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Chemotherapeutic drugs: Cell death- and resistance-related signaling pathways. Are they really as smart as the tumor cells?

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ABSTRACT

Chemotherapeutic drugs kill cancer cells or control their progression all over the patient's body, while radiation- and surgery-based treatments perform in a particular site. Based on their mechanisms of action, they are classified into different groups, including alkylating substrates, antimetabolite agents, anti-tumor antibiotics, inhibitors of topoisomerase I and II, mitotic inhibitors, and finally, corticosteroids. Although chemotherapeutic drugs have brought about more life expectancy, two major and severe complications during chemotherapy are chemoresistance and tumor relapse. Therefore, we aimed to review the underlying intracellular signaling pathways involved in cell death and resistance in different chemotherapeutic drug families to clarify the shortcomings in the conventional single chemotherapy applications. Moreover, we have summarized the current combination chemotherapy applications, including numerous combined-, and encapsulated-combined-chemotherapeutic drugs. We further discussed the possibilities and applications of precision medicine, machine learning, next-generation sequencing (NGS), and whole-exome sequencing (WES) in promoting cancer immunotherapies. Finally, some of the recent clinical trials concerning the application of immunotherapies and combination chemotherapies were included as well, in order to provide a practical perspective toward the future of therapies in cancer cases.

Introduction

Cancer is characterized by the uncontrolled cell proliferation, invasion, and check-point evasion of abnormal cells that are mostly nonfunctional. Cancer can arise due to diet insufficiencies, inherited mutations, and tobacco consumption, to say the least [1, 2]. Cancer's incident is increasing due to the sedentary lifestyle, overpopulated, polluted megacities, and individuals' growing desire for consuming processed foods containing preservatives additives [3-5]. Since cancers might not manifest symptoms in their early onset, it would be difficult or even improbable to treat them when they are diagnosed in their late stage. By and large, tumors are composed of two main parts, including the proliferating cells and stroma, which contains connective tissue and blood supply [6]. Chemotherapy has been among our best options against malignancies.

Chemotherapy is defined by the administration of numerous drugs and chemicals either alone or in combination to kill the cancer cells. Chemotherapeutic drugs kill cancer cells or control their progression all over the patient's body, while radiation- and surgery-based treatments are directed to a particular site. Cure, control, and palliation are the three objectives of chemotherapies. Killing cancer cells by implementing chemotherapy drugs means "Cure", whereas "Control" defines the situation that full remission seems far-fetched; therefore, the objective of the therapy would be to decrease the tumor size or to diminish the growth rate and angiogenesis. Palliation aims to alleviate the pain, symptoms, and medical conditions arisen due to cancer. It is mostly accomplished when cancer is in the advanced stages and cannot be eradicated; therefore, our aim would be to improve the quality of life.

The chemotherapy prescription approaches rely on various elements, including the cancer's type, the cancer's stage, the patient's age, the patient's general health status, the other concurrent health issues, and the history of receiving chemotherapies. Since chemotherapeutic drugs cannot distinguish normal cells against cancerous cells, the prescribed dosage is the other crucial aspect toward achieving the best possible response. The administration dosage depends on the patient's weight, body surface area, age, nutrition status, history of radiation therapy, and blood cell count. Besides, a suitable drug administration schedule might help obtain the most efficient anti-cancer activity and minimum side effects [7, 8].

Chemotherapeutic agents target different stages of the cell cycle. They are classified into different groups based on their mechanisms of action, including alkylating substrates that damage the DNA and

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Table 1
The category of chemotherapy drugs.

Category		Drugs	Mechanisms of action
Alkylating agents		Altertamine Busulfan Carboplatin Carmustine Chlorambucil Cisplatin Cyclophosphamide Dacarbazine Lomustine Melphalan Oxaliplatin Temozolomide Thiotepa	Damage the DNA
Antimetabolite		5-fluorouracil (5-FU) 6-mercaptopurine (6-MP) Capecitabine (Xeloda) Cytarabine (Ara-C) Floxuridine Fludarabine Gemcitabine (Gemzar) Hydroxyurea Methotrexate Pemetrexed (Alimta)	Substitute the RNA and DNA blocks
Anti-tumor Antibiotics	Anthracyclines	Epirubicin Idarubicin Daunorubicin Doxorubicin (Adriamycin)	Interfere with the activity of DNA replication enzymes
	non-Anthracyclines	Actinomycin-D Bleomycin Mitomycin-C Mitoxantrone	
Topoisomerase inhibitors	Topoisomerase inhibitor I	Topotecan Irinotecan (CPT-11)	Interfere with the topoisomerase enzymes and incorporate the unwinding DNA in replication and transcription
	Topoisomerase inhibitor II	Etoposide (VP-16) Teniposide Mitoxantrone	
Mitotic inhibitors		Docetaxel Estramustine Ixabepilone Paclitaxel Vinblastine Vincristine Vinorelbine	Hinder the cell proliferation and division
Corticosteroids		Prednisone Methylprednisone (Solumedrol) Dexamethasone (Decadron)	Palliate the chemotherapy side effects
EGFR inhibitors		Tarceva (Erlotinib) Erbitux (Cetuximab) Iressa (Gefitinib)	Blocks the epidermal growth factor receptors on tumor cells

(http://www.drugs.com) (http://www.cancer.org)

interfering with cell reproduction in various cell cycle phases. These elements leave impacts on both bone marrow stem cells and somatic cells, making them a preferred option for solid tumors and leukemia. On the other hand, antimetabolite agents replace the typical structures of RNA and DNA and are known as RNA and DNA blockers. The so-called process blocks the multiplying of chromosomes that makes these drugs suitable against leukemia, breast, and ovary cancers. While, anti-tumor antibiotics, unlike traditional antibiotics, hinder the activity of DNA duplication-related enzymes. These are known as Anthracyclines, which have been prescribed for numerous malignancies. However, since permanent heart failure is one of their serious side effects, non-Anthracyclines have been developed to mitigate these side effects. Moreover, topoisomerase I and II Inhibitors impede the activity of topoisomerases, therefore hindering the replication of DNA. Nevertheless, topoisomerase II inhibitors enhance the risk factors for secondary cancers, such as acute myeloid leukemia (AML). Besides, mitotic inhibitors are compounds driven from plants that interfere with different phases cell cycle phases resulting in cell proliferation blockage; nonetheless incidental damages to the nerve system are among their disadvantages. Finally, corticosteroids have been prescribed to palliate the chemotherapy drug's side effects, such as nausea, vomiting, and allergic reactions [7, 9] Table 1.

Having said that, two significant and severe complications during chemotherapy are chemoresistance and tumor relapse. Resistance is either intrinsic or extrinsic (acquired); in one way, cancer cells become resistant to different chemotherapeutic drugs through common resistance mechanisms, which is called multi-drug resistance. In other ways, cancer cells develop resistance through the increased drug efflux, dampened apoptosis, enhanced drug detoxification, altered expression in the drug target, and improved DNA repair mechanisms [10].

In this regard, we have selected representatives in each chemotherapeutic drug family to discuss their molecular and cellular mechanisms toward cell death and resistance. Besides, we have summarized the current combination chemotherapy applications, including numerous combined-, and encapsulated-combined-chemotherapeutic drugs. We further discussed the possibilities and applications of precision medicine, machine learning, next-generation sequencing (NGS), and whole-exome sequencing (WES) in promoting cancer immunotherapies.

Finally, some of the recent clinical trials concerning the application of immunotherapies and combination chemotherapies were included as well, in order to provide a practical perspective toward the future of therapies in cancer cases.

Current chemotherapeutic drugs and their mechanisms of action

Cisplatin

Cisplatin mechanism of action

Cis-diamminedichloroplatinum, known as cisplatin, is one of the most beneficial chemotherapeutic drugs which is prescribed for half of the malignancies [11]. Cisplatin is administered intravenously, where it binds to plasma proteins like albumin and is conveyed through the bloodstream, and ultimately enters the target cells via copper transporters [12, 13]. Interestingly, just about 1 percent of the administered drug impacts DNA [14]. Cisplatin contains platinum-based combinations that construct inter-, and intra-strand adducts within the DNA strands between guanine and adenine located in the opposite strands [15], resulting in cell cycle arrest and ignition of apoptosis [16, 17]. To illustrate this, cisplatin forms these adducts in a two-steps manner. Initially, it constructs a bond with N7 guanine; after that, it forms the second link with guanine or adenine in the opposite or the same strand. Since N7 atoms in adenine and guanine are easily accessible, cisplatin forms numerous adducts and cross-links within the DNA structure, leading to a general distortion in the DNA framework [15].

Mechanisms of cisplatin in cell death through signaling cascades

As cisplatin binds to DNA, it causes a bend within the DNA structure. Various proteins, such as the high mobility group (HMG), which are a kind of non-histone- and chromosome-structural protein, identify this bend and selectively bind to cisplatin adducts in DNA [18]. HMG proteins cover the affected DNA from being recognized by nucleotide excision repair (NER) and mismatch repair (MMR) [19]; therefore, p53, the genome security guard, is activated, which increases the activity of waf1, p21, and MDM2, leading to cell cycle arrest [20]. More on that, cisplatin triggers the oxidative stress within the cell. Reactive oxygen species (ROS) cripple DNA, proteins, and cell lipids [21]. Providing that the damage is severe or irreparable, the intrinsic pathway of apoptosis is ignited through BCL2 inhibition and caspase activation [22, 23]. The inhibition of BCL2 impacts the mitochondrial membrane integrity as well. Besides, cisplatin decreases the mitochondrial glutathione leading to hydroxyl radicals and oxidative stress, which damage the mitochondrial membrane integrity [21, 24]. Consequently, cytochrome *C* is released, where it further interplays with Apaf-1. This interaction activates procaspase 9, which activates caspase 3 and 7, known as the executioner caspases, leading to the cleavage and activation of poly ADP-ribose polymerase (PARP). PARP commences cell death due to the loss of function and degradation of numerous vital proteins and DNA fragmentation [25-27].

In addition, cisplatin is considered a mitochondrial-DNA-targeting element. Since mitochondrial DNA (mtDNA) has abundant guanine-rich stretches, cisplatin forms more adducts within the mtDNA structure than cellular DNA. Therefore, it can be conjectured that mitochondrial functions would be impaired as well [28].

Moreover, studies have thoroughly appreciated that MAPK family is impacted by cisplatin. MAPK includes serine/threonine kinases, such as JNK, p38, and ERK, which are incredibly crucial for cell proliferation and survival [29-32]. To illustrate this, cisplatin activates ERK, which further allows the phosphorylation and activation of p53, which induces the transcription of BAX [33], overexpression of p21, and cell cycle arrest [34, 35]. Besides, DNA damages caused by platinum-based combinations in cisplatin activate JNK which further stabilizes and activates p73, a pro-apoptotic protein. P73 promotes cisplatin-mediated apoptosis in correlation with JNK [36]. Furthermore, P18 interacts with p53, which stabilizes and increases the correlation of p53 with a pro-apoptotic gene called NOXA; hence, cisplatin has the potential to stimulate the cell death pathways through p18-p38 as well [37]. Interestingly, p38 makes another contribution to cisplatin-induced cell death, which is accomplished through inducing the internalization of epidermal growth factor receptors (EGFRs) via the activation of p38 [38].

Besides, it has been reported that cisplatin arrests the cell cycle at the G2 phase through the phosphorylation of Chk1 and Chk2. It also stimulates the activation of Cdc25C and its trafficking to the cytoplasm, which blocks the cell cycle transition to the M phase [39].

Mechanisms of cisplatin resistance through signaling cascades and how to be tackled

Chemoresistance is an unwelcome phenomenon in cancer cells. It has limited the application of different drugs against various cancers. To be precise, chemoresistance is subcategorized into two main categories: 1) innate resistance, in which the administered drug has no impact in the first place, 2) acquired resistance, in which although the chemotherapeutic drug was responsive at the beginning, it loses its beneficiary impacts consequently. The so-called condition arises due to alterations in the cellular drug absorption pattern, changes in drug influx and efflux pattern, conjugation to glutathione or metallothionein, increased drug detoxification, stimulation of DNA repair mechanisms, and inhibition of apoptosis pathways [21, 40].

There have been arguments about cisplatin resistance in patients suffering from colorectal, lung, and ovarian cancer [41, 42]. Numerous mechanisms have been demonstrated in the context of cisplatin resistance; including 1) tumor cells increase drug efflux, therefore decreasing the intracellular accumulation of cisplatin, 2) escalated intracellular level of glutathione and metallothioneins, that are intracellular scavengers, increases drug detoxification, 3) stimulation of DNA repair machinery such as, nucleotide excision repair (NER), inter-strand bound repair and mismatch repair (MMR) which attenuates the impact of cisplatin, and finally 4) adjustment in the approaches of apoptosis-based cell death [43-46]. The aforementioned events give rise to cisplatin inactivation and prevent the formation of cisplatin-DNA adducts.

Three copper transporters (CTRs) play a distinct role in cisplatin transportation [21, 47]. CTR1 improves cisplatin uptake; however studies on human ovarian carcinoma have represented a decrease in CTR1 expression level [48]. Therefore, loss of CTR1 has been reported to decrease the intracellular accumulation of cisplatin, which leads to cisplatin resistance [49, 50]. Besides, high amounts of ATP7A and ATP7B, which contribute to copper efflux, have been shown to enhance cisplatin resistance [51].

Moreover, many elements such as RNA, thiol peptides, and cell microfilaments bind to cisplatin subsequent to its intracellular accumulation, which results in the blockage of cisplatin [21]. To illustrate this, thiol peptides and RNA strands create adducts with cisplatin within the cell. Glutathione S transferase (GST), an enzyme with a regulatory sensor formed of cysteine residues [52], modulates glutathione and cisplatin conjugation. Therefore, resulting in the blockage of cisplatin-DNA adducts as well. According to studies, high levels of glutathione and GST is associated with cisplatin resistance [53, 54]. Furthermore, metallothionein binds to cisplatin, attenuating the administered dosage and contributing to drug inactivation and resistance [55, 56].

Various proteins like xeroderma pigmentosum A (XPA), XPG, and replication protein A (RPA), are involved in NER [57, 58], and studies have demonstrated that NER deficiencies increase the sensitivity to platinum-based chemotherapeutic drugs [59, 60]. Therefore, overexpression of NER proteins is believed to correlate with cisplatin resistance [61].

