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Review

The pivotal role of mitochondrial disorders in cancer development with a special focus on mitochondria-mediated apoptosis

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Abstract

Emerging evidence indicates that mitochondrial dysfunction is not merely a consequence but a driving force in cancer progression. Unlike normal cells, cancer cells rewire their mitochondrial metabolism to support uncontrolled proliferation, a process that includes aerobic glycolysis, persistent reactive oxygen species production, and adaptation to hypoxic conditions. A common hallmark across many tumors is the suppression of the intrinsic apoptotic pathway, primarily achieved through an imbalance between anti-apoptotic and pro-apoptotic BCL-2 family proteins. This evasion of cell death not only facilitates tumor initiation and metastasis but also contributes to resistance against conventional therapies. Here, we provide an overview of major mitochondrial alterations in cancer, with a detailed focus on how the mitochondrial apoptotic machinery is disabled in malignant cells. We then discuss current therapeutic strategies designed to re-activate mitochondria-mediated apoptosis, including BH3 mimetics, direct activators of pro-apoptotic proteins like BAX, immune checkpoint inhibitors, CAR-T cell therapy, and mitochondria-targeted nanomedicine. Finally, we address the limitations and safety concerns of existing pro-apoptotic drugs and propose future directions to develop more selective and effective cancer treatments. Understanding the molecular mechanisms that govern mitochondrial apoptosis may open new avenues for inducing tumor cell death while minimizing harm to normal tissues.

Keywords: Cancer, mitochondria-mediated apoptosis, apoptosis evasion, pro-apoptotic proteins, anti-apoptotic proteins.

1. Introduction

Cancer is a disease in which abnormal or cancerous cells grow and divide uncontrollably. When these abnormal cells divide and proliferate uncontrollably, they can invade and damage surrounding tissues and organs and also spread (metastasize) throughout the body via the bloodstream or lymphatic system. The total risk of developing cancer in people aged 0 to 74 years is 20.2% (22.4% in men and 18.2% in women, respectively). In 2021, a total of 19.3 million new cases were reported, the most common of which were lung cancer (2.09 million cases), breast cancer (2.09 million cases) and prostate cancer (1.28 million cases) [1]. In terms of mortality, cancer is the second leading cause of death worldwide (8.97 million deaths) following coronary heart disease, but is expected to become the number one cause of death in 2060 (~18.63 million deaths). In the general population, cancers of lung, liver, and stomach are the three most lethal types, while lung and breast cancers are the major causes of cancer death in men and women, respectively [2]. Interestingly, after rising for much of the 20th century, cancer death rates have declined continuously from their peak in 1991 to 2018, resulting in an overall decline of 31% due to reduced smoking and improved early diagnosis and treatment [3].

Conventional clinical treatments for cancer mainly include surgery, radiation therapy (RT), and chemotherapy. RT utilizes radiation to obliterate local tumor tissue. Surgery implies the direct removal of the tumor or all of the tissue. And chemotherapy hampers cell division of rapidly dividing cells in non-specific fashion, that is, by inhibiting DNA replication or segregating newly formed chromosomes. These traditional methods of cancer therapy

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have their own limitations or disadvantages when applied in clinical practice. In surgical treatment, it is difficult to avoid residual tumor, while RT and chemotherapy lead to systemic toxicity, causing varying degrees of side effects in normal tissues, which limits their clinical use [4].

Uncontrolled proliferation of cancer cells results from accumulated abnormalities that affect many mechanisms of cellular regulation. This relationship is determined by several attributes of cell behavior that discriminate cancer cells from normal ones. As a rule, cancer cells display aberrant mechanisms that regulate biological cell proliferation, differentiation, and survival. Together, these typical features of cancer cells underlie the development of malignancy at the cellular level. In general, cell growth is governed by various signaling mechanisms. For example, structural and molecular damage to cells triggers a process of programmed cell death termed apoptosis [5]. However, this mechanism does not work correctly in cancer cells, leading to uncontrolled cell division with the formation of tumors [6].

Since the existing methods of cancer treatment have a large number of disadvantages and side effects, new strategies in the treatment of oncological diseases are needed. Currently, a new approach is being considered, which is aimed at modulating regulatory cellular processes that cause apoptosis of tumor cells [4]. Because early-stage tumor cells lack apoptotic mechanisms, targeting mitochondria-associated mechanisms may be a reliable approach. In this review, we discuss the key mitochondrial alterations in cancer, focusing on the dysregulation of the intrinsic apoptotic pathway, current therapeutic strategies to reactivate this pathway, and approaches to overcome the limitations of existing pro-apoptotic drugs.

2. Molecular mechanism of mitochondria-mediated apoptosis

There are two main pathways leading to apoptosis: the intrinsic and the extrinsic pathways of apoptosis. Both pathways result in the activation of cysteine aspartyl-specific proteases or 'caspases', which are the ultimate effectors of apoptosis that cleave certain proteins, leading to cell death [7]. In particular, the intrinsic apoptosis is a type of programmed cell death governed by the mitochondria-mediated caspase activation pathway, the major apoptotic pathway, involving mitochondrial outer membrane permeabilization (MOMP) following the release of cytochrome *c* into the cytoplasm to induce the catalytic activity of the cysteine proteases, such as caspase-3 and caspase-7 [8,9]. Molecular mechanism of mitochondria-mediated apoptosis is presented in **Figure 1**

Apoptotic stimuli such as DNA damage or growth factor deficiency trigger conformational changes in BAX and BAK. These proteins then oligomerize, leading to irreversible MOMP. Subsequently, cytochrome c is released from mitochondria into the cytosol. Released cytochrome *c* forms an apoptosome with APAF1 and, consequently, activates caspase-9, the initiator caspase, which cleaves and activates the effector caspases, caspase-3 and 7, finally leading to cell apoptosis. Proapoptotic proteins, such as SMAC and OMI, suppress IAPs and enhance apoptosis. Abbreviations: APAF1, apoptotic peptidase activating factor 1; BAX/BAK, pro-apoptotic proteins, members of the BCL-2 family; Casp, caspase; IAPs, apoptosis inhibitory proteins; MOMP, mitochondrial outer membrane permeabilization; OMI, mitochondrially-located serine protease; SMAC, second mitochondria-derived activator of caspase.

