2013). The absence of caspases in cancer cells is influential to the apoptosis pathway. The deletion and mutation in caspase molecules such as caspase-3, -7, -8, -9 have been reported in some cancer types (Jia et al., 2012). The anti-cancer effects of therapy approaches based on the activation of caspase molecules have been proven. Justicin A, a derivative of Justicin, a herbal medicine, increases Cyt-c release by inactivation of anti-apoptotic proteins concurrently with caspase-8 activation and activating intrinsic and extrinsic pathways (Hensley et al., 2013). It is known that the hypermethylation in the promoter regions in the caspase-8 gene in some types of cancer. The gene transfer or dimethylation treatments to caspase-8 were examined in these cancer types (MacKenzie and Clark, 2008). Xie. et al. (2001) created an adenoviral vector (ADV ARR-PB-iCasp9) prostate cell-specific promoter (ARR-PB) to increase the expression of caspase-9. This vector-activated caspase-9 in prostate cancer cells caused apoptosis in mice. Another study showed that LY2181308 oligonucleotide activates caspase-3 and inhibits survivin mRNA. It also has been determined that this oligonucleotide activates the caspase-dependent apoptosis death pathway in

tumor cells and suppresses survival (Carrasco et al., 2011; Tanioka et al., 2011).

3.1.3. The Activation of the Extrinsic Pathway Using TRAIL Agonists

Mutations in the TRAIL gene or down expression of TRAIL protein receptors contribute to developing apoptosis resistance in tumor cells (Dai et al., 2015). TRAIL agonists designed for treatment include recombinant TRAIL proteins and DR4 /DR5 agonist antibodies. The dulanermine is a recombinant TRAIL agonist as rhApo2L.0 / TRAIL, binding to DR4 and DR5 to eliminate cancer cells and lead to apoptosis. Dulanermine acts apoptosis activity selectively only in cancer cells. The clinically tested TRAIL agonists are mapatumumab for DR4, drozitumab, conatumumab, lexatumumab, tigatuzumab, LBY-135 antibody for DR5. The use of agonistic antibodies combination increases the quality of life of cancer patients and is promising (Ralff and El-Deiry, 2019). Karstedt et al. (2017) demonstrated that the TRAIL agonists induced apoptosis in metastatic breast cancer and kidney cancer. Moreover, NK-T cells stimulated by the α-galaxylceramide molecule enhance TRAIL-mediated antitumor function (Falschlehner et al., 2009). A new TRAIL agonist (Karstedt et al., 2017; Yagolovich et al., 2019) mimicking TRAILR1 and TRAILR2, a fusion protein called APG350, contains the TRAIL receptor domains that can bind to the Fc portion of the IG1 antibody. It has been reported it induced apoptosis in cancer types such as breast, colon, and lung (Legler et al., 2018).

3.1.4. XIAP / IAP Suppression Using SMAC / DIABLO Mimetic

IAPs, antiapoptotic proteins, are inhibitor proteins that inhibit caspase, negative regulators of apoptosis, and play a role in controlling many cellular pathways. Expressions of XIAP (X-linked IAP) and IAPs have tried to inhibit treatment in several cancer types (Cossu et al., 2019). cIAP-1 and cIAP-2 exert weaker effects on caspases than XIAP. However, they interact with two TNFRs (TRAF-1 and TRAF-2) in the TNFα-initiated NF-Kβ pathway (Wu et al., 2007). Smac/Diablo mimetics (second mitochondria-derived activator of caspase) lead to the induction of caspase release and activation of apoptosis by interacting with IAP proteins. Thus, immortalized cells become more sensitive to chemotherapy and radiotherapy (Zhao et al., 2020). The molecule receives ONE; for Smac / Diablo mimetics, XIAP agonists were used. Studies on Smac/Diablo mimetics have observed that besides targeting XIAP, it interacts with proteins such as IAP-1 (cIAP-1) and cIAP-2, providing proteasomal degradation-related degradation (Cossu et al. 2019). Smac/Diablo mimetics are designed as monovalent and divalent. The univalent protein attaches to a single AVPI binding motif by mimicking IAPs. The other type is bivalent, which binds to two AVPI motifs by imitating IAP and prevents caspase inhibition. Smac/Diablo mimetics in the melanoma cell line lead to XIAP degradation, thereby sensitizing the cells to TRAIL treatment (Lecis et al., 2010) and supporting the degradation of procaspase 8 to caspase 8. The antitumor activity of APG-1378 (bivalent), one of the newly identified Smac/Diablo mimetics, was observed in hepatocellular carcinoma (HCC), APG-1378 reduced IAP protein levels (Chen et al., 2018). In addition, it has been observed that it is insufficient for apoptosis. It has been shown to induce apoptosis in combination with IAP-1378 and TRAIL; APG-1378 increases the killing capacity of NK (Natural Killer) cells.

3.1.5. BCL-2 Suppression with BH3 Mimetic

Many cancer types cancer carry mutations preventing the activation of BH3-specific proteins. Mutations in BH3 pro-apoptotic proteins make cancer cells resistant to radiation, chemotherapy, and cytotoxic agents. Therefore, it attempted to design molecules that mimic only BH3 pro-apoptotic proteins named therapeutic BH3 mimetics (Bouillet and Strasser, 2002; Adams and Cory, 2018). A BH3 mimetic drug approved is venetoclax / ABT-199, a BCL-2 inhibitor that links to the BH3 domains (Merino et al., 2018). Combining BH3 mimetics with treatments such as oncogenic kinase inhibitors is suggested in new studies. Kinase inhibition increases pro-apoptotic expression of BH3 only, like BIM and PUMA. Thus, BCL-2 proteins that BH3 mimetics cannot target are also inhibited (Adams and Cory, 2018).

CONCLUSION

One of the critical ways cancer cells achieve immortality is resistance to apoptosis. Under normal conditions, for cancer cells to survive in the organism and gain the ability to reproduce continuously, they need to get rid of many obstacles that will enable the activation of apoptotic pathways. In future studies, the tools used by cancer cells for apoptotic resistance and the mechanisms of apoptosis should also be clarified. Many ways can activate preventing

cancer cell proliferation and expanding cancer cells. With the clarification of these pathways, therapeutic agents will play a more active role in cancer treatments. This review reviewed the target strategies for cancer treatment by giving information about apoptotic pathways and their status in cancer cells.

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