Moreover, aberrant activation of cell survival signaling pathways, including PI3K, AKT, and mammalian target of rapamycin (mTOR), is related to increased tumor mass [62-64]. RSK proteins, such as Ras-ERK mediators that play a significant role in cell survival necessities [65,

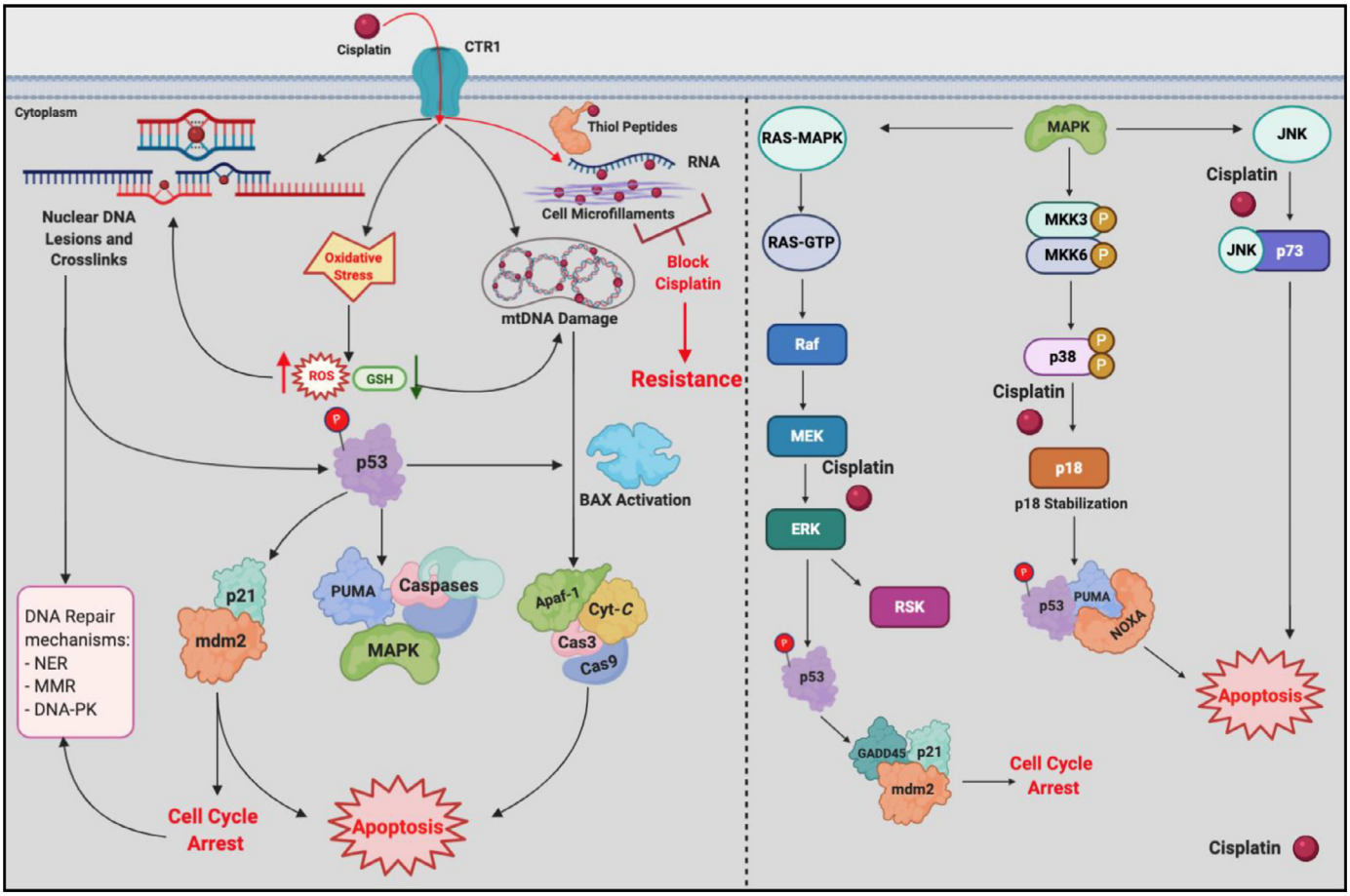

Fig. 1. Platinum-based combinations in cisplatin constructs inter- and intrastrand adducts, namely lesions, within the nuclear and mitochondrial DNA. Besides it stimulates ROS and oxidative stress. Through the activation of p53, in which p21, Waf1, and MDM2 are recruited, and through the activation of Bax, in which the pro-caspase-9 and -3 are activated, the programed cell death, apoptosis pathways are ignited. To illustrate this, theses apoptosis pathways are accomplished through RAS-MAPK, p38-p18, and JNK cascades.

66], have been shown to activate BCL-2 and NHE1 to dampen apoptosis pathways [67, 68]. Fig. 1.

Paclitaxel

Paclitaxel mechanism of action

Paclitaxel is a member of the chemotherapeutic drug family known as taxane, which agitates the polymerization of tubulins. All taxanes stabilize microtubules, except for vinblastine, which stacks up tubulin and depolymerizes the microtubules [69-72]. Tubulins are bricks for the structure of microtubules. By impeding the polymerization of microtubules, taxanes can block the cell division in metaphase and anaphase. Needless to mention that, microtubules are vital frameworks in a variety of cell activities, including mitosis, transportation, cell shape sustainability, cell secretion, and phagocytosis, to say the least [73]. Paclitaxel targets these microtubules and wreaks the havoc on spindles during the G2 and M phases, especially during prophase [74, 75]. According to Horwitz, paclitaxel prevents cell division and replication through increasing the polymerization of β-tubulin microtubules and preventing their depolymerization; therefore, poisoned cells will be arrested in the G2/M phases [76] and undergo apoptosis [77]. Shreds of recent evidence have indicated that low concentration, approximately less than nanomolar, inhibits the depolymerization of microtubules, whereas high-dose administration of paclitaxel stimulates an excessive polymerization of microtubules, which renders them nonfunctional owing to their increased stability [78]. To be precise, paclitaxel couples directly and specifically to the N-terminal of the β-tubulin units in a reversible manner instead of binding to the tubulin dimers [79, 80]. Interestingly, paclitaxel has the potential to stimulate the tubulin polymerization even in 4-degree centigrade condition independent of GTP [77].

Mechanisms of paclitaxel in cell death through signaling cascades

It is assumed that weekly consumption of paclitaxel has a dose-dependent apoptotic impact on malignant cells independent of its microtubule stabilization potential. 10 nM of paclitaxel in 12 h brings about apoptosis in the S phase without mitotic arrest [78]. Besides, administration concentration of ≥9 nM stimulates the activation of Raf-1, which promotes further apoptosis mechanisms, whereas administration of ≤9 nM induces p53 and p21, furthering apoptosis independent of Raf-1 activation [78, 81, 82].

In addition, paclitaxel is capable of inducing other pro-apoptotic pathways. The toll-like receptor-4- (TLR-4) related pathway, JNK, MAPK, NF-KB, JAK, and STAT, are associated with the cell-death activity of paclitaxel. The activation of MAPK leads to the dephosphorylation of Bad and Bax as well as the phosphorylation of Bcl2, which ultimately triggers apoptosis cascade [83-86].

Weekly administration of paclitaxel has displayed anti-angiogenic activities as well [87, 88]. In other words, pieces of evidence have lent support to the fact that low-dose administration of paclitaxel inhibits the expression of vascular endothelial growth factor (VEGF) [89, 90].

The other mechanism of action for paclitaxel is accomplished through the promotion of ROS generation. This process is triggered by the induction of nicotinamide adenine dinucleotide phosphate (NADPH)

oxidase that results in the oxidative stress and the subsequent cell death pathways [91, 92].

Paclitaxel has impacts on the immune system as well. It suppresses the immune system in a dose-dependent manner. Providing that it is administered in a standard dose, it dampens the function of macrophages, natural killer (NK) cells, and effector T cells [93]. Whereas, prescribing low-dose paclitaxel stimulates immune responses and anti-tumor properties in immune cells [93, 94].

As it has been mentioned earlier, paclitaxel is capable of binding to TLR-4, which is expressed on innate-immunity cells. The binding of paclitaxel on macrophages, for instance, recruits MyD88, MAPK, and NF-KB, further leading to the expression and secretion of TNF-α, IL-1, IL-6, and IL-8 [95-97]. These stimulated macrophages can either directly lyse tumor cells through secreting nitric oxide (NO) and lysosomal enzymes or activate dendritic cells (DCs), NK cells, and cytotoxic T lymphocytes (CTLs) to invade tumor cells indirectly [93]. In addition, DCs can also be directly stimulated by paclitaxel through TLR-4. This leads to DC maturation through increasing the expression level of antigen-presenting related genes, costimulatory molecules, and IL-12P70 [94]. Therefore, it promotes the function of DCs to stimulate T cells toward anti-tumor responses [98].

It is now well appreciated that tumor cells can evade cytotoxic T lymphocytes by reducing the specific tumor antigens and MHC class I. However, NK cells seem to assist in eliminating tumors in this regard. It has been shown that paclitaxel induces mRNA transcription and protein expression of perforin in NK cells, therefore stimulating their cytotoxic ability against tumor cells [99]. However, one should bear in mind that the impact of paclitaxel on NK cells is dose-dependent as well [100, 101].

Paclitaxel also has other impacts on immune-related functions. To illustrate this, paclitaxel upregulates mannose-6-phosphate, which increases the cellular permeability to granzyme B, hence improving the cytotoxic function of T lymphocytes. It also promotes the secretion of type I cytokines, including IL-2 from $CD4^+$ T cells and IFN-γ form $CD8^+$ T cells [97, 102]. Activated $CD8^+$ T cells can further differentiate into MHC I-CTL type 1 (Tc1) secreting IFN-γ, responsible for tumor cell lysis [103]. $CD4^+$ $CD25^+$ Tregs are known to favor tumor cells by suppressing immune responses and promoting cancer progression [78]. Murine studies have demonstrated that paclitaxel diminishes both the number and the size of Tregs, enhancing the anti-tumor properties in immune cells [104-106]. Paclitaxel also diminished the expression level of Bcl-2, an anti-apoptotic agent, whereas increasing the pro-apoptotic factor, namely Bax, in Tregs, rendering them more susceptible to undergo apoptosis [107].

Furthermore, myeloid-derived suppressor cells (MDSCs), which are being labored by tumor cells to expand and to suppress immune responses, are dampened in a C57Bl/6 mice study by implementing an ultra-low dose of paclitaxel. To be precise, an ultra-low dose administration of paclitaxel stimulates the differentiation of MDSCs into DCs independent of TLR-4 [102]. Owing to the data mentioned above, altogether with the suppression of Tregs, paclitaxel can promote immune responses against tumor cells and ignite the apoptosis pathways within the these cells.

Mechanisms of paclitaxel resistance through signaling cascades and how to be tackled

Multifactor approaches and numerous genes correlate with paclitaxel resistance, yet not all are well elucidated [78]. It has been proposed that paclitaxel-resistant cells mainly contain changes in their mRNA and protein synthesis level, including numerous ribosomal genes and transcriptional factors. They also represent shifts in oxidative stress-related genes such as UGT1A6, MAOA, and CYBA, as well as in glycolysis, including ADH1A, HK1, and ENO3, and glutathione metabolism pathways [108]. Findings of a study, in which tumor cells were treated with paclitaxel and other chemotherapeutic drugs, have lent support to this proposal. In other words, the expression level of 337 genes among a total of 845 genes was changed [109]. Alterations in their gene expression profiles interfere with the drug impacts, tumor microenvironment, cellular structure, and metabolism shifts that can lead tumor cells toward resistance [78].

Moreover, due to the aggressive proliferation in cancers, new malformed vessels are constructed to meet their oxygen demand; nonetheless, their growth rate leads to oxygen depletion and hypoxia [110]. Tumor cells evolve and adapt to this microenvironment condition. Therefore, they remain alive with the potential to increase their proliferation rate, dissemination, invasion, progression [111], and diminishing their chemosensitivity [112].

This does not end here; hypoxia induces chemoresistance through changing both the genomics and proteomics profiles. In other words, oxygen depletion activates P53, inhibits apoptosis, and enhances angiogenesis through increasing VEGF and angiogenin. It also promotes the production and secretion of growth factors such as platelet-derived growth factor (PDGF), transforming factor-beta (TGF-β), and insulin-like growth factor (IGF), as well as inducing glycolysis, which altogether contribute to cell survival [112]. Tumor cells avoid apoptosis, which as discussed above, is mediated by the hypoxic tumor microenvironment and hypoxia-induced factor-1 (HIF-1), that arrests cells at G0/G1 checkpoint, rendering them resistant to chemotherapeutic drugs, including paclitaxel [109, 113]. Furthermore, other transcriptional factors like NF-KB and STAT3, which stimulate pro-inflammatory responses, cell survival, angiogenesis, cell division, and metastasis, are activated under hypoxic conditions. Besides, paclitaxel phosphorylates BCL-2, an anti-apoptotic factor, through NF-KB, which dampens apoptosis and promotes chemoresistance under hypoxic conditions [114]. It has been shown that inhibiting the activation of the over-expressed STAT3 has reduced resistance against paclitaxel [115]. Moreover, the activation of lipopolysaccharide-inducible genes, MAPK, Raf-1 kinase, PI3K, as well as increased pro-inflammatory cytokines such as TNF-α, IL-6, and IL-8 contribute to paclitaxel resistance [84, 107, 116, 117].

Drug efflux is a commonplace mechanism of chemoresistance in tumor cells treated with various chemotherapeutic drugs. Drug efflux is accomplished through ATP-binding cassette (ABC) transporters such as P-glycoprotein (P-gp). P-gp is encoded by MDR-1 and has been shown to contribute to chemosensitivity to paclitaxel [83]. It has been reported that P-gp is over-expressed in paclitaxel-resistant tumor cells [109].

In addition, tubulin-related mechanisms have been introduced to play a role in paclitaxel resistance. In one way, their intracellular concentration is reduced and they are not sufficient for paclitaxel to perform its action. On the other hand, point mutations in tubulin genes and changes in the expression level of various tubulin isotypes, such as class-III β-tubulin, contribute to paclitaxel resistance [118-120]. Fig. 2.