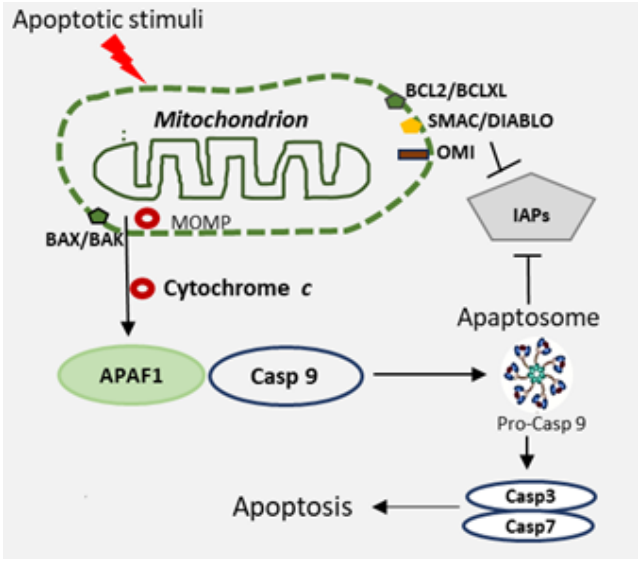


Fig. 1. Molecular mechanism of mitochondria-mediated apoptosis: caspase activation pathway.

The proteolytic activation of caspase-3 is catalyzed by caspase-9, which, consequently, develops catalytic activity within an "apoptosome", a supramolecular complex that also encompasses deoxyATP, the cytosolic adaptor apoptotic peptidase activating factor 1 (APAF1) and an extramitochondrial pool of cytochrome *c* [10,11]. This pathway is important not only for the normal development, maintenance of tissue homeostasis, and immune system regulation, but it is also implicated in the development of human pathologies, such as immune disorders [12], neurodegenerative disorders [13] and cancers [14]. The mitochondria-mediated apoptotic pathway is primarily regulated by a delicate balance of pro- and anti-apoptotic B cell lymphoma (BCL-2) family of proteins [15] and triggered by a variety of intracellular disturbances, such as oxidative stress, DNA damage, disruption of calcium regulation, and stress of endoplasmic reticulum [16]. In the mitochondrial pathway, MOMP supports the secretion of intermembrane space proteins in mitochondria, including cytochrome *c*, a major component of the mitochondrial electron transport chain, which interacts with APAF1 [17]. Such interaction induces large conformational changes in APAF1, resulting in its oligomerization into a wheel-shaped heptameric structure and the opening of caspase activation and recruitment domains (CARD) [18]. The CARD domains of APAF1 join to the CARD domains of the initiator of caspase procaspase-9 to configure the apoptosome. On the apoptosome, caspase-9 dimerization triggers its activation, which consequently cleaves and stimulates the activity of caspases-3 and -7, directly leading to cell apoptosis. Cytochrome *c* is required for mitochondrial pathway of caspase activation; cells lacking cytochrome *c* or expressing a mutant that insufficiently activates APAF1 (but preserves respiratory function) fail to induce caspases after MOMP [18]. In addition to cytochrome *c*, other mitochondrial proteins promote activation of caspases. These comprise the second mitochondria-derived activator of caspase (SMAC) (also called DIABLO) and mitochondrially-located serine protease OMI (also called high temperature requirement factor A2 (HTRA2)). Both proteins populate

the intermembrane space of mitochondria and are secreted into the cytosol. In normal cells, OMI functions as a mitochondrial chaperone. The non-apoptotic role of SMAC, however, remains unclear. These mitochondrial proteins support caspase activation via binding to and neutralizing the caspase inhibitor X-linked inhibitor of apoptosis protein (XIAP). However, unlike cytochrome *c*, the failure of OMI or SMAC alone or both does not confer resistance to the activation of caspases and cell death [19]. The intrinsic apoptotic pathway also includes caspase 8 activation, which facilitates the cleavage of BID (a member of the BCL-2 family). The product of BID cleavage, also recognized as truncated BID (tBID), is a permeabilizing peptide of mitochondria [20]. tBID activates cytosolic BAX and BAK, which localized on the outer mitochondrial membrane, triggering MOMP and cellular apoptosis. A study identified compound A, a mitochondrial apoptosis inhibitor, which can suppress the activation of BAX [21]. Noteworthy, MOMP leads to a substantial water intrusion into the mitochondrial matrix, resulting in the enlargement of mitochondria and spreading of the inner membrane, abolishing its cristae. MOMP, mediated by the BCL-2 family, is believed to be a crucial control point in apoptosis, exhibiting the point along the pathway at which a cell is doomed to die [21]. The suggested mechanism of MOMP activation by proapoptotic BAX and BAK is predominantly based on their oligomerization to form lipid pores in the outer mitochondrial membrane. Without apoptotic stress, BCL-2 forms heterodimers with BAX and BAK (proapoptotic) to maintain the integrity of the outer mitochondrial membrane (OMM) and hinder mitochondrial apoptosis. In the presence of apoptotic stimuli, the expression of proapoptotic BAX and/or apoptosis initiators such as BH3-only proteins is enhanced, followed by their binding to survival-maintaining BCL-2 proteins, preventing the inhibition of BAX/BAK. Free BAX and BAK form oligomers, which leads to the release of cytochrome *c* from the mitochondrial intermembrane space into the cytoplasm [22].

While the release of cytochrome *c* from mitochondria results in caspase activation and causes apoptosis, this process is also closely regulated by other endogenous mediators. The apoptosis inhibitory protein (IAP) family encompasses baculoviral IAP repeat (BIR) domains. The BIR domain was initially identified in baculovirus proteins that can bind to caspase-3, 7, and 9 to suppress apoptosis. Interestingly, various IAP proteins can interact with some pro- apoptotic proteins in a tissue-specific fashion to inhibit apoptosis provoked by different signals [20].

Lacking caspase activity, cells naturally undergo a gradual, poorly defined form of death, namely, caspase-independent cell death (CICD). CICD can serve as a largely reliable cell death mechanism even when caspases are inhibited, for example, by a viral caspase inhibitor. Comprehensive morphological analysis showed that CICD can lead to cell death of up to 10% under physiological conditions [8].

3. The role of mitochondrial disorders in cancer development: oxidative phosphorylation and ROS generation

Mitochondrial metabolism differs from that of their counterparts in cancer cells. Aerobic glycolysis ("Warburg effect"), accumulation of reactive oxygen species (ROS), antiapoptotic signals, and hypoxia are the main impaired features of mitochondria in tumor cells [23].

Oxidative phosphorylation produces adenosine triphosphate (ATP) via the electron transport chain (ETC), containing I to IV complexes in the inner mitochondrial membrane, through which electrons are transferred. The continuous flow of H+ from the matrix generates a high electrochemical potential at the inner mitochondrial membrane. ETC leakage promotes the generation of reactive oxygen species (ROS), such as superoxide, free hydroxyl radicals, and hydrogen peroxide [24]. In healthy cells, mitochondrial ROS (mtROS) levels are tightly regulated and are significant in a number of cellular processes, such as differentiation, autophagy, and metabolic reprogramming [25]. mtROS affect all stages of tumor development from its inception to proliferation and metastasis, causing mutations in nuclear or mitochondrial DNA (mtDNA) and influencing various biological processes, such as cell proliferation, resistance to apoptosis, and metabolic adaptation [25]. In addition, mtROS can initiate different potentially oncogenic signaling pathways, such as the epidermal growth factor receptor (EGFR) signaling pathway [26] or serine/threonine-specific protein kinase (AKT)/nuclear factor kappa B (NF- κB) mitochondrial transcription factor B2 (TFBM2)-dependent signaling pathway [27], which is known to be linked to tumor proliferation. MAFK can induce several signaling cascades related to metastatic spread, including protein tyrosine kinase 2 (PTK2B) and Src signaling [28].