Gefitinib and erlotinib

Gefitinib and erlotinib mechanism of action

Tyrosine kinase inhibitors (TKIs) are non-peptide combinations prescribed orally and are structurally identical to adenosine triphosphate (ATP). They compete for the ATP-binding domains in kinases, therefore stopping the subsequent signaling transduction, which ultimately leads to apoptosis and the prevention of cell proliferation [121, 122]. Lapatinib, gefitinib, and erlotinib are representatives for TKIs. The expression level of tyrosine kinase receptors of epidermal growth factors is increased on cancer cells; therefore, gefitinib, for instance, is administered to block them. EGFRI-gefitinib prohibits cell proliferation and survival by stopping the growth signaling through EGFRs [123-125]. Gefitinib has decreased the size of thyroid tumors [126], and has had beneficial impacts on non-small cell lung cancer as well [125, 127], yet chemoresistance is inevitable [128]. Erlotinib acts through similar approaches; however, it is expensive, and chemoresistance has limited its application [129, 130]. The half-life of erlotinib is about 36 hours, and it has a high affinity for plasma proteins such as albumin and α-1 acid glycoprotein [131]. Erlotinib is mainly metabolized by cytochrome P450 (CYP)

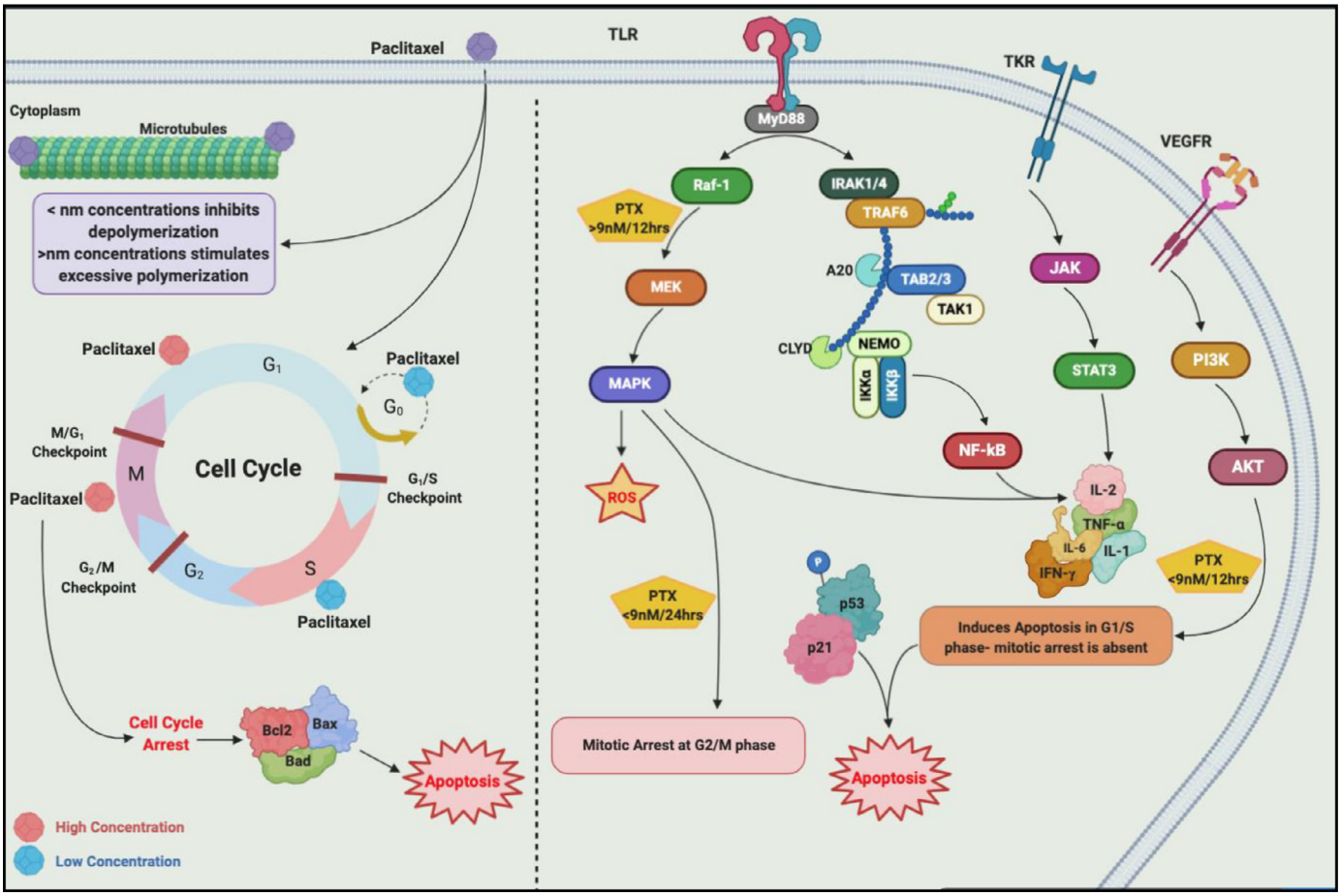

Fig. 2. Paclitaxel targets microtubules and wreck the havoc on spindles in G2, prophase, and M phase. To be precise, it increases the polymerization of β-tubulin microtubules and prevents their depolymerization, which leads to the cell cycle arrest in G2/M phase. 10 nM of paclitaxel in 12 hrs stalls the cell cycle at the S phase, and by the administration of ≥9 nM ignites the apoptosis through the activation of Raf-1, whereas, administration of ≤9 nM recruits p53 and p21. TLR-4 is involved in two manners as well. Regarding apoptosis, JNK, NF-KB, MAPK, JAK, and STAT participate, where they lead the cell's fate to apoptosis through the dephosphorylation of Bad and Bax, and through the phosphorylation of Bcl2. Regarding the immune system, through the stimulation of TLR-4, paclitaxel recruits MyD88, MAPK, NF-KB which results in the expression and secretion of IL-1, IL-6, IL-2, IL-8, TNF-α, and IFN-γ.

3A4, yet it can slightly be metabolized by CYP1A2. It has been reported that co-administration of erlotinib and a CYP3A4 inhibitor, namely ketoconazole, has enhanced the plasma level of erlotinib [132].

Mechanisms of gefitinib and erlotinib in cell death through signaling cascades

EGFRs are overexpressed in a variety of malignancies including, non-small cell lung cancer (40–80%), colorectal cancer (72–82%), head and neck cancer (95–100%), breast cancer (14–91%), and renal cell cancer (50–90%) [133]. Moreover, numerous studies proposed a cross-talk between EGFR and VEGF pathways [134].

As mentioned earlier, gefitinib and erlotinib are EGFR-tyrosine kinase inhibitors, which means that they act as an ATP antagonist and compete for their intracellular binding sites on the tyrosine kinase domain of EGFRs, therefore dampening their tyrosine kinase activity. EGFR is a 170-kDa transmembrane glycoprotein and is a member of the ErbB family, including ErbB-2/Neu/HER2, ErbB-3/HER3, and ErbB-4/HER4. These cell surface receptors contribute to cell growth regulation, differentiation, and cell survival [135]. EGFR dimerizes in either hetero or homo manner by the time their extracellular domain binds to its ligand. This dimerization allows the intracellular domains to perform their tyrosine kinase activity, which leads to the autophosphorylation of their cytoplasmic tyrosine residues. The tyrosine residues further provide a docking platform, where a variety of intracellular signaling proteins bind to and become activated, which ultimately impact the expression level of multiple genes [132, 135].

Various central downstream signaling cascades associate with EGFR activation. These cascades include PI3/Akt, Jak2/STAT3, extracellular signal-regulated kinase (ERK1,2), phospholipase C (PLCγ), Ras/Raf mitogen-activated protein, and modulation of calcium channels which inhibit apoptosis, nonetheless, promote cell proliferation, angiogenesis, metastasis, and invasion [132, 136]. Therefore, inhibiting EGFRs and their downstream signaling cascades dampen cell proliferation, metastasis, invasion, and angiogenesis, as well as the induction of apoptosis and assisting the concurrent radiotherapy treatments.

Recent somatic mutation discoveries in the ATP-binding domain of EGFR genes have shed light on achieving desired responses in EGFR-TKIs like gefitinib and erlotinib [137-139]. To be precise, frame deletion mutations in exon 19, codons 746–750, which has the frequency of 45–50% among all EGFR mutations, and missense mutations at codon 858, that lead to the substitution of leucine with arginine in exon 21 with the frequency of 35–45%, were among the most interesting mutations [139]. A population of non-small cell lung cancer that contained the aforementioned somatic mutations represented better responses subsequent to EGFR-TKIs administration [140, 141]. Recent studies have lent support that erlotinib/gefitinib responders carry at least one of these EFGR gene mutations [132].

In addition to similar functions among different TKIs, gefitinib has other impacts as well. In other words, gefitinib administration increases

the level of P27, while reduces cyclin D1 and Cdk4 during sub-G1/G1 phases in the cell cycle. Moreover, gefitinib diminishes the phosphorylation of glycogen synthase kinase-3 beta (GSK-3β), which is an AKT kinase target [142, 143]. Shreds of evidence supported that gefitinib induces apoptosis partly through an increased level of P38 MAPK, dephosphorylation of FOXOs with a successive enhanced level of P27, and increasing the expression of caspase 3 and BIM [143-145]. Besides, mTOR signaling has been reported to be down-regulated following gefitinib administration [146].

Mechanisms of gefitinib and erlotinib resistance through signaling cascades and how to be tackled

Most patients develop resistance against TKIs within just a year. Although some mechanisms have been discovered so far, many others have remained elusive.

Dysregulated microRNAs are shown to contribute to TKI-chemoresistance [147]. To be precise, for instance, miR-21 is dramatically overexpressed in erlotinib-resistant non-small cell lung cancer, which gives rise to the downregulation of PTEN and PDCD4, leading to an increased cancer progression and proliferation through the activation of AKT [148, 149]. However, the tumor-suppressive miR-34 is shown to be downregulated in TKI-resistant cancers, including those which were treated with erlotinib. MiR-34 has been overexpressed alone or in concurrence with erlotinib administration to resensitize tumors and promote cell cycle arrest [147]. Interestingly, it is now well established that miR-147b can stimulate resistance against even the third generation of EGFR TKIs, namely osimertinib, through altering the TCA cycle [150]. Moreover, miR-17-5p and miR-641 are also involved in erlotinib resistance. It has been shown that the overexpression of miR-17-5p resensitizes tumor cells to erlotinib through EZH1 in non-small cell lung cancer [151]; nonetheless, the overexpression of miR-641 works in favor of erlotinib resistance via the downregulation of NF1 [147]. A.S Pal, et al. have firmly demonstrated that miR-5693, miR-3618, and miR-432-5p regulate erlotinib resistance and drug efflux. Besides, miR-5693, miR-3618, and miR-432-5p were evaluated in the presence of other EGFR TKIs, including gefitinib and afatinib. Interestingly, they have significantly promoted cell proliferation and cancer progression in the presence of these TKIs [147].

Recent studies have demonstrated that the stimulation of epithelial-mesenchymal transition (EMT) promotes resistance to EGFR TKIs [152, 153]. It is well appreciated that EMT is triggered by the activation of the transforming growth factor-beta (TGF-β) pathway, which seems to be one of the main drivers of tumor invasiveness and metastasis by inducing migration in various cancers, such as lung malignancies. To illustrate this, TGF-β ligands bind to the TGF-β receptor complex, which is constructed from TGF-βRI and TGF-βRII. After that, the receptor phosphorylates and activates Smad2 and Smad3, which further construct a transcriptional complex with Smad4, that, accompanying other transcriptional factors, can stimulate the expression of tumor-progression related genes [154]. Therefore, a high expression level of TGF-β contributes to tumor expansion, proliferation, and metastasis [155]. It has been envisaged that EGFR TKIs can dampen TGF-β-induced cell movements [156]. Therefore, Serizawa et al. have shown that administration of TGF-β inhibitors, namely LY364947, along with EGFR TKIs such as erlotinib and gefitinib, dampens the progression and invasion of EGFR TKI-resistant cancer cells [157].

In addition, integrins have been reported to be involved in erlotinib-resistant cancers. Kanda et al. have represented that all resistant cells showed an increased level of β1, α2, and α5 integrins. Furthermore, they illustrated that using siRNA, in order to knockdown integrin β1, they could resensitize malignant cells to erlotinib, in which Akt phosphorylation was thoroughly dampened after the administration of erlotinib. This notion signifies the fact that silencing integrin β1 alleviates erlotinib-chemoresistance. Nevertheless, silencing α2 and α5 integrins resulted in moderate inhibition of Akt phosphorylation in these cancers. Moreover, the expression level of integrin α5 was also downregulated when silencing integrin β1, suggesting a link between integrin β1 and α5. Altogether these findings signify the role of integrins in erlotinib-chemoresistance [158].

In addition, ras-associated binding protein-25 (Rab25) mediates EGFR TKI-resistance in non-small cell lung cancer. In this regard, Wang et al. have reported that the overexpression of Rab25 stimulated resistance against erlotinib. To be precise, Rab25 interacts with integrin β1, which facilitates its migration toward the membrane, where it induces the phosphorylation of Akt. It further triggers the activation of the Wnt/β-catenin signaling cascade and promotes cell proliferation and cancer progression. They also represented when silencing Rab25, Wnt/β-catenin and Akt-related signaling cascades were dampened, which resensitized cancer cells to erlotinib [159].

The activation of EGFR downstream cascades correlates with gefitinib resistance as well [160]. The hyperactivation of the MAPK pathway, especially P42-MAPK, contributes to the intrinsic and acquired resistance in breast cancer models. Therefore, inhibition of cell proliferation and induction of apoptosis were witnessed by dampening MAPK-related pathways [161, 162]. Interestingly, some studies have indicated a transcriptional role for gefitinib, which is accomplished by increasing the expression of HER-specific ligands and augmenting the importation and nuclear accumulation of an HER ligand, namely neuregulin [163]. Moreover, some results demonstrated the upregulation of PI3K, which results from a non-functioning PTEN, as another reason underlying gefitinib resistance. In other words, in studies carried out on subtypes of breast cancer overexpressing EGFR, but without PTEN activity, gefitinib terminated the phosphorylation of EGFR and MAPK, leaving AKT intact. However, regarding the cell populations subjected to gefitinib with restored-function PTEN, the phosphorylation of AKT, GSK-3β, and translation repressor protein 4EBP1 were dampened. They were also resensitized to gefitinib and were arrested at the G1 phase [164-166].

Other pathways related to the interaction between EGFRs and hepatocyte growth factor receptor (MET) also correlate with gefitinib chemoresistance. MET is a tyrosine kinase receptor that increases the phosphorylation of EGFR through the activation of c-Src kinase; therefore, it is involved in breast cancer progression and gefitinib resistance. It has been shown that, by inhibiting MET in HER-2 positive and EGFR-overexpressed breast cancers, cell proliferation was dampened, and cells were resensitized to gefitinib [167]. Furthermore, The interplay between EGFRs, G-coupled protein receptors (GCPRs) [168], K-RAS —an EGFR-downstream executioner— [169], and EGFR mutations have all been reported to be involved in erlotinib-, gefitinib-resistant lung cancer, breast cancer [170], and adenocarcinomas [171, 172]. Fig. 3.