4. Tricarboxylic acid cycle

Mutations in genes encoding tricarboxylic acid (TCA) enzymes and abnormal accumulation of intermediates may contribute to carcinogenesis. The main enzymes that have been found to be altered in cancer are succinate dehydrogenase (SDH), fumarate hydratase (FH), and isocitrate dehydrogenase (IDH) [23].

During cancer development, SDH is commonly affected by a loss-of-function (LOF) mutation. This mutation causes succinate to accumulate, primarily within the mitochondria, from which it then leaks into the cytoplasm [29]. Excess succinate subsequently inhibits prolyl hydroxylase (PHD), an oxygen-dependent hydroxylase, which is capable of regulating the expression of hypoxia-inducible factor 1 (HIF-1) governed by oxygen homeostasis, leading to the stabilization and stimulation of HIF-1α under normoxic conditions [30]. In this way, defects in this enzyme are responsible for the creation of pro-oncogenic pseudohypoxic environment.

Fumarate hydratase is the enzyme that catalyzes the conversion of fumarate to malate; it is encoded in the nucleus and located in the mitochondrial matrix. The FH LOF mutation reduces the respiratory rate as a result of loss of complex II function and improves lactate production, hence maintaining the glycolytic metabolic switch. It was found that FH is able to mutate primarily in hereditary leiomyomatosis of renal cell carcinoma [31]. Like SDH, the oncogenic action of FH is largely dependent on the accumulation of fumarate, which, similar to succinate, activates HIF-1α stabilization through PHD inhibition [32], α-ketoglutarate (α-KG)-dependent histone inhibition, and DNA methylation, and regulates epigenetic modifications [33]. Besides, fumarate can covalently bind to protein cysteine residues during a reaction called succination, regulating their function [32].

The IDH enzyme also supports tumor proliferation and survival. IDH1 and IDH2 isoforms have monoallelic gain-of-function mutations that lead to neomorphic enzymatic activity, where α-KG is converted to its R-enantiomer, D-2-hydroxyglutarate (D-2-HG), as opposed to L-2-hydroxyglutarate [34]. Accumulation of D-2-HG is associated with colon cancer, gliomas, acute myeloid leukemia, and osteosarcoma, as well as DNA hypermethylation and extensive epigenetic changes [31]. Additionally, D-2-HG reduces the enzymatic activity of complex V and changes gene expression in cancer cells [34]. Like fumarate and succinate, D-2-HG also exhibits effects on PHD, α-KG-dependent dioxygenases, and histone demethylases, downregulating genes involved in reducing metastasis and promoting epithelial-mesenchymal transition and invasiveness [35].

4.1. Hypoxia

Low levels of oxygen contribute to a hypoxic milieu in the cells. Hypoxia promotes ROS production via ETC, and ROS release into the cytosol, activating oxidative stress and associated signaling. It also initiates HIF and the proliferation of cancer cells [36]. In addition, the accumulation of ROS in the cytosol activates oxidative signaling and the following transcription factors: p53, AP1, NRF2, and NF-kB, which are tightly linked to the expression of genes involved in oncogenesis [25].

Phosphoproteome screening revealed phosphorylation of pyruvate dehydrogenase kinase 1 on Thr346 in PC3 prostate adenocarcinoma cells. In cancer cells, deactivation of the pyruvate dehydrogenase complex can lead to metabolic reprogramming towards glycolysis, thus counteracting apoptosis and autophagy and enabling proliferation of tumor cells under severe hypoxic conditions [37]. TCA metabolite accumulation also promotes the occurrence of hypoxia.

4.2. Apoptosis

Apoptosis disruption leads to a clonal growth of populations of mutated cells, which leads to the development of cancer [23]. Excessive expression of anti-apoptotic proteins, such as BCL-2 proteins, is coupled with the initiation of tumors, their progression, and resistance to treatment. In the course of MOMP, cytochrome *c* is released and cleaved by E3 ligase, the parkin-like cytoplasmic protein, PARC/CUL9, in neurons and brain tumor cells, ensuing long-term survival of tumor cells [38]. In addition, the oncogenic potential of apoptotic mechanisms is confirmed by a decrease in MOMP, which leads to limited caspase activation and further DNA damage, genome instability, cell transformation, and oncogenesis [6]. Survivin is a mitochondrial protein overexpressed in tumor cells that is promptly released into the cytosol in response to stimulation of cell death, where it stops activation of caspases and inhibits apoptosis [23]. The interaction between heat shock protein 60 (HSP60) and survivin inhibits apoptosis. Removal of HSP60 by small interfering RNA destabilizes the survivin complex in mitochondria and causes mitochondrial dysfunction with caspase-dependent apoptosis activation. There are other mitochondrial molecular chaperones, such as HSP90 and its related molecule, tumor necrosis factor receptor-associated protein 1 (TRAP-1), that are also capable of inhibiting apoptosis. The HSP90/TRAP-1 complex interacts with cyclophilin D, a promoting mitochondrial cell death immunophilin, and prevents death of cells. This network disruption accelerates apoptosis in cancer cells [23]. In general, mitochondrial HSPs typically promote survival of tumor cells by inhibiting apoptosis via protein folding or refolding mechanisms [23].

Accumulation of TCA metabolites caused by nDNA mutations, initiation of the NRF2 pathway, ROS-induced cancer cell proliferation through HIF-1α, dysregulation and resistance to apoptosis, and aerobic glycolysis are hallmarks of cancer cells. In addition, cancer cell mitochondria influence the metabolism of ROS production. In particular, oxidative phosphorylation via ETC leakage promotes ROS generation; mtROS affect all stages of tumor development from its inception to proliferation and metastasis, causing mutations in nDNA or mitochondrial mtDNA and influencing various biological processes, such as cell proliferation, resistance to apoptosis, and metabolic adaptation. Cancer cell mitochondria also influence activation of oncogenes, mitochondrial membrane potential, and cytosolic Ca2+ concentrations. Excessive expression of anti-apoptotic proteins such as BCL-2 is associated with tumor initiation, progression, and resistance to treatment. Abbreviations: BCL-2, B cell lymphoma family of proteins; ETC, electron transport chain; HIF-1α, hypoxia-inducible factor 1 alpha; mtDNA, mitochondrial DNA; nDNA, nuclear DNA; NRF2, nuclear factor erythroid 2-related factor 2; ROS, reactive oxygen species; TCA, tricarboxylic acid.