Gemcitabine

Gemcitabine mechanism of action

2′,2′-difluoro-2′-deoxycytidine (dFdCTP), which is known as gemcitabine, acts as the analog of deoxycytidine during a process called “masked chain termination” [173]. Implementing the dFdCTP enables its substitution with typical nucleoside, therefore stopping the DNA polymerase movements and DNA duplication. Nonetheless, DNA repair mechanisms fail to detach gemcitabine from the DNA strands [174].

The second mechanism that gemcitabine acts through is by empowering its ability to inhibit crucial enzymes in deoxynucleotides metabolism. Deoxycytidylate deaminase (dCTD), a member of these enzymes, is inhibited directly and indirectly by dFdCTP and dFdCDP, respectively. To be precise, dFdCDP binds covalently to the active sites of ribonucleotide reductase (RR), impeding the conversion of ribonucleotides into deoxynucleotides, which results in dNTP pool shortage. This shortage consequently leads to a diminished activity in dCTD. Moreover, deoxycytidine kinase (dCK) is modulated by dCTP; therefore, diminished-dNTP pool stimulates dFdC phosphorylation through the activation of dCK, which ultimately increases the level of dFdCTP and its interference within the DNA structure [175-178].

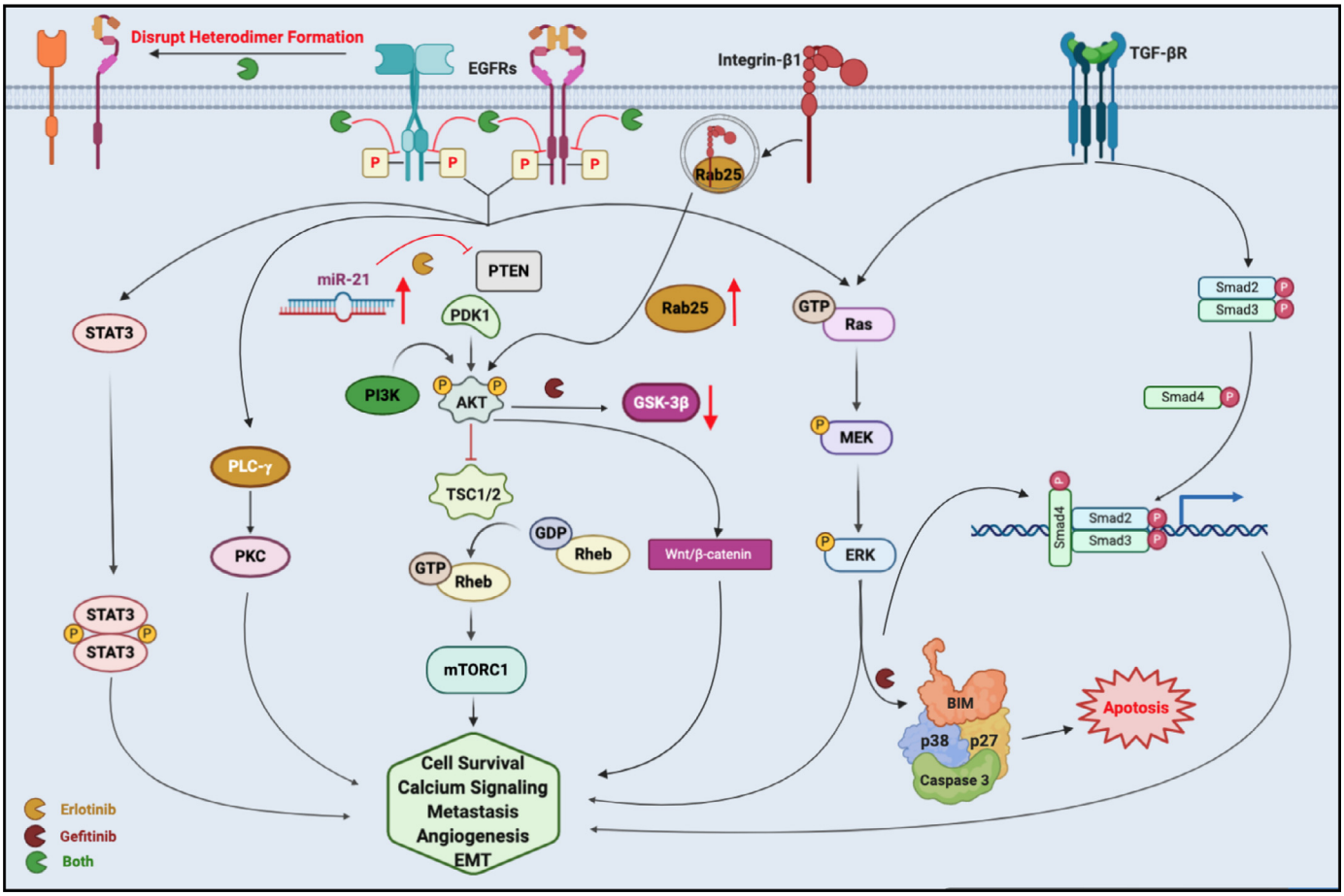

Fig. 3. Tyrosine kinase inhibitors (TKIs) are similar to ATP, hence they compete for ATP-binding domains in kinases of EGFRs. They inhibit PI3K/Akt, JAK/STAT, PLCγ, and Ras/Raf, therefore they are able to ignite apoptosis machinery in the absence of the aforementioned pathways. Gefitinib also increases the level of p27 and induces p38-MAPK as well which give rise to apoptosis. One major signaling that cells develop resistance against EGFR TKIs is through TGF-β signaling. Recruiting Smads 2,3, and 4, it stimulates cell survival and EMT. Moreover, Rab25 which has close interplay with integrin β1 correlates with TKI resistance. To be precise it phosphorylates Akt and ultimately assists survival and proliferation signaling cascades.

Moreover, caspase signaling cascades are the third mechanism of action leading to cell apoptosis that has been defined for gemcitabine [179, 180].

Gemcitabine is among the most energetic chemotherapeutic drugs with a wide range of prescription for numerous malignancies, including bladder cancer [181], pancreatic cancer [182], non-small cell lung cancer [183], and breast cancer [184]. There have been promising results for approval of gemcitabine for ovarian cancer. Needless to mention that, it has fewer side effects and toxicity in comparison to the other chemotherapeutic agents, hence suggesting gemcitabine as a better option for chemotherapies [173]. However, the responses are not always satisfying, which brings about the demand for developing new approaches in its application, like combination chemotherapy, or even develop new regimens.

Mechanisms of gemcitabine in cell death through signaling cascades

Interestingly, gemcitabine activates p38 mitogen-activated protein kinase (MAPK), which ignites apoptosis in cancer cells, leaving normal cells intact [185, 186]. Besides, gemcitabine activates MAPK-activated protein kinase (MK2), which induces the phosphorylation of heat-shock protein-27 (HSP-27), resulting in the suppression of tumor cell growth [187].

There have been pieces of evidence representing that the S-phase checkpoint is activated and slowed due to the breaks and lesions in DNA replication after gemcitabine treatment [188, 189]. Typically, as the replication comes to a halt, probably due to a break in DNA, the ataxia-telangiectasia mutated kinase (ATM) and checkpoint kinase 2 (Chk2) are activated, which manage the cell cycle arrest, apoptosis, and DNA repair. Besides, when there is a DNA lesion, the ataxia-telangiectasia mutated and Rad3-related kinase (ATR), checkpoint kinase 1 (Chk1), and Rad9-Hus1-Rad1 (9-1-1 complex) are activated that inhibit cell cycle progression, stabilize the replication fork, and induce DNA repair mechanisms by the assist of Rad17 and replication factor C [190, 191]. The criteria mentioned above argue that gemcitabine administration leads to cell cycle arrest initially; however, ATM facilitates the cell cycle progression independent of p53. Supporting this idea, Larry et al. showed that ATM depletion sensitizes tumors toward gemcitabine [189].

Mechanisms of gemcitabine resistance through signaling cascades and how to be tackled

Similar to any other chemotherapeutic drugs, tumor cells develop either intrinsic or acquired chemoresistance against this gemcitabine. Gemcitabine has been the first-line treatment for pancreatic cancer. However, one major obstacle toward tackling pancreatic cancer is the extensive desmoplastic reaction, which constructs approximately 90% of the tumor mass. Desmoplastic reaction accounts for poor drug delivery and innate-gemcitabine chemoresistance in pancreatic cancer cases [178, 192]. Besides, Hedgehog (Hh) signaling has been shown to play a distinct role in gemcitabine chemoresistance. Hh signaling correlates with morphogenesis [193], tumorigenesis, desmoplastic reaction, and the alteration in extracellular matrix construction [194, 195]. In this regard, genetic analyses were accomplished to locate frequent mutations

in pancreatic tumors. Hh is the most genetically shifted signaling in this cancer [196]. Interestingly, Olive et al. have shown that by inhibiting the Hh signaling in mice, they could increase the intratumor drug delivery up to 60% [197].

Moreover, the activation of MK2 plays an essential role in apoptosis induction after gemcitabine administration. A study carried out by Cöpper et al. has shown that the translesion polymerase activity has inhibited the activation of MK2, which ultimately facilitated osteosarcoma survival [198].

Since a successful drug delivery is the first step toward achieving desired chemotherapy responses, any disturbances or dysfunctions in this process might facilitate chemoresistance. In this regard, studies have represented that a low level of hENT1, which is the primary transporter of gemcitabine, is associated with gemcitabine resistance and a low survival rate among pancreatic cancer patients [199, 200].

It is well appreciated that gemcitabine is a prodrug that needs to be processed by dCK. There has been evidence that loss of dCK mRNA in ovarian and pancreatic cancer cell lines was associated with gemcitabine resistance [201, 202].

Besides, ribonucleotide reductase (RR) is a holoenzyme formed of RRM1 and RRM2 and has been shown to downregulate the gemcitabine activity. There have been shreds of evidence indicating that an increased level of these subunits is associated with gemcitabine resistance [203-205].

Transcription factors are responsible for gemcitabine resistance as well. One of them is high mobility group A1 (HMGA1), which are framework-related transcription factors that modulate various genes and are escalated in various tumors [206]. Moreover, NF-KB is the other transcription factor that is related to gemcitabine resistance. Arlt et al. represented that among five different pancreatic cancer cell lines, resistant cell lines, including BxPc-3, Capan-1, and PancTu-1, have displayed an overexpressed level of NF-KB [207]. Gemcitabine resistant cells exhibiting overexpressed NF-KB might have correlations with the impact of Apurinic/apyrimidinic endonuclease 1/redox factor-1 (APE1/Ref1) on the activation of transcription factors such as NF-KB [208]. Moreover, NF-KB has been shown to assist gemcitabine resistance by inhibiting the expression of hCNT1, a nucleoside transporter, in pancreatic cancer cell lines [209]. Excessive cellular accumulation of NF-KB targets hypoxia-inducible factor 1-α (HIF-1α) that contributes to gemcitabine resistance. Firstly, HIF-1, a transcription factor that plays a role in angiogenesis, invasiveness, metastasis, and chemoresistance in tumors [210]; secondly, there has been related evidence that HIF-1α down-regulates hENT1 and hENT2 [211, 212]. There are also other mechanisms that both NF-KB and HIF-1α might act through, ultimately resulting in gemcitabine resistance. To illustrate this, CXCL12/CXCR4 downstream pathway stimulates cell survival and proliferation factors, such as NF-KB [213]. Solid witnesses claim that CXCL12/CXCR4 interaction gives rise to gemcitabine resistance by promoting PI3K/Akt, extracellular-signal-regulated kinase (ERK), and focal adhesion kinase (FAK) in pancreatic cancer cells [214]. What is more, gemcitabine induces the expression of CXCR4 through NF-KB and HIF-1α, which leads to increased invasiveness in pancreatic cancer cells [215]. This is in accordance with other experiments reporting that low doses of gemcitabine stimulate the expression of NF-KB in non-small cell lung cancer and pancreatic cancer [207, 216]. Besides, reports show that CXCL12/CXCR4 downstream pathway promotes Hh signaling through NF-KB [217]. Altogether creates a cycle that facilitates cancer cell survival via NF-KB signaling, perhaps the key player in gemcitabine resistance.

Besides, Nagano, et al. have represented that miRNA-29a induces gemcitabine resistance through Wnt/β-catenin in pancreatic cell lines [218]. Wnt/β-catenin signaling pathway contributes to cell differentiation, cell proliferation, the onset of numerous malignancies, and chemoresistance [218-220]. Studies have demonstrated that roughly 65% of pancreatic cancer patients display activated Wnt/β-catenin signaling, which helps generate chemoresistant cancer stem cells [221-223]. Lately, Kapinas et al. has shown that Wnt/β-catenin is activated through Dikkopf-1 (Dkk1), Kremen2, and secreted frizzled-related protein 2 (sFRP2) by miRNA-29a [224].

As mentioned earlier, gemcitabine is the best option for pancreatic cancer treatment [182]. However, due to the central-tumor hypoxic condition, chemotherapy responses are not satisfactory. Hypoxia is associated with poor prognosis, chemo- and radio-resistance, metastasis, and apoptosis inhibition [225]. PI3K, Akt, and MAPK as vital downstream signaling pathways associated with cell proliferation, cell migration (metastasis in this regard), inhibition of apoptosis, and responding to the growth factors, are phosphorylated and activated under hypoxic condition [226, 227]. Yokoi et al. have shown an enhancement in the DNA-binding activity of NF-KB and in the activation of PI3K/Akt and MAPK under hypoxia, which leads to gemcitabine resistance in L3.6pl cells, nonetheless, by inhibiting PI3K using PKI166, they were able to induce apoptosis in this cell population [228].

Another factor associated with gemcitabine resistance is Annexin II. There has been evidence arguing that the overexpression of Annexin II is related to tumor relapse in pancreatic cancer patients receiving gemcitabine; nevertheless, by inhibiting Annexin II, the toxicity of gemcitabine has increased [229]. Besides, Kagawa et al. have demonstrated that Akt/mTOR signaling is involved in Annexin-II-related gemcitabine resistance, to say the least [230]. Fig. 4.

Doxorubicin

Doxorubicin mechanism of action

Doxorubicin is a non-selective class-I anthracycline chemotherapeutic agent that contains aglyconic and sugar components. It binds to the plasma protein carriers and enters its target cell through passive diffusion subsequent to its administration, where it further accumulates intracellularly. After that, it mainly traffics into the nucleus excelling its cytosolic concentration [6]. It is mainly prescribed for breast, bladder, stomach, lung, ovaries, thyroid cancers, and soft tissue sarcoma [231].