In summary, mutations in SDH, FH, and IDH lead to accumulation of succinate, fumarate, and D-2-HG, respectively. All three metabolites inhibit PHD, stabilize HIF-1α, and induce epigenetic reprogramming, collectively contributing to a pseudo-hypoxic state and promoting tumor progression.

5. Evasion mechanisms of mitochondria-mediated apoptosis in tumor cells

Evasion of cell death is one of the distinct features of cancer [39]. Unlike normal cells, tumor cells are in a state of oncogenic stress, which is enhanced by increased genome instability and the development of cellular hypoxia. It should be noted that, as a result of stress conditions, tu-

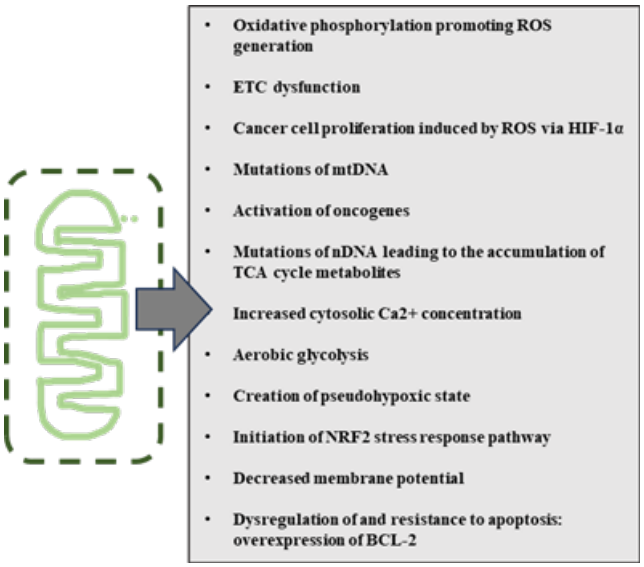


Fig. 2. Key mitochondrial characteristics of cancer cells. Adapted from [23].

mor cells have an increased potential to activate apoptosis, but tumor cells use a whole arsenal of molecular mechanisms that promote the predominance of growth and proliferation processes over cell death [40]. In general, each cell contains systems of proapoptotic and antiapoptotic proteins [40]. In normal cells, in a stable state, both systems are in equilibrium; however, in tumor cells, the action of anti-apoptotic proteins is enhanced, while that of pro-apoptotic proteins is weakened, and the regulatory mechanisms underlying the change in the state of the cell cycle can be carried out in different ways. The general ways for apoptosis evasion of tumor cells are summarized in **Table 1.**

In addition, the phosphorylation status of apoptosis mediators mentioned in Table 1, which controls their activity, is presented in **Table 2.**

5.1. Regulation by changing the level of expression

The most transparent mechanism of escape from apoptosis in tumor cells is based on suppression of the expression of proapoptotic proteins and (or) an increase in the expression of antiapoptotic proteins [70]. For the best-known antiapoptotic proteins, from the BCL-2 family, overexpression is associated with a poor prognosis, an

Table 1. The ways for the evasion of evading tumor cells.

Changing expression	Post-translational regulation	Tumors	References
Increased expression of BCL-2 and MCL-1	Increased stability of MCL-1	Non-Hodgkin lymphoma of B- and T-cell origin Breast cancer Lung cancer	[40–44]
Decreased expression of PUMA, BIM, BAX, and NOXA by p53 mutations	Increased degradation of BAX and BIM	Chronic lymphocytic leukemia Breast cancer, Ovarian cancer, Renal cancer Colon cancer	[40,45,46]
Decreased expression of BIM by AKT/ERK activation	Decreased activity of pro-apoptotic proteins by phosphorylation with PAK1, AKT, RSK, and etc.	Lung cancer Chronic myeloid leukemia Cutaneous T-cell lymphoma	[47–51]
Decreased expression of caspase 9 and APAF1	-	Leukemias Cutaneous melanomas Colorectal cancer Bladder cancer Gastric cancer Glioblastoma	[52–57]

Table 2. Apoptosis evasion in cancer: phosphorylation mechanisms.

Apoptosis regulator	Kinase (phosphatase)/site	Phosphorylation outcome	References
BCL-2	ERK1/2, PKC on Ser70	Activation	[58,59]
	JNK1 on Ser70	Inactivation at G2/M phase	
MCL-1	CDK1/2, JNK1 on Ser64	Increases binding to BIM, NOXA, BAK	[60,61]
	CDK1/CYCLIN B on Thr92	Ubiquitination and degradation mediated by APC/CCDC20	
BAX	PKA on Ser60	Activation	[62–64]
	GSK3 on Ser163	Activation	
	ERK1/2 on Thr167	Inactivation	
PUMA	IKK on Ser10	Ubiquitination and degradation	[65]
NOXA	CDK5 on Ser13	Inactivation	[66]
BIM	ERK on Ser55 Ser65, Ser73, Ser100 (mouse)	Inactivation	[67,68]
APAF1	RSK1/2 on Ser268	Inhibition [118]	[69]

increased likelihood of recurrence, and the emergence of resistance to therapy in various forms of cancer [40]. Thus, it was shown that the expression of the MCL-1 protein is increased in breast cancer and lung cancer through the activity of response element-binding protein and signal transducer and activator of transcription 3 transcription factors [40]. Suppression of apoptosis can develop indirectly through the inhibition of miRNA expression. So, in the normal state, miR-15 and miR-16 inhibit mRNA translation BCL -2, however, in chronic lymphocytic leukemia, their expression is reduced, which leads to further tumor development [71]. Reduced expression of pro-apoptotic proteins (P53 up-regulated modulator of apoptosis (PUMA), BID and phorbol-12-myristate-13-acetate-induced protein 1 (NOXA)) may be a result of the presence of mutations in the tumor suppressor p53, which under normal conditions activates the transcription of these proteins [40]. Also, the expression of proapoptotic proteins can be directly inhibited, for example, under the influence of AKT or extracellular signal-regulated kinases (ERK), for example, the expression of the pro- apoptotic BIM protein is suppressed [48,49]. Apoptosis can also be inhibited by suppressing the expression of participants in the final stage of the mitochondria-dependent apoptotic pathway, such as caspase 9 and APAF1 [40].

5.2. Post-translational regulation

Evasion of apoptosis by tumor cells can also occur through post-translational modifications via ubiquitination processes, which involve changes in protein stability and phosphorylation, which affects the proper functioning of the protein [72,73]. Tumor cells can interfere with the ubiquitination process, leading to increased degradation of pro-apoptotic proteins and/or increasing the stability of anti-apoptotic proteins. In many types of cancer, tumor cells include mechanisms for stabilizing the antiapoptotic protein MCL-1, which is an extremely unstable protein and rapidly undergoes proteasomal degradation in normal cells [74]. Deubiquitinating enzymes (DUB) negatively regulate protein degradation, which occurs by ubiquitination, since DUB stabilizes their substrate proteins, resulting in the removal of polyubiquitin chains. Ubiquitin-specific peptidase 9 causes inhibition of ubiquitination of antiapoptotic protein MCL-1, thus preventing its degradation [75]. An increase in the stability of the MCL-1 protein also occurs as a result of increased glycolysis, which is observed in tumor cells [76]. It has been shown that increased glucose metabolism leads to negative regulation of the activity of the GSK-3α/3β enzyme, which also activates the degradation of MCL-1 [77]. Increased degradation of proapoptotic proteins has been shown for the apoptosis proteins BAX and BIM, which are characterized by a short half-life, which facilitates the process of ubiquitinylation [40]. Additionally, it was shown that rapid degradation of the BAX protein was associated with a high incidence of adverse clinical outcomes and high proliferation of tumor cells in chronic lymphocytic leukemia and prostate cancer [78].

Changes in the strength of function of proapoptotic and antiapoptotic proteins may occur as a result of their phosphorylation by specific kinases. For example, phosphorylation of AKT and ERK kinases leads to decreased activity of apoptotic proteins, while phosphorylation of glycogen synthase kinase 3 (GSK3) and c-Jun N-terminal kinase (JNK) is associated with the development of functional activity of proapoptotic proteins and a decrease in the activity of antiapoptotic proteins [40]. For example, the proapoptotic action of the BAD protein is restrained by a number of kinases, such as serine/threonine-protein kinase PAK1 and AKT, which promote the proliferation of tumor cells [79]. Simultaneously, phosphorylation of BIM by ERK kinase precludes the interaction between BIM and BAX, leading to inhibition of an important step in mitochondria-mediated apoptosis, while phosphorylation of BIM by JNK kinase or p38 MAP kinase enhances BIM activity [67]. The final stages of apoptosis can also be inhibited as a result of phosphorylation of proapoptotic protein kinases: APAF1 is inhibited through phosphorylation by kinases such as ribosomal S6 kinase (RSK) and tyrosine-protein kinase BCR- ABL [52]; caspase 9 is inhibited by the action of cyclin-dependent kinase-1 (CDK1) and AKT kinases [80,81]. In addition, proteins of the IAP family can inhibit the function of proapoptotic proteins in cancer; they directly bind caspases, preventing the final stage of apoptosis [82]. IAP proteins are translated through the IRES internal ribosome entry site, and since this type of translation is the most stable even under cellular stress, which occurs in cancer, when cap-translation is inhibited and the expression of most proteins decreases, stable expression of IAP proteins leads to permanent inhibition of apoptosis in tumor cells [82].

6. Therapeutic strategies aimed at induction of mitochondria-mediated apoptosis in tumor cells

One of the ways to treat malignant neoplasms is to control the uncontrolled proliferation and growth of tumor cells [83]. At the same time, the use of cell apoptosis as the basis of such therapy is a highly effective strategy as a non-surgical treatment method, as well as a useful preparation for chemo- and radiation therapy, since it has been noted that, as a result of inhibition of apoptosis, resistance of tumor cells to low doses of radiation and chemotherapeutic agents occurs [83]. Induction of mitochondria-mediated apoptosis can be used as a treatment strategy for all types of cancer, since apoptosis evasion is a universal mechanism for increasing tumor cell survival. At the moment, there are already many registered drugs that affect different stages of apoptosis [84]. Here we consider the most well-known and promising, in our opinion, development options, their advantages and disadvantages.

6.1. Inhibition of antiapoptotic proteins

One of the first antiapoptotic protein inhibitor drugs is Navitoclax, which targets several antiapoptotic proteins belonging to the B-cell lymphoma protein family: BCL-2, BCL-XL, and BCL-W [85]. Despite undergoing clinical trials, the use of Navitoclax has not found wide distribution due to the emerging thrombocytopenia, the survival of which depends on BCL-XL [86]. A more promising option turned out to be its analogue Venetoclax, which targets only BCL-2, eliminating the problem of thrombocytopenia. Venetolax was initially approved for the treatment of chronic lymphocytic leukemia, with a complete remission rate of 20% [87]. In addition, Venetolax proved to be an effective drug for the treatment of other cancers, such as acute myeloid leukemia and multiple myeloma [83]. In total, more than 40 clinical trials involving Venetolax have been completed and more than 280 clinical trials

have been opened, including both single and combined use [88]. In patients with chronic lymphocytic leukaemia, toxicities were relatively mild in Venetoclax monotherapy studies, and included mild gastrointestinal adverse events including diarrhea and nausea and upper respiratory tract infections (at least one of which occurred in approximately half of patients); hematological toxicities were also reported, including neutropenia (~40–50% of patients), anemia (~20% of patients), and thrombocytopenia (~15% of patients) [87,89,90].

An interesting development is the use of antisense oligonucleotide BCL-2-G3139, which has been investigated in several clinical trials for various forms of cancer, including breast cancer, lung carcinoma, and non-Hodgkin's lymphoma [91]. High expression of the MCL-1 protein has been observed in many forms of cancer, making it a promising target. Currently, a clinical study of the compound AMG 176 is being carried out, which has shown a high selectivity and inhibitory effect towards MCL-1 in hematological tumor cell models and multiple myeloma mouse models [92]. At the same time, when developing MCL-1 inhibitors, side effects should be carefully assessed, since it has been repeatedly shown that the loss of MCL-1 gene function leads to the development of damage to the heart, intestine, liver, and nervous system [83].

Furthermore, by targeting and modifying the BCL-2 gene, its overexpression or dysregulation can be disrupted. Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-based gene editing technology offers a clear-cut and effective technique to modify the BCL-2 gene and potentially hinder tumor growth [93]. Guide RNAs (gRNAs) designed to match specific sequences within the BCL-2 gene are used for this technique [94]. Once the gRNA identifies a complementary match, it directs the Cas9 enzyme to that location, inducing a double-stranded DNA breakdown at the target site [95]. Off-target site effects represent unexpected DNA alterations at sites similar to the target sequence [96]. Bioinformatic tools are employed for accurate design of gRNAs with high specificity in order to minimize undesirable site effects [95]. Other CRISPR-based strategies have also been suggested for cancer therapy [97,98].