Although its mechanism of action is elaborate, it is proposed to act as an anti-cancer agent through two main mechanisms. a) Doxorubicin interferes with DNA, and in a process known as intercalation, dampens the biosynthesis of numerous macromolecules as well as disrupting the progress of topoisomerase II. In other words, doxorubicin stabilizes the DNA following the DNA breaks created by topoisomerase II, therefore stops the release of the DNA double helix, which further prohibits the DNA replication [232]. b) Doxorubicin stimulates free radicals which further triggers damages in DNA, proteins, and membrane [231].

Mechanisms of doxorubicin in cell death through signaling cascades

Doxorubicin is oxidized into an unstable metabolite, namely semiquinone, a process in which the reactive oxygen species (ROS) are generated. ROS damages organelle membranes, DNA, and proteins, to say the least. It also causes oxidative stress, increases the alkylation and lipid peroxidation [231], and induces apoptotic pathways [233]. For instance, The apoptotic pathway is triggered when cells fail to repair the damaged DNA, which leads to cell cycle arrest in the G1 and G2 phases [231].

Moreover, doxorubicin induces autophagy in response to DNA damage. The activation of the nuclear enzyme, namely poly (ADP-ribose) polymerase-1 (PARP-1), is known to be crucial in order to determine whether cells undergo autophagy or not. DNA stresses can stimulate PARP-1 hyperactivation, which further results in the shortage in NAD^+ and ATP resources. Consequently, cells would experience energy-resource depletion, which leads them toward apoptosis, providing that it is irreversible [234]. These findings reinforce that the normal-dose administration of doxorubicin, but not in high-dose, directs cells toward autophagy and necrosis due to the cellular energy collapse subsequent to PARP-1 hyperactivation [231].

Besides, doxorubicin stimulates the activation of AMP-activated protein kinase (AMPK). This activation is accomplished by activating ROS-dependent liver kinase B1 (LKB1), which supplies AMPK with neces-

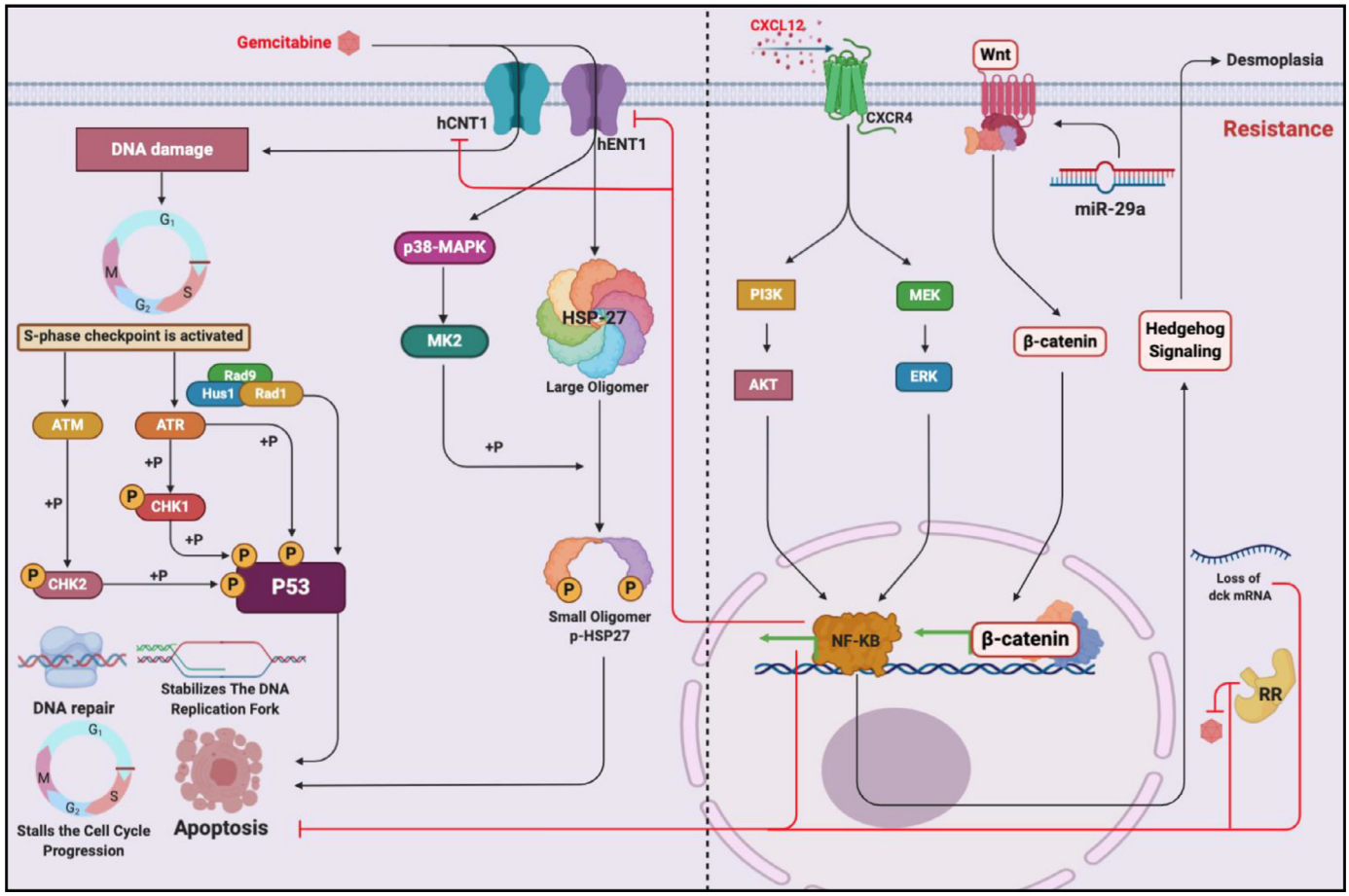

Fig. 4. By the time gemcitabine is administered, it activates p38-MAPK that ignites apoptosis through MK2 and phosphorylation of HSP-27. Moreover, due to the DNA damage caused by gemcitabine, S phase checkpoint is activated, ATM/Chk2 and ATR/Chk1 are recruited which altogether with the company of 9-1-1-complex phosphorylate and activate p53. Regarding resistance, desmoplastic reaction seems to be accomplished through Hh signaling which accounts for poor drug delivery. RR also has been shown tot attenuate the activity of gemcitabine. Furthermore, CXCL12/CXCR4 stimulates PI3K/Akt, ERK, and NF-KB which along with Wnt/β catenin decreases the efficiency of gemcitabine therapy.

sary upstream signals [6]. Activated AMPK stimulates the activation and phosphorylation of serine 15 in P53, which further triggers apoptosis in B16 melanoma cells [235]. Therefore, AMPK induces cell death pathways through activating JNK kinase in liver and insulin-secretor β-Langerhans cells [236, 237].

Moreover, studies on MCF-7 have shown that doxorubicin diminishes the concentration of Bcl-2, an anti-apoptotic agent, whereas it enhances the amount of Bax, which acts against Bcl-2 [238]. It was first conjectured that doxorubicin decreases the mRNA level of Bcl-2 in a P53-independent manner. However, according to MCF-7 studies [238], it has been suggested that doxorubicin impacts the expression level of Bcl-2 through P53, owing to the fact that the ratio of Bcl-2/Bax must be altered in order for caspases to be activated [6].

Besides, some argued that doxorubicin acts partly through recruiting some components in Fas/Fas-ligand apoptotic pathway; nonetheless, others provided contradictory outcomes [239, 240].

Mechanisms of doxorubicin resistance through signaling cascades and how to be tackled

Autophagy can either stimulate or dampen chemoresistance, depending on the tumor's nature, the drug properties, the treatment duration, and how drugs influence metabolic stress [6]. The high mobility group box 1 protein (HMGB1) is a crucial regulator of both selective and non-selective autophagy. It also plays a critical role in DNA replication and DNA repair mechanisms [241]. Different studies indicated that tumor cells become sensitive to doxorubicin by the time both autophagy and HMGB1 are blocked, meaning that HMGB1 contributes to doxorubicin resistance during tumor progression. In other words, subsequent to doxorubicin administration, the mRNA and protein levels of HMGB1 are enhanced. Besides, HMGB1 competes with Bcl-2 in binding to BECN1; therefore, establishing the BECN1-PtdIns3KC3 complex induces autophagosome formation and triggers autophagy. Moreover, the upstream signal, namely ULK1-mATG12-FIP200, is required for the interplay between HMGB1 and BECN1 [6].

Ceramides also have provoked interest in contributing to doxorubicin resistance. Ceramide is known as a cellular lipid messenger and plays a distinct role in regulating doxorubicin-induced cell death. Results indicate that doxorubicin induces the cellular level of ceramides, resulting in the upregulation of glucosylceramide synthase (GCS). Increased glycosylation of ceramides and cellular stress caused by doxorubicin administration results in cellular drug resistance. Possible mechanisms in which doxorubicin increases the level of ceramides remains elusive to some part; nonetheless, some believe it is either accomplished through activating enzymes responsible for ceramide synthesis or by stimulating sphingomyelinase [242].

Furthermore, it has been reported that doxorubicin resistance in melanoma cells is considerably modulated through ABCB8, which seems to play a role in the preservation of the mitochondrial genome; nevertheless, the exact mechanisms are yet to be discovered. It is worth mentioning that, although ATP-binding cassette (ABC) proteins are involved in numerous chemoresistant tumors, ABCB8 is explicitly involved in doxorubicin resistance, but not in other chemotherapy agents. It has been

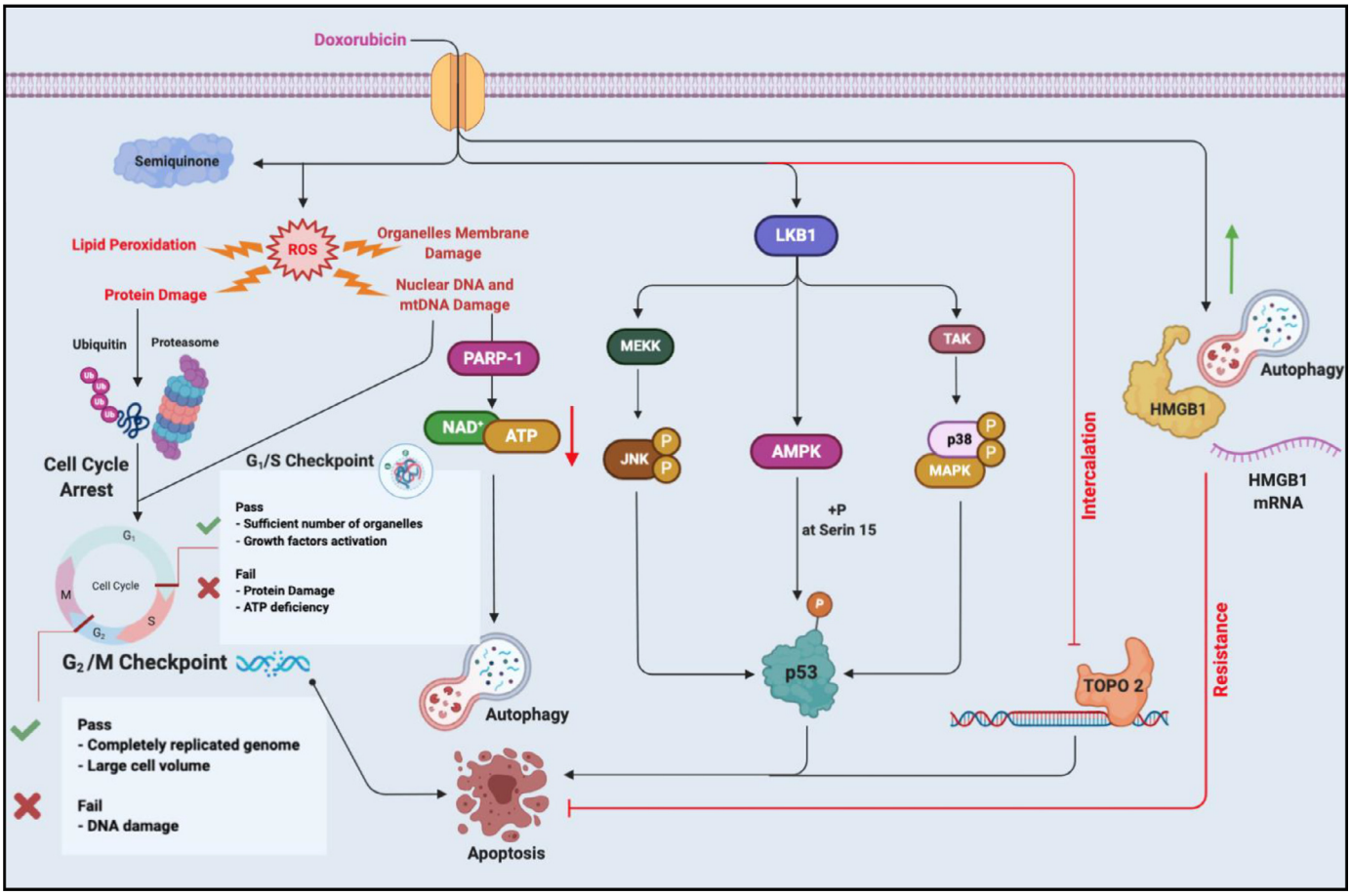

Fig. 5. Doxorubicin forms adducts with Topoisomerase and DNA in a process, namely intercalation. When entered in to the target cell, DOX is oxidized into semiquinone which ROS are generated in its process. ROS further, causes lipid peroxidation, organelles' membrane damage, DNA damage, and protein damage. Following the DNA damage PARP-1 is activated which leads cell toward either autophagy (providing that ATP and NAD^+ resources are low), or G1/S arrest and apoptosis. Protein damages also lead to G2/M arrest which gives rise to apoptosis. Moreover, DOX can phosphorylate and activate p53 through JNK,AMPK, and p38-MAPK. However, increase in the protein or mRNA level of HMGB1 attenuates apoptosis and favors cell survival and resistance.

reported that ABCB8 knockdown using specific shRNA could diminish doxorubicin resistance [243, 244]. Besides, other ABC transporters have been shown to partially correlate with doxorubicin resistance including, ABCB1 (MDR1, Pgp) [245] ABCC1 (MRP1) [246], as well as ABCC2, ABCC3, ABCG2, and RAPBP1 [247-249].