6.2. Activation of proapoptotic proteins

Targeted activation of proapoptotic proteins is an alternative strategy to the inhibition of antiapoptotic proteins, in which proapoptotic proteins are activated indirectly. Direct activation of proapoptotic proteins is a relatively new approach in cancer therapy, in contrast to inhibition of antiapoptotic proteins. The BAX protein is one of the key participants in mitochondria-mediated apoptosis, which makes it a promising target in the induction of apoptosis in tumor cells. Cellular proapoptotic proteins Bim, Bid, and Puma containing the BH3 domain are involved in the direct activation of the BAX protein; therefore, a convenient option to start the development of a direct BAX activator is to search for or synthesize mimetics containing the BH3 domain [99]. For example, BH3 mimetic peptides capable of directly activating BAX were developed: Bid SAHBA and Bim SAHB [99]. However, despite their initial efficacy, the disadvantages of peptide molecules, such as low bioavailability, poor membrane permeability, and metabolic instability, make peptides less desirable therapeutic candidates compared to small molecules. A promising approach is the development of compound 106, an activator of the proapoptotic protein BAX. This compound promotes BAX accumulation inside mitochondria, leading to BAX-dependent permeabilization of the outer mitochondrial membrane and subsequently inducing mitochondria-dependent apoptosis. Compound 106 was shown to be effective in activating apoptosis in various tumor cell lines, including the ability to induce a synergistic therapeutic effect when combined with the chemotherapeutic drug carboplatin [100]. Also promising is the compound BAM 7, which showed high selectivity in interaction with BAX with no competitive binding interaction with other protein targets of the BCL -2 family. The interaction between BAM7 and BAX led to structural changes, which, in turn, led to functional oligomerization of the BAX molecule and subsequent cell death [99]. Another focus is the activation of caspase. Thus, it was shown that the low molecular weight natural compound MX-2167 induced apoptosis in various cancer cell lines. In animal models, MX-2167 reduced tumor growth by up to 90% in a syngeneic model of prostate cancer [101]. However, it should be taken into account that if inhibition of apoptosis predominantly occurs at earlier stages, then the activating effect on caspases will be ineffective.

6.3. Immune checkpoint inhibitors targeting apoptosis pathways

Over the past decade, immunotherapy has emerged as a new treatment option for cancer, and particularly, immune checkpoint blockades have achieved significant advances. Immune checkpoint blockade-based therapies have transformed cancer treatment, but resistance remains common, often due to dysfunctional lymphocytes infiltrating the tumor [102]. Mitochondrial dysfunction is a key factor in lymphocyte dysfunction and is characterized by defective oxidative phosphorylation, maladaptation and depolarization, which contributes to T cell exhaustion and profoundly reduces antitumor efficacy. Studies have shown that mitochondrial function is positively correlated with the ability of cancer cells to evade the immune system. N-acetyltransferase 1-depleted breast cancer cells showed decreased oxidative phosphorylation and mitochondrial biogenesis proteins, along with increased antigen-presenting proteins [103]. The increased expression of CD147, which is upregulated in different malignancies, is associated with elevated glucose transporter type 1 (GLUT1) and monocarboxylate transporter-1 (MCT1) levels [104]. Notably, GLUT1 and MCT1 are important transporters responsible for the transport of glucose and lactic acid across cell membranes, respectively, thereby maintaining the metabolic phenotype of tumor cells.

Immune checkpoint antagonist monoclonal antibodies can stimulate T cells and promote antitumor immunity. The first checkpoint inhibitor Ipilimumab, targeted cytotoxic T-lymphocyte-associated protein 4 (*CTLA4*), a protein found on T cells, and exhibited remarkable clinical results in phase II and III clinical trials, including long-term survival in approximately 23% of patients with advanced melanoma [105]. Expressed in T cells, *CTLA-4* is an immune inhibitory molecule that interacts with B7 family of ligands (CD80 and CD86), producing immunosuppressive effect. In cytotoxic T cells, *CTLA-4* competitively disrupts the binding of ligands to its co-receptor CD28, thereby destroying its antitumor function. In 2011, Ipilimumab was

approved as an anti-CTLA-4 monoclonal antibody to interrupt B27/CTLA-4 binding and restore T cell cytotoxicity [106].

Second-generation checkpoint inhibitors (anti-programmed death 1 (anti-PD1) and anti-programmed death-ligand 1 (anti-PD-L1) showed good efficacy in various cancers, including melanoma, urothelial carcinoma, head and neck squamous cell carcinoma, renal cell carcinoma and non-small cell lung cancer [107–110]. Of note, Pembrolizumab, Nivolumab, and Cemiplimab represent anti-PD-1 drugs and Atezolizumab, Avelumab, and Durvalumab are examples of anti-PD-L1 drugs [107,111,112]. PD-1 regulates the immune system by stimulating apoptosis of mature T cells [113]. Nonetheless, most patients fail to benefit from anti-PD-1 therapy, and a large number of patients who respond to anti-PD-1 therapy develop acquired resistance following an initial response [114]. The development of resistance to anti-PD-1/PD-L1 therapy is associated with the limited tumor immunogenicity, major histocompatibility complex (MHC) dysfunction, presence of other inhibitory receptors, IFN-γ signal resistance, and an immunosuppressive microenvironment [114].

Another immune checkpoint molecule is lymphocyte activation gene-3 (LAG-3). Like PD-1 and CTLA-4, LAG-3 is overexpressed on exhausted T cells in the tumor microenvironment, promoting cancer cell evasion of the immune response. At least 16 drugs that target the LAG-3 molecule have undergone clinical trials worldwide, with the most advanced being BMS's BMS-986016 [115].

The toxicity profiles of these agents have been reviewed [116]. A dose-dependent toxicity resulting from the use of CTLA-4 inhibitors and high-grade toxicity were observed in 16%, 27%, and 55% of patients receiving nivolumab, ipilimumab, and the combination, respectively [117–120]. PD-1/PD-L1 blockade resulted in high-grade toxicity in 10–20% of treated patients, but at clinically relevant doses, it is not dose-dependent [121]. Combined LAG-3/PD-1 blockade results in a moderate increase in toxicity; serious adverse events were observed in 18.9% of patients (compared to 9.7% with nivolumab alone) [111].

There are other immune checkpoint inhibitors for monoclonal antibodies, such as T cell immunoglobulin and mucin-domain-containing 3 (TIM-3) and T cell immunoglobulin and ITIM domain (TIGIT). The transmembrane protein TIM-3, expressed on the surface of immune cells including T cells, macrophages, and dendritic cells, is associated with Th1 suppression and proinflammatory responses. TIM-3 interaction with phosphatidylserine facilitates the recognition of apoptotic cells [122]. Monoclonal antibody drugs against TIM-3 are being actively studied in clinical trials, listed in [122]. TIGIT is predominantly expressed on the surface of T cells and natural killer cells, and CD155 on tumor cells is its high-affinity ligand. TIGIT can supress immune activation by binding to CD155. Anti-TIGIT antibody drugs such as Tiragolumab and BMS-986207 currently undergoing clinical trials [123].

6.4. Chimeric antigen receptor T-cell therapy

Chimeric antigen receptor (CAR) T-cell therapy is a cutting-edge strategy in immune cell therapy, proposing a personalized cancer immunotherapy approach. By modifying patients' T cells to express CARs, which consist of antibodies and T-cell receptors on their surface, these cells can recognize tumor-associated antigens in an MHC-independent fashion, thus triggering the identification and destruction of tumor cells [124,125]. CAR-T-cell therapy has been effective in treating both hematological tumors and solid tumors [126,127]. However, CAR-T-cell therapy is not without limitations. Its main limiting factor is early T-cell exhaustion, characterized by impaired function and dynamics of mitochondria [126].