Besides, replication of the TOP2A gene is the other defined mechanism in doxorubicin resistance [250]. The amplification of this gene has been reported to influence doxorubicin response [251, 252]. Interestingly, TOP2A has a neighboring interplay with HER-2, a marker for breast cancer progression and chemotherapy response. It is now clear that the amplification of HER-2 also impacts doxorubicin response [252]. Fig. 5.

Etoposide

Etoposide mechanism of action

By and large, etoposide is an anti-topoisomerase II and a semi-synthetic podophyllotoxin derivative agent that interrupts DNA replication and other mechanisms, in which topoisomerase II is required including, chromatin remodeling, DNA transcription, and DNA repair. Two essential transesterification reactions enable topoisomerase to create a transient break within the double helix strain. The tyrosine motif at the active site of the enzyme establishes a covalent bond with one phosphate residue within the DNA backbone, resulting in a temporary interruption in DNA strain integrity during the first step. The second reaction takes place to re-ligate the double helix by releasing the DNA break. The cleaved double-helix DNA resulting from the first reaction is temporary; however, it can be stabilized using toxic agents [253].

Etoposide is one of the recommended agents, which poisons the topoisomerase-II cleavage complex (TopoIIcc) and prevents the second transesterification reaction, namely re-ligation. To be precise, etoposide has a low affinity toward naked DNA, whereas it shows a high affinity toward the Topo-II-DNA complex by stabilizing the short-term-topoisomerase-cleaved DNA. Topoisomerase II has two isotypes, namely Topo-IIα and Topo-IIβ. Topo-IIα serves cell cycle events such as DNA replication, DNA repair, and chromosome segregation; nonetheless, Topo-IIβ is mainly involved in transcription and developmental progression [254-257]. Etoposide interferes with specific amino acid residues within the structure of both isotypes of topoisomerase to enter the Topo-II-DNA complex as a Topo-inhibitor [258, 259].

Moreover, it has been recently reported that etoposide has a high affinity toward histones and chromatin, which brings about other possible mechanisms of action [260].

Additionally, it has been reported that etoposide has other impacts on replication machinery as well. In other words, the distribution of replication proteins undergoes a progressive impact by etoposide during the S phase. This spreads the replication sites along the DNA strain, creating huge nuclear foci containing single-strand DNA binding protein RPA [261].

There is also another mechanism of action for etoposide, in which it can negatively impact the transcription of some specific genes. Takami, et al. have revealed that transcription factor E2F-4 binds to etoposide,

leading to the downregulation and inhibition in the transcription of some genes mediated by the heterodimeric E2F-4/DP complexes in the nucleus [262].

Mechanisms of etoposide in cell death through signaling cascades

A 5′-phosphodiesterase has been identified that can excise the Topo-II-DNA bonds and repair topoisomerase-mediated DNA damages [263]. To illustrate this, TRAF and TNF receptor-associated protein (TTRAP), which has recently been renamed to TDP2 (tyrosine phosphodiesterase 2), is an Mg^{2+}/Mn^{2+}-dependent member of the phosphodiesterase group, enabling the religation of 5′-phosphate residues in the cleaved double helix strain. It has been demonstrated that TDP2 depletion leads to an increased cellular sensitivity to etoposide-induced double-strand breaks [264, 265], therefore, suggesting the possible contribution of TTRAP/TDP2 in etoposide chemotherapeutic response [263].

Besides, Adachi, et al. have demonstrated that the low-fidelity non-homologous end-joining (NHEJ) is the primary pathway in which cells repair the etoposide-induced DNA damage through [266]. In other words, cells repair DNA damages through various pathways based on the different cell cycle phases that the damage has occurred in [267]. For instance, G1 damages are repaired through NHEJ, whereas those in the S and G2 phases are repaired by homologous recombination (HR). It has been shown that dampening the NHEJ pathway via knocking out the DNA ligase IV and Ku70 subunit ($LIG4^{-/-}$, $Ku70^{-/-}$) in DT40 cells makes them severely sensitive to etoposide. However, $RAD54^{-/-}$ (a DNA repair and recombination protein) knocked-out, as HR-defective cells, are much less sensitive toward etoposide [253, 267]. Malik et al, have lent support to this idea by representing the importance of Ku70 and Ku80 existence for NHEJ and cell survival after etoposide treatment [268]. Furthermore, Chen and colleagues have also acknowledged that dysfunctional Ku70 decreases the DNA repair capacity in cells exposed to etoposide earlier. Moreover, they have mentioned the impact of Ku70 acetylation in histone deacetylase (HDAC) inhibitors. To be precise, Ku70 mutations are shown to mimic the acetylation of some lysine residues, rendering Ku70 unable to bind DNA, which ultimately makes prostate cancer cells more sensitive to etoposide [269].

In addition, etoposide stimulates the activation of ataxia-telangiectasia mutated (ATM) and its downstream kinase, namely checkpoint kinase 2 (Chk2). The activation of ATM kinase consequently causes the construction of the Mre11/Rad50/NSB1 (MRN) complex and ionizing radiation-induced foci (IRIF), which altogether signify severe DNA damages [270]. ATM mutations lead to etoposide hypersensitivity. Besides, loss of G2/M checkpoint in AT cells allows mitosis to occur, although DNA breaks and chromosomal abnormalities have happened following etoposide administration [271, 272].

Furthermore, etoposide administration increases the interaction between transcription factor E2F1 and bridging integrator-1 (BIN1) promoter. It has been shown that dampening BIN1 using an antisense-RNA diminishes the cell-death rate mediated through the interaction of E2F1 and etoposide [273].

Moreover, the alternative splicing mechanism is also affected by etoposide. Etoposide treatment stimulates the dephosphorylation of serine/arginine-rich splicing factor-1 (SRSF1), a splicing element, which monitors and regulates whether the anti- or pro-apoptotic genes such as Ron oncogene and tumor suppressor BIN1 should be alternatively spliced. Moreover, alteration in the phosphorylation of SRSF1 subsequent to DNA damages alters the alternative splicing pattern in caspase 9. This signifies the active influence of etoposide on alternative splicing mechanisms and its correlation with the modulation of apoptosis in target cells [274-277].

Various studies have supported that high concentrations of etoposide stimulate cytochrome *C*-caspase-9-mediated pathways. Activating Apaf1, it constructs an apoptosome complex capable of cleaving procaspase 9 into the active caspase 9, which ultimately leads to cellular apoptosis through the cleavage and activation of caspase 3 and 7 [278].

Moreover, new pieces of evidence signify the correlation of Fas/FasL in etoposide-related apoptosis [279]. To illustrate this, etoposide administration induces the interaction between FasL and its receptor, namely FasR, resulting in the construction of a death-inducing signaling complex (DISK), where FADD activates pro-caspase 8 into functional caspase 8, which further activates caspase 7.

Etoposide also triggers DNA damage responses (DDRs) in tumor cells and resting cells like T lymphocytes. ATM is phosphorylated in this regard, which results in the phosphorylation of H2AX and p53. Ultimately, this leads to the activation of a pro-apoptotic protein, namely p53-upregulated modulator of apoptosis (PUMA). It has been reported that inhibition of ATM functions in dormant cells, using Ku55933, dampens DDR and apoptosis by diminishing the expression level of PUMA and decreasing the activation of caspases, whereas performing the same procedure in tumor cells increases the cytotoxic impact of etoposide [280].

It should be noted that p53 plays a distinct role in etoposide-induced cell apoptosis. To be precise, Nemo-like serine/threonine kinase (NLK) is essential for the activation of p53 following the DDR caused by etoposide administration [281]. Although the exact mechanism is still elusive, NLK is upregulated subsequent to DDR. NLK stabilizes p53 through the inhibition of protein degradation mediated by Double minute 2 (MDM2) and ubiquitin-proteasome system [281, 282]. It has also been suggested that NLK enhances the cellular sensitivity to etoposide through dampening some transcriptional factors such as NF-KB [283, 284].

Furthermore, studies have shown that etoposide treatment induces some stress pathways, including JNK and MAPK. These pathways are supposed to have double-edged functions in anti- and pro-apoptotic pathways. WWOX is an oxidoreductase and a tumor suppressor that acts through stabilizing p53, resulting in cell death. It has been reported that WWOX is increased following the etoposide-induced DDR [285].

Mechanisms of etoposide resistance through signaling cascades and how to be tackled

Likewise other chemotherapeutic regimens, chemoresistance is one of the complications during etoposide treatment. MDM2 gene, which encodes ubiquitin ligase involved in protein degradation, contributes to etoposide resistance. In other words, a single-nucleotide polymorphism, known as SNP 309 T/G, that is located within the MDM2 promoter causes its upregulation, which results in a diminished response to numerous DNA-damaging drugs such as etoposide. It has been reported that homozygote-SNP309 cell lines are etoposide resistant. MDM2 in these cell lines represented an increased affinity toward binding and degrading Topo-II. Furthermore, by the time MDM2 was knocked-down by RNAi, Topo-II was stabilized, and etoposide resistance was decreased [286].

Furthermore, Zhang, et al. have reported that a proteasome-mediated degradation procedure is involved in etoposide resistance. Using knock-out-Topo-IIβ mice, and knock-down-Topo-IIβ, they have represented that etoposide-mediated DNA damages were attenuated by MG132 dampening proteasome [287].

Shreds of evidence have indicated the correlation of MAGE family proteins with regulating cell survival. It has been reported that MageA2 recruits HDACs to the P53 transcription sites, which stimulate histone hypoacetylation, therefore, suppressing its activity in melanoma cells. Hence, melanoma cells expressing MAGE-A genes are resistant to etoposide-induced apoptosis [253, 288].

Shreds of evidence suggest that etoposide is also involved in autophagy. Katayama et al. have represented the feasibility of autophagy-dependent ATP production in glioma cells. Surprisingly, not only it does not kill them, but also it favors their survival; therefore, it might contribute to etoposide resistance [289]. It has been indicated that this crisis is irreversible even when cells experience glucose starvation. Nonetheless, it can be inhibited by the preincubation with autophagy inhibitor 3-methyladenine (3-MA), mitochondrial inhibitor oligomycin, as well as through the siRNA-mediated downregulation of beclin 1, which reduce

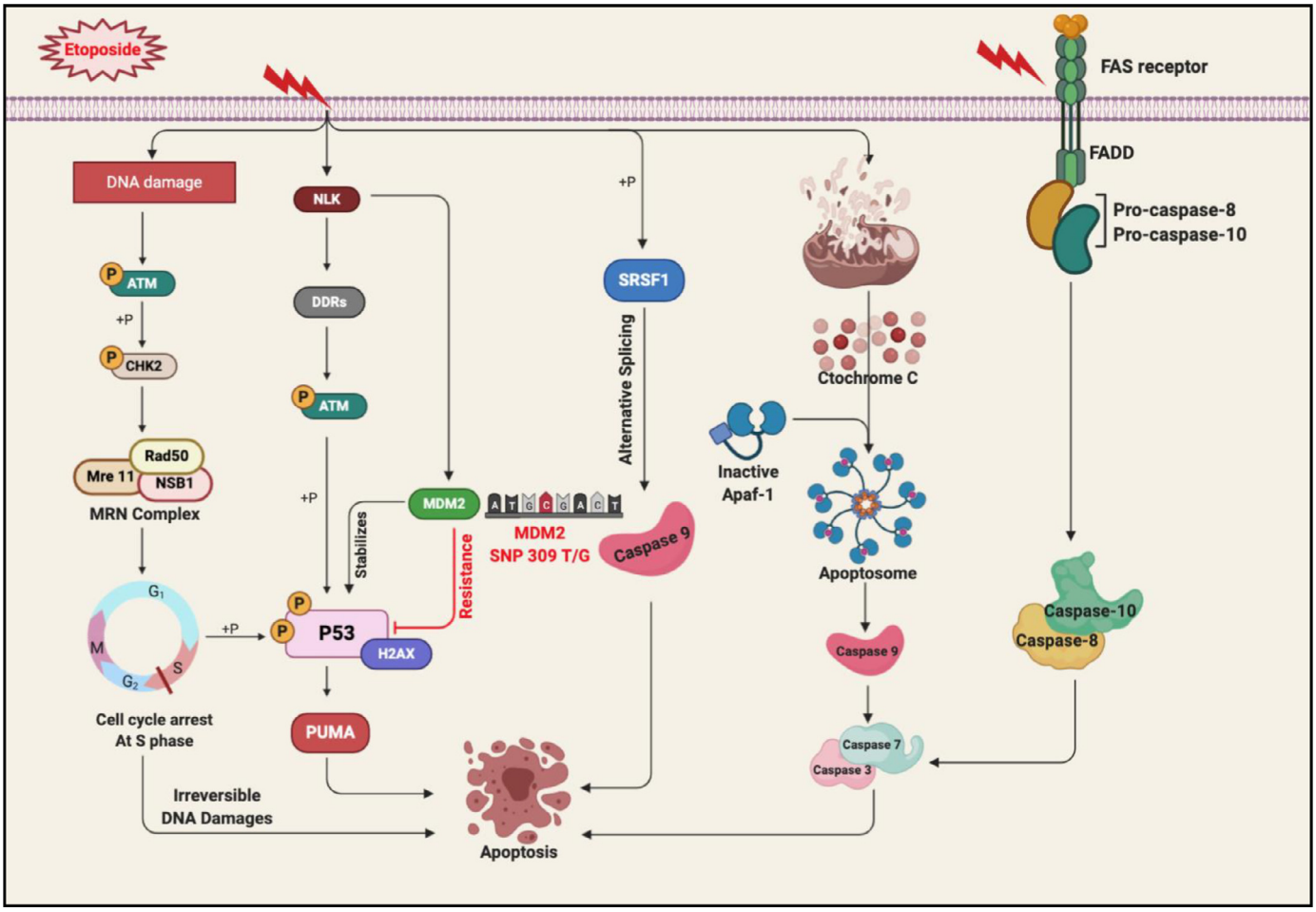

Fig. 6. Etoposide, an anti-topoisomerase II agent, poisons the TopoIIcc and prevents the religation of DNA strands. Following the persistent DNA damage caused by etoposide, ATM/Chk2 are recruited that by the assist of Mre11/Rad50/NSB1 cause the S phase arrest which leads to apoptosis. Also through alternative signaling, namely NLK, ATM is phosphorylated which ultimately phosphorylates and activates p53 leading to p53. Nonetheless, SNP mutations like SNP 309 T/G forms a different subtype of MDM2 which inactivates p53 and accounts for etoposide resistance in some cases. Cyto C/Apaf-1/Cas-9 as well as Fas/FasL/Cas-8,10 are among other possible mechanisms described to play role in etoposide-cell death mechanisms.

the autophagy-induced ATP level and lead cells to non-apoptotic cell death [290].