It is known that T cells, which play a key role in the antitumor immune response, rely on their mitochondrial activity at various stages of the immune response. Mitochondria play an essential and diverse role in T cells, including their activation, proliferation, differentiation, polarization, migration, and the immune synapse formation. Mitochondria produce ATP, contribute to calcium homeostasis regulation, lipid synthesis, cell apoptosis, and other processes [128]. Thus, targeting mitochondria may be a useful strategy for preventing T cell exhaustion in CAR-T-cell therapy. Mitochondrial transplantation boosts the number of mitochondria in T cells, improving their function. By acting as a positive regulator, "supercharging" T cells with mitochondria makes them more efficient at attacking tumor cells [129]. The possibility of transplanting mitochondria from human dermal fibroblasts into human Jurkat cells (immortalized T cells) has been demonstrated [130]. Moreover, transfer of prepared Q-mitochondria into CAR-T cells enhanced metabolic adaptability, proliferation capacity and cytokine production ability, and improved anti-tumor capabilities of CAR-T cells [129], potentially enhancing the therapeutic effects of CAR-T-cell treatment. These results suggest that mitochondrial transplantation has the potential to complement CAR-T- cell therapy and may be combined with other pharmacological approaches to further enhance the efficacy of CAR-T-cell therapy.

6.5. Mitochondria-targeted nanomedicine

For cancer therapy, multifunctional nanoplatforms have been created with modifications of various mitochondriotropic ligands that allow the initiation of mitochondria-mediated apoptosis of tumor cells. In particular, mitochondria-targeted chemotherapy delivered via a nanoplatform provides enhanced efficacy by initiating mitochondria-mediated apoptosis through various mechanisms, including disrupting mtDNA and overcoming drug resistance by blocking the energy supply of drug-resistant proteins [4]. Yoong et al. (2014) functionalized multi-walled carbon nanotubes (MWCNTs) with rhodamine-110 (Rho) as a delivery vehicle for the platinum (IV) prodrug cisplatin (PtBz) into mitochondria to disrupt mtDNA [131]. Besides, synergistic effect was also investigated by co-loading MWCNT-Rho nanocarrier with PtBz and chemo-potentiator, 3-bromopyruvate (BP). BP inhibits hexokinase II-voltage-dependent anion channel (VDAC) interaction at mitochondrial outer membrane, which would interrupt cell metabolism, making them prone to apoptosis. This mechanism was further explored, showing that MWCNT-Rho(PtBz + BP) resulted in a two-fold decrease in mitochondrial membrane potential compared to free PtBz in human ovarian and breast cancer cell lines measured with the JC-1 probe, indicating additional mitochondrial damage.

Paclitaxel (PTX), a taxoid chemotherapeutic drug used as first-line and consequential therapy for the treatment of advanced carcinoma of the ovary, and other various can-

cers including breast and lung cancers, was found to bind to antiapoptotic protein BCL-2 family in mitochondria and open the mitochondrial permeability transition pore channels [132], which regulate the mitochondrial permeability of small molecules, then depolarize mitochondria membrane, facilitating the initiation of apoptosis. Therefore, the underlying mechanism of mitotoxicity provides the opportunity for PTX to target mitochondria for increased efficacy. It was demonstrated both *in vitro* and *in vivo* that the delivery of PTX based on liposomes modified with TPP-polyethylene glycol-phosphatidylethanolamine (TPP-PEG-PE) to mitochondria targets provides superior antitumor effects [133]. This study also showed that TPP-PEG-PE modified liposomes (TPP-PEG-L) possess low toxicity. Moreover, to reduce drug resistance of lung cancer, TPP-Pluronic F127-HA/PTX (TPH/PTX) nanocarrier composed of TPP, Pluronic F127, and hyaluronic acid to deliver model drug PTX to mitochondria to restrict ATP production, thereby reducing the expression of drug efflux pump was developed [134]. The study showed that PTX delivered by this nanocarrier significantly increased the apoptosis rate of A549/ADR cell to 22.10%. Permeabilization of the mitochondrial outer membrane suggests that the mechanism of cytotoxicity is mediated by PTX-induced mitochondrial apoptosis.

By utilizing physical energy, hyperthermia therapy can elevate temperature of the tumor tissues and induce the apoptosis or necrosis of cancer cells. Therefore, photothermal nanoparticles were designed to specifically accumulate in mitochondria, resulting in a sharp temperature increase focused in the region of mitochondria for a given amount of heat, a direct induction of mitochondria-mediated apoptosis or necrosis, and promote photothermal damage to cancer cells [135]. A mitochondria-targeting photothermal coumarin-based iron oxide nanoparticle, Mito-CIO, by modifying TPP was designed [136]. The results of this study indicated that using TPP as a vector to carry Mito-CIO to mitochondria resulted in hyperthermia in mitochondria. It was also shown that hyperthermia was responsible for a significant improvement in cytotoxicity on cancer cell was attributed to a combination of cell apoptosis and necrosis. In addition, a new supra-carbon dots (SCDs) were conjugated with mitochondria-targeting peptide (MT) to enhance the photothermal therapeutic efficacy for cancer cells [137]. The mechanism underlying the enhanced photothermal efficiency of SCD-MT was elucidated using the JC-1 probe, and it was found that the mitochondrial membrane potential of HepG2 cells was lost. This result evidenced that the apoptosis of cancer cells was caused by the effect of SCD-MT on mitochondria, by the disruption of mitochondrial functions. The real-time dynamics of cellular molecules during the process were further assessed using surface-enhanced Raman spectroscopy, and it was found that the resulting hyperthermia led to structural changes in lipids, proteins, and DNA, and then caused cell apoptosis.

7. Emerging concepts and future directions

7.1. Challenges and current limitations of metabolism-targeting drugs in cancer

Cancers are not only genetic diseases, but also metabolic disorders, as proven by the fact that even with sufficient oxygen supply, tumor cells prefer to undergo glycolysis, promoting the secretion of lactic acid, denoted as the "Warburg effect" [138]. The dihydrofolate reductase inhibitor, the antifolate drug aminopterin, which blocks the synthesis of nucleic acids and proteins in acute leukemia in children, was described by Sidney Farber in 1948. Since then, a large class of chemotherapeutic substances has been discovered and research continues into drugs that affect tumor metabolism. Fatty acid metabolism is significant in tumor development and progression. Fatty acids elaborate the following processes in tumor cells: structural synthesis, signaling of phospholipids on the surface of cancer cell membranes, maintaining energy needs through β-oxidation, and using nicotinamide adenine dinucleotide phosphate (NADPH) to maintain redox balance. There is a study showing that the gluconeogenic enzyme phosphoenolpyruvate carboxykinase 1 (PCK1) has protein kinase activity and phosphorylates protein substrates using guanosine-5'-triphosphate as a phosphate donor, continuously stimulating tumor lipid synthesis and promoting progression [139]. At the same time, drugs that block certain metabolic pathways can affect the uptake of normal cells, making the development of lipid metabolism drugs extremely difficult. For example, clinical development of hexokinase inhibitors such as 2-deoxyglucose has been ceased because of high toxicity or low efficacy [140]. To date, only a limited number of drugs that target cancer metabolism have been successfully used in clinics (Enasidenib and Ivosidenib for acute myeloid leukemia gained FDA approval), but this may change as our perception of tumors expands in the future.