Besides, Alpsoy et al. [291] have demonstrated that MRP1 (ABCC1 transporter) mainly contributes to etoposide efflux and chemoresistance. Besides, they have reported the mismatch repair mechanisms to be involved in MCF7-etoposide resistant cells. In other words, they argued that MLH1 and MSH2, which are involved in DNA damage repair, have significantly downregulated in etoposide-resistant cells. Moreover, they have investigated the expression rate of topoisomerase IIβ-binding protein 1 (TOPBP1) and E3 ubiquitin-protein ligase EDD. TOPBP1 functions in DNA replication, proliferation, and DNA damage response signaling pathways. It causes cell cycle arrest and ignites the apoptosis pathway [292, 293]. EDD is a tumor suppressor protein and one of its interplay partners contributing to checkpoint responses and DNA damage signaling [294]. Alpsoy and colleagues found a decrease in the expression of both TOPBP1 and EDD. Altogether, it addresses resistance in etoposide-treated cells [291]. Fig. 6.

The role of mTOR/Akt/PI3K signaling pathways in human cancer

The mammalian target of rapamycin (mTOR) and phosphatidylinositol-3-kinase/Akt signaling cascades act as a crucial double-edged sword within intracellular signaling pathways under both physiological and pathological conditions, including cell survival, cell proliferation, apoptosis, and invasion. These pathways are neatly interconnected with numerous cell signaling pathways such as HIF and NF-KB, to say the least [295].

PI3K/Akt signaling cascade is considered the essential modulator favoring cell survival under stressful circumstances [296]. To illustrate this, PI3K is formed of a lipid kinase family that can phosphorylate inositol rings 3′-OH in inositol phospholipids [297]. Class-I PI3K is formed of catalytic subunits (CAT), namely p110, and adaptor-regulatory domain, known as p85. In this regard, the signaling cascade is commenced by the stimulation and phosphorylation of tyrosine kinases in growth factor receptors. Thereafter, PI3K is recruited to the cell membrane, where it binds to tyrosine residues in receptors via SH2 domains within the adaptor subunit. This brings about the stimulation of CAT residue, which further leads to the generation of phosphatidylinositol-3,4,5-triphosphate (PI3,4,5-P3), namely the second messenger. Then, PI3,4,5-P3 recruits other signaling proteins including, protein serine/threonine kinase-3′-phosphoinositide-dependent kinase 1 (PDK1) and Akt/protein kinase B (PKB), which then regulate cell survival and cell cycle progression [295, 297, 298].

Regarding cell survival, Akt/PKB inactivates pro-caspase9 and Bad, besides it dampens related transcription factors that trigger the expression of apoptotic elements such as Fas/FasL [299, 300]. Moreover, Akt/PKB has been introduced to perform as a resistant-inducing agent through modulating TNF-related apoptosis-induced ligand (TRAIL)/APO-2L [301]. It also activates the survival signaling element in NF-KB signaling, namely IKB kinase (IKK) [302].

Regarding the cell cycle progression, numerous protein synthesis procedures, glycogen metabolism pathways, and cell cycle regulators have close interplay with Akt downstream signaling pathways, including mTOR, glycogen synthase kinase-3 (GSK-3), insulin receptor substrate-1 (IRS-1), p21, p27, and Raf-1 [298, 303].

On the other hand, Akt kinases themselves are members of the AGC family that correlate with AMP/GMP kinases and protein kinase C (PKC). To be precise, Akt kinases are constructed of three main domains, including a PH domain (N-terminal), CAT domain (central domain), and a regulatory hydrophobic residue (C-terminal). CAT domain is highly conserved among all Akt family and is highly related to PKC, PKA, and SGK [304].

MTOR is exceptionally considered as the most vital element within the realm of cell signaling, because it serves different aspects of cell fate. In other words, mTOR acts through its two main complexes. The mTOR complex-1 (mTORC1) is constructed of mTOR, Raptor, mLST8, and PRAS40. It is highly sensitive to rapamycin and generally stimulates S6K and dampens 4E-BP1, which leads to the translation of proteins and cell growth [305]. The mTORC2, which is less sensitive to rapamycin, on the other hand, is formed of mTOR, Rictor, Sin 1, and mLST8. The mTORC2 is appreciated for its stimulatory impact on Akt, which promotes cell survival and proliferation. The canonical pathway in mTOR signaling is believed to act through PI3K/Akt and Ras/MEK/ERK [306].

Different upstream signaling pathways regulate mTOR in normal cells [305]. These regulators are subcategorized into positive and negative modulators. Regarding positive regulators, for instance, insulin growth factor-1 (IGF-1) and its receptor, human epidermal growth factor receptors (HER family) and their ligands, and vascular endothelial growth factor receptors (VEGFRs) and their ligands, channel signals through PI3K/Akt. Nonetheless, the negative regulators include an energy-sensing element, namely LKB1, phosphatase and tensin homolog (PTEN), tuberous sclerosis complex-1 (TSC-1), and -2 (TSC-2). In other words, PTEN performs its negative impacts through PI3K/Akt, and TCS-2 also releases its inhibitory effects on mTOR by the time it is phosphorylated by Akt [295, 307].

PTEN acts as the regulator of PI3K/Akt/mTOR signaling cascades [295]. PTEN has impacts on both lipids and proteins. It is a tumor-suppressor agent that assists in inhibiting cell growth and leads target cells toward apoptosis [308]. However, PTEN is mutated in numerous cancers; for instance, PTEN is mutated in Cowden's syndrome, leaving the patient at high risk of being diagnosed with multiple cancers simultaneously [309]. PTEN indeed acts as the negative regulator of PI3K/Akt signaling; nevertheless, by losing the PTEN activity, cells experience non-stop and uncontrolled activation of PI3K/Akt signaling, which leads to excessive and unnecessary cell survival and proliferation [295].

As the mTORC1 signaling is concerned, it is activated by external and internal stimuli, including nutrients, hormones, and growth factors, as well as intracellular accumulation of DNA damages, amino acids, glucose, ATP, and oxygen. For instance, subsequent to DNA damages, mTORC1 is dampened through p53, which induces the activation of TSC-2 [310]. Besides, AMPK is stimulated following a period of energy exhaustion, leading to the formation of the TSC1/2 complex that ultimately inhibits mTORC1 through the phosphorylation of Raptor [311].

However, by the time mTORC1 is activated, as it was mentioned earlier, it transfers signals to S6K and 4E-BP1 [312]. Following the involvement of S6K and 4E-BP1, eukaryotic initiation factor (eIF)-4E and eukaryotic initiation factor-3 (eIF-3) are recruited, which promotes ribosomal biogenesis [313]. To illustrate this, the low activity of mTORC1 phosphorylates and stimulates 4E-BP1, which ignites protein translation. Besides, S6K phosphorylates elF-4B and S6 ribosomal protein (S6RP), which allow the translation process to continue and commence the elongation phase [314-316]. Thereafter, elF-4E constructs the elF-4F complex that stimulates protein translation, a stage that is vital, providing that the G1/S transition is concerned [312]. Therefore, it is conjectured that the activation of mTORC1 favors the translation of oncogenic proteins, which give rise to cell invasion, metastasis, and proliferation [317]. Moreover, mTORC1 activation also modulates other elements, including HIF-α, Protein phosphatase 2A (PP2A), and STAT3, which assists the biogeneration of essential lipids, proteins, and nucleotides in malignant cells, facilitating their survival, progression, and invasion [312].

On the other hand, the mechanisms in which mTORC2 performs its regulatory impacts remain partially elusive, probably owing to the fact that distinguishing between mTORC1 and mTORC2 is quite elaborate [318]. The mTORC2 is modulated by mTORC1 and PI3K/Akt signaling. In this regard, PI3K stimulates mTORC2 to bind to ribosomes under both physiological and pathological circumstances [319]. Akt is highly correlated with mTORC2, and studies have lent support to its increased expression level in various malignancies, where it collects signals from PI3K/mTORC2 and PI3K/PDK1, which induces cell survival and proliferation. Moreover, Akt impacts on mTORC1 in other complicated approaches [320].

It is well appreciated that mTORC1 negatively modulates mTORC2. To be precise, S6K1 stimulates the degradation of insulin receptor substrate-1 (IRS-1), which results in the inhibition of mTORC2 and PI3K/Akt signaling. Besides, Grb-10 is also recruited by mTORC1, which blocks mTORC2 [321-323].

Regarding the downstream pathways involved in mTORC2-related signaling cascades, glucocorticoid kinase (SGK) and protein kinase C (PKC) are considered as two key phosphorylation substrates, which lead cell survival machinery under hypoxia and malnutrition or even during PI3K blockage. It has been demonstrated that mTORC2 modulates cytoskeletal reorganizations and cell movements, necessary for cell invasion and tumorigenesis, by exploiting various PKC members [312].

To summarize, therefore, since mTOR regulates the production of numerous vital proteins and is involved in various signaling, including cell survival, cell proliferation, glucose metabolism, cell cycle, as well as protein and lipid synthesis, it is closely related to different tumors pathology. Moreover, mTOR plays a role in chemoresistance. In other words, some elements including, cyclin D1 [324], and HIF [325], are among essential proteins that interact with the aforementioned signaling pathways and give rise to the survival and expansion of the tumors by allowing the progression of the cell cycle and provoking the expression of angiogenic factors like VEGF, respectively. More importantly, mTOR and its upstream and downstream signaling pathways have been reported to be directly and indirectly the reason for the onset of different malignancies [312]. Fig. 7.

Recent outcomes in the application of combination chemotherapy

As discussed earlier, single-chemotherapy applications have been limited by chemoresistance and tumor relapse in the majority of cases. Every chemotherapeutic agent targets various intracellular-signaling cascades and different phases in the cell cycle. Therefore, the application of combination chemotherapy seems to boost chemotherapy responses; nonetheless, antagonistic impacts, variations in pharmacokinetics, and different drug distribution patterns have limited this application [326, 327].

For instance, gemcitabine was administered in combination with cisplatin on numerous solid tumors. In-vitro studies in this regard demonstrated synergetic impacts between gemcitabine and cisplatin, which seems to be due to an increase in platinum-DNA adducts. The synergism was also witnessed in gemcitabine-etoposide combined therapy in ovarian and lung cancer [173]. Moreover, the impact of gemcitabine-nab-paclitaxel, nanoliposomal irinotecan-5-fluorouracil-leucovorin, and gemcitabine-capecitabine was analyzed on elderly people diagnosed with pancreatic cancer. The results showed beneficiary outcomes for these combination therapies [328].

Furthermore, in a retrospective study, 113 advanced gastric cancer patients were subjected to combination chemotherapy of paclitaxel, 5-fluorouracil, and leucovorin (TFL) as their first-line treatment protocol, which represented 43.4% overall response with moderate toxicity. Therefore, Wan-Cai et al. have claimed TFL as an active and safe

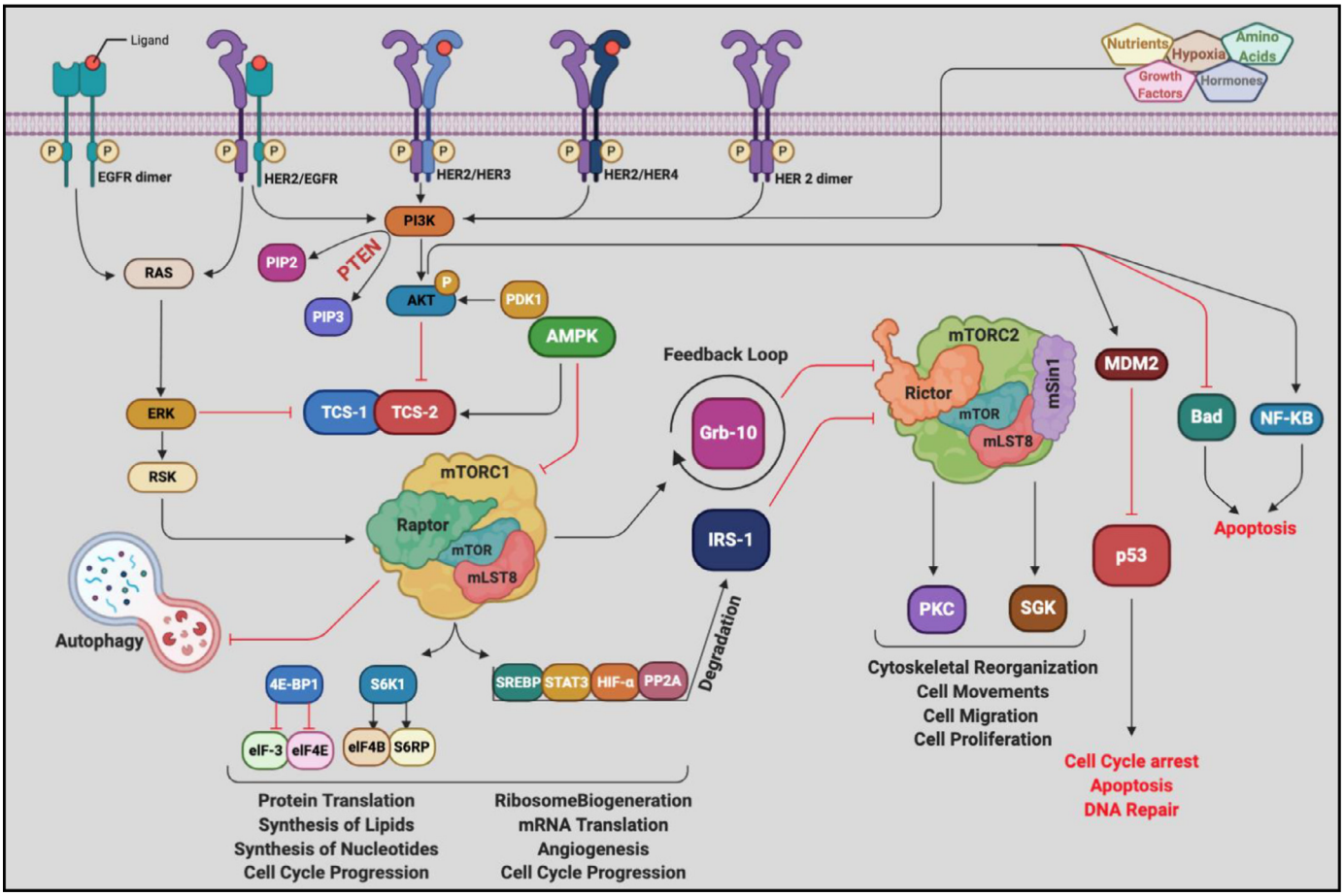

Fig. 7. MTOR is considered as the vital signaling cascade and as the crossroads within the realm of intracellular signaling owing to the fact that it serves different cellular functions under both physiological and pathological circumstances. It mainly acts through two complexes, namely mTORC1 and mTORC2. These complexes have a close interaction with upstream signaling cascades including, PI3K/Akt, Ras/ERK, and AMPK. The phosphorylation of Akt by the upstream signaling dampens the inhibitory function of TCS 2 which allows mTORC1 to perform its activities. The mTORC1 further regulates $E-BP1, S6K1, SREBP, STAT3, HIF-α, and PP2A in order to bring about lipid, protein, and nucleotide synthesis, as well as cell cycle progression and angiogenesis. The mTORC2, on the other hand, is modulated by mTORC1 through Grb-10 (in a feedback loop) and IRS-1 which ultimately favors cytoskeletal reorganization, cell movements, cell migration, and cell proliferation.

approach for these patients [329]. However, Choi, et al. have mentioned that the results of combination chemotherapy in patients with recurrent or primary metastatic gastric are somewhat conflicting. They further discussed, although combination chemotherapy is recommended for these patients, single chemotherapy administration can be considered as the logical approach for certain cases, especially elderly patients [330].