7.2. The gut microbiota as a modulator of immunotherapy response in cancer

It is well-known that bacteria, fungi, and viruses populate the digestive tract. The occurrence and development of many types of cancer, as well as the effectiveness of their immunotherapy, are reported to be associated with the intestinal microbiota. Known enteric carcinogenic bacteria include *Salmonella typhi*, which is associated with gallbladder cancer, and *Helicobacter pylori* (*H. pylori)*, which is related to primary liver cancer and gastric cancer. The World Health Organization recognized *Helicobacter* as a Group 1 carcinogen. A recent study has shown that a non-*H. pylori*-related bacterium, *Streptococcus anginosus*, also promotes gastric tumorigenesis, suggesting the important role of carcinogenic bacteria [141]. The role of gut microflora in inflammation, carcinogenesis, and cancer therapy was reviewed [142]. In particular, the microflora's modulating effects on checkpoint inhibitors have attracted special attention [143]. Immune checkpoint inhibitors can produce remarkable tumor regressions. Currently approved drugs include antibodies that block CTLA-4, PD-1, and PD-L1 for the treatment of various cancers. For example, the antitumor effects of CTLA-4 blockade are determined by distinct *Bacteroides* species. In mice and humans, T cell responses specific for *B. thetaiotaomicron* or *B. fragilis* were linked to the efficacy of CTLA-4 blockade [144]. The research teams led by Zitvogel, Gajewski, and Jennifer Wargo published three studies showing that the efficacy of anti-PD-1 immune checkpoint inhibitors in patients with melanoma and epithelial tumors depends on gut commensal bacteria [145]. The research has demonstrated that gut microbiota is closely related to the occurrence and progression of tumors; therefore, further studies elucidating the direct relationship between gut microbiota

and therapeutic effects of anticancer drugs are necessary to discover novel substances for cancer treatment.

8. Discussion

Proteins that regulate mitochondria-mediated apoptosis are attractive targets for anticancer drug development. Because this pathway is frequently disrupted in tumor cells, drugs that target pro-apoptotic or anti-apoptotic proteins may be effective across various cancer types. Currently, several agents have already been approved and show antitumor efficacy, while others are in development with high therapeutic potential. Although effective drugs are available, developing new therapeutic agents is still advisable. New agents could help eliminate or reduce the shortcomings of existing pro-apoptotic drugs. Anti-apoptotic proteins also play an essential role in cell cycle regulation, and disrupting their function in normal cells can cause severe adverse reactions, as demonstrated with approved drugs. Notably, the link between programmed cell death and the cell cycle has long been established [146,147]. Accumulated evidence suggests that manipulation of the cell cycle may either block or induce an apoptotic response [148]. This connection was recognized for tumor suppressor genes (p*53* and *RB*, the dominant oncogene) [149,150], c-*Myc* [151], some cyclin-dependent kinases and their regulators [152]. Therefore, drugs under development should be highly targeted to tumor cells to avoid negative effects on normal tissues. One possible approach is to combine inhibitors of anti-apoptotic proteins with antibodies directed against tumor-specific antigens, which would increase selective binding to tumor cells. Furthermore, experience with already approved drugs indicates that a therapeutic compound should be highly effective against a single specific apoptosis regulator protein. This strategy reduces the risk of side effects that may arise from targeting multiple molecular targets simultaneously. Identifying new apoptosis evasion pathways and discovering new protein targets involved in their regulation remains an important direction for future research. It is also worth investigating in more detail whether synergistic effects occur when mitochondria-targeted pro-apoptotic agents are used together with other anticancer drugs. Comparing the efficacy of such combination therapies with single use of apoptosis modulators would help guide the development of future treatment regimens.

9. Conclusion

Disruption of mitochondria-mediated apoptosis **is** one of the main factors in the development of oncological diseases. This dysfunction is associated with decreased function of proapoptotic proteins and increased activity of antiapoptotic proteins. Targeting apoptosis regulators in cancer can be achieved at different levels, including transcription, translation, and post-translational modifications. Despite the proven efficacy of marketed apoptosis inducers, concerns about their safety remain. These safety issues may be addressed by selecting a single suitable target and increasing the affinity of the drug for its protein target.

Abbreviations

α-KG, α-ketoglutarate; AKT, serine/threonine-specific protein kinase; APAF1, apoptotic peptidase activating factor 1; BAK, BAX, BID, BH3, MCL-1 are members of the BCL-2 family; BIR, baculoviral IAP repeat domains; CARD, caspase activation and recruitment domains; CDK1, cyclin-dependent kinase-1; CICD, caspase-independent cell death; CREB, response element-binding protein; D-2-HG, D-2-hydroxyglutarate; DUB, deubiquitinating enzymes; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinases; ETC, electron transport chain; FH, fumarate hydratase; GSK3, glycogen synthase kinase 3; HIF-1, hypoxia-inducible factor 1; HSP60, heat shock protein 60; IAP, apoptosis inhibitory protein; IDH, isocitrate dehydrogenase; JNK, c-Jun N-terminal kinase; LOF, loss-of-function; MOMP, mitochondrial outer membrane permeabilization; mtDNA, mitochondrial DNA; mtROS, mitochondrial ROS; NOXA, phorbol-12-myristate-13-acetate-induced protein 1; NF-κB, nuclear factor kappa B; PAK1, serine/threonine-specific protein kinase; PHD, prolyl hydroxylase; PTK2B, protein tyrosine kinase 2; PUMA, P53 up-regulated modulator of apoptosis; ROS, reactive oxygen species; RSK, ribosomal S6 kinase; RT, radiation therapy; SDH, succinate dehydrogenase; SMAC, second mitochondria-derived activator of caspase; STAT 3, signal transducer and activator of transcription 3; tBID , truncated BID; TCA, tricarboxylic acid; TFBM2, mitochondrial transcription factor B2; TRAP-1, tumor necrosis factor receptor associated protein 1, XIAP, X-linked inhibitor of apoptosis protein.

Author contribution

It is hereby acknowledged that all authors have accepted responsibility for the manuscript's content and consented to its submission. They have meticulously reviewed all results and unanimously approved the final version of the manuscript.

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Use of Artificial Intelligence Tools

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