In another retrospective study, patients with advanced gastric cancer were subjected to a combination of paclitaxel and oxaliplatin as their first-line treatment every 14 days. The disease control was about 80%, making this combination therapy a new, effective, and safe regimen for these patients [331]. Besides, since peritoneal metastasis in advanced or recurrent gastric cancer is the common cause of death among these patients, better chemotherapy approaches are essential; however, the current treatments maintained defective. Ohnuma et al. have suggested the prescription of docetaxel, cisplatin, and S-1 as feasible and effective combination chemotherapy for these patients [332].

Pancreatic cancer has been treated with gemcitabine for many years. Nonetheless, chemoresistance against this regimen has significantly limited its application. Li et al. [333] have co-administered gemcitabine with valproic acid (VPA) and reported their synergistic impact in a dose-dependent manner. It has been reported that this combination therapy, with high-dose VPA, could successfully increase the sensitivity of pancreatic cancer cells to gemcitabine. However, they further indicated that low-dose VPA combined with gemcitabine promoted the migration and invasion potency in pancreatic cancer cells through increasing the level of ROS, as well as the activation of Akt, STAT3, and Bmi1. Whereas, administration of high-dose VPA-gemcitabine enhanced excessive ROS retention, which stimulated the activation of p38 resulting in the inactivation of STAT3 and Bmi1.

Besides, advanced non-small cell lung cancer patients were subjected to bevacizumab combined with gemcitabine-cisplatin (GC) combination chemotherapy in a study. Dividing the cases into two groups, one received GC as the control group and the other one received GC-bevacizumab as the observation group. The results were somewhat promising. Duan et al. reported that the efficiency rate and disease control were approximately 41% and 71%, respectively, in the control group, and 71% and 90%, respectively, in the observation group. Moreover, the level of tumor markers, namely CEA and CYFRA21-1, as well as the concentration of serum vascular endothelial growth factor (VEGF) were significantly lower [334].

Combination chemotherapy has represented promising outcomes in multidrug-resistant cancers as well. To illustrate this, Polymeric nanogels were used to encapsulate cisplatin and doxorubicin. They could successfully deliver more concentration of drug into MCF7/ADR cells and killed more cancer cells, which altogether lends support to its synergetic impacts [335]. Furthermore, multidrug delivery was also performed using magnetic nano-carriers. Rahimi et al. have developed dendritic chitosan grafted mPEG coated magnetic nanoparticles for delivering doxorubicin and methotrexate into MCF7 cells. They demonstrated that several peripheral bloodstream proteins could bind to these

nano-carriers and improve drug delivery. Besides, they confirmed that the anticancer activity of combined drugs was significantly more in comparison to free drugs [336].

In another study, the combination of paclitaxel and doxorubicin were co-encapsulated using recombinant high-density lipoprotein nanoparticles (rHDL). The results showed an enhanced intracellular accumulation of drugs, and improved cytotoxicity properties [326]. Also, Zhu et al. have utilized bilayered folate (FA) receptor-targeted polymersomes to encapsulate paclitaxel and doxorubicin. The results demonstrated more sustainability in drug release and dampened cell growth more sufficiently compared to free drug cocktail [327]. This technique has also been experimented on breast cancers that metastasize into the brain. This subtype cannot be cured with current chemotherapies due to poor drug delivery to the brain. Therefore, Bao et al. [337] have encapsulated oleanolic acid (OA), an excellent anti-tumor agent with penetration potency to the brain, and paclitaxel (PTX) in nanoparticles. They reported the synergistic efficacy of PTX-OA-NPs combination chemotherapy to effectively dampen breast and metastasized brain cancer progression.

Polymers seem to be interesting for encapsulation drug delivery approaches as well. An armed amphiphilic star copolymer was utilized to encapsulate doxorubicin and avasimibe. The cytotoxicity assays showed considering synergistic anticancer activity. Moreover, co-administration of avasimibe could reduce the required dose of doxorubicin, which reduced its side effects, suggesting a promising combination therapy against K562 and HeLa cells [338].

There are crucial risk factors in approaching any combination chemotherapy protocol that needs to be addressed in advance. For instance, although the combined gemcitabine-cisplatin (GC) chemotherapy has become standard for patients with urothelial cancer (UC), the subsequent hematological toxicity is still one major limitation in this regard. The results of a retrospective study indicated grade four neutropenia in roughly 48% of patients and grade 3 thrombocytopenia in 21% of all cases. Although some believed that age is the risk factor, they further discussed neutrophil count, platelet count, and K level as prominent risk factors among UC patients receiving GC combined therapy-induced hematological toxicity [339]. Moreover, in a study by Toffalorio et al. [340] they discussed cN-II expression level correlating with gemcitabine-platinum combination chemotherapy fate in patients suffering from non-small-cell lung cancer.

Besides, as discussed earlier, multiple-drug resistance (MDR) is a challenging event in chemotherapies. Therefore, it is important to tackle this crisis by increasing the intracellular accumulation of chemotherapeutic drugs. Regarding this issue, celastrol (CST) and doxorubicin (DOX) were co-encapsulated into carrier-free nanoparticles (CST/DOX NPs) in order to overcome DOX-resistance. Hopefully, this formulation has increased the water solubility and decreased the required DX dosage. Therefore, it could significantly enhance the drug concentration within the target cells, activate heat-shock factor-1 (HSF-1), dampen NF-KB to suppress P-gp expression, which altogether induced apoptosis and autophagy through ROS/JNK signaling cascade in DOX-resistant cells [341].

Paclitaxel has been prescribed for numerous cancers, yet chemoresistance and side effects such as neuro-, hepato-, and cardio-toxicity have limited its application. Ashrafizadeh et al. [342] have combined curcumin as an anti-tumor and anti-inflammation agent with paclitaxel and reported this combination chemotherapy application successful in enhancing the anti-tumor potency and decreasing the primary side effects of single-paclitaxel administration.

The results of combination chemotherapy applications are not just limited to patients with a promising prognosis. Interestingly, a 79-year-old man diagnosed with hilar cholangiocarcinoma which had metastasized into his lymph nodes, was subjected to neoadjuvant gemcitabine/cisplatin/S-1 combination in a case-report study. Although they could not save the liver due to massive impairments, biopsy and cytology results showed no local cancer cells after resection [343]. However, in another case study, a 61-year-old man diagnosed with stage IV papillary and anaplastic thyroid cancer was subjected to the combination of dabrafenib and trametinib, which resulted in life-threatening arrhythmia. The patient's condition was severe enough was undergone plasmapheresis to remove the chemotherapeutic drugs [344].

The list of combination chemotherapy applications is not limited to the regimens mentioned above. These results reinforce the fact that this approach can be a potential approach against numerous cancers. Although it might leave disappointing outcomes in some cases, there are beneficiary responses as well. However, there is still room for understanding the exact mechanisms of action underlying the function of combined drugs in order to develop combinations with fewer side effects and favorable responses.

The contribution of precision medicine in chemotherapy

Cancers might represent pathologically identical, yet even the same cancer subtypes might respond to a particular chemotherapeutic drug differently [345]. Although current chemotherapy selections are mostly based on the cellular and genetic mechanisms underlying chemoresistance, various tumor-specific and patient-specific criteria contribute to chemotherapy response. Therefore, in addition to an optimized drug, specific measurements are required to select chemotherapeutic drugs and their administration schedule based on the specialized pharmacokinetics and pharmacodynamics for each patient to achieve the best possible response [8].

Although new chemotherapeutic drugs have been developed and combination chemotherapies are becoming commonplace, the responses are not entirely satisfactory in some cases. This is due to the heterogeneity of causes underlying the onset of each cancer case in different patients. However, current signs of progress regarding genomics and next-generation sequencing (NGS) can help to identify genetic variations in different patients to narrow the development of drugs into precise and single-patient designed approaches for their specific biological, molecular, and cellular variations rather than stochastic chemotherapy applications [346, 347]. Furthermore, the diversity of natural compounds has contributed to developing new chemotherapeutic agents for about a half-century. Using the combined chemistry and highthrouput technology will help predict the behavior of each molecule and design personalized chemotherapy approaches and overcome chemoresistance based on the specifications in each case [348].

Mathematical models and omics technologies play key roles in this regard. For instance, shreds of evidence have been provided by McKenna, et al. that mathematical models can predict, specify, and improve chemotherapies in the realm of precision medicine when applying to breast cancer [8].

Besides, oral squamous cell carcinoma is a complex malignancy representing tumor heterogeneity and plasticity in different cases. Omics technologies are being used to address these variations. Omics are highthrouput technologies capable of screening different target molecules qualitatively and quantitatively. In other words, genomics, transcriptomics, proteomics, and metabolomics are used to find personalized biomarkers in tumor biopsies, circulating tumor cells, or body fluids like saliva [349]. Dissimilar to conventional chemotherapies that merely target one signaling cascade, using omics, one can acquire a thorough and unbiased perspective through specific genomics and proteomics, and perhaps target cells and molecules more specifically [350].

Intriguingly, Cammarota et al. have discussed the application of gut microbiota, big-data mining, and machine learning in the context of precision medicine as well. The gut microbiome is identical to fingerprints for individuals and has complicated cancer therapies by stimulating tumor progression, tolerability, and modulating immune-system responses to cancers. Using omics, we can collect beneficiary data, and by data mining, one can design more precise approaches. Moreover, machine learning is quickly developing, and it is becoming one crucial element in precision medicine. This technology goes beyond merely genomics and proteomics, yet it collects all data, and by designing different algorithms,

Table 2
Clinical trials for chemotherapies, immunotherapies, and combination chemotherapies.

A. Immunotherapies Vs. Chemotherapies in recent clinical trials on solid tumors

Clinical trial name	Target cancer	Phase of study	Intervention and dose	Control treatment	Ref
No-name	Melanoma or non-small-cell lung cancer with untreated brain metastases	II	Pembrolizumab 10 mg/kg	Investigator's choice	Goldberg, et al, 2016 [376]
No-name	Melanoma with active brain metastases	II	Pembrolizumab 10 mg/kg	Investigator's choice	Kluger, et al, 2019 [381]
GETUG-AFU 26 NIVOREN	Stage IV-metastatic brain form clear cell renal cell carcinoma	II	Nivolumab 3 mg/kg	VEGFR-directed therapy	Flippot, et al,2019 [374]
JAVELIN Solid Tumor	Stage IIIC or IV unresectable melanome	Ib	Avelumab 10 mg/kg	Investigator's choice	Keilholz, et al, 2019 [380]
Javelin Gastric 300	Gastric or gastroesophageal junction adenocarcinoma	III	Avelumab 10 mg/kg	Investigator's choice	Bang, et al, 2018 [362]
Javelin Lung 200	Non-small-cell lung cancer	III	Avelumab 10 mg/kg	Docetaxel	Barlesi, et al, 2018 [363]
KEYNOTE-045	Urothelial carcinoma	III	Pembrolizumab 200 mg	Investigator's choice	Bellmunt, et al, 2017 [364]
CheckMate 057	Non-small-cell lung cancer	III	Nivolumab 3 mg/kg	Docetaxel	Borghaei, et al, 2015 [366]
CheckMate 015	Small-cell lung cancer	III	Nivolumab 3 mg/kg	Docetaxel	Brahmer, et al, 2015 [367]
CheckMate 026	Non-small-cell lung cancer or small-cell lung cancer	III	Nivolumab 3 mg/kg	Platinum-based	Carbone, et al, 2017 [368]
KEYNOTE-040	Head and neck squamous cell carcinoma	III	Pembrolizumab 200 mg	Investigator's choice	Cohen, et al, 2019 [369]
POPLAR	Non-small-cell lung cancer	II	Atezolizumab 1200 mg	Docetaxel	Fehrenbacher, et al, 2016 [371]
CheckMate 141	Head and neck squamous cell carcinoma	III	Nivolumab 3 mg/kg	Investigator's choice	Ferris, et al, 2016 [372]
CheckMate 227	Non-small-cell lung cancer	III	Nivolumab 3 mg/kg	Platinum-doublet therapy	Hellmann, et al, 2018 [378]
KEYNOTE-010	Non-small-cell lung cancer	II/III	Pembrolizumab 2 mg/kg	Docetaxel	Herbst, et al, 2016 [379]
KEYNOTE-042	Non-small-cell lung cancer	III	Pembrolizumab 200 mg	Investigator's choice	Mok, et al, 2019 [386]
IMvigor 211	Urothelial carcinoma	III	Atezolizumab 1200 mg	Investigator's choice	Powles, et al, 2018 [389]
IFCT-1603	Small-cell lung cancer	II	Atezolizumab 1200 mg	Investigator's choice	Pujol, et al, 2019 [390]
KEYNOTE-024	Non-small-cell lung cancer	III	Pembrolizumab 200 mg	Investigator's choice	Reck, et al, 2016 [391]
No-name	Melanoma	III	Tremelimumab 15 mg/kg	Investigator's choice	Ribas, et al, 2013 [392]
KEYNOTE-002	Melanoma	II	Pembrolizumab 2 mg/kg	Investigator's choice	Ribas, et al, 2015 [393]
OAK	Non-small-cell lung cancer	III	Atezolizumab 1200 mg	Investigator's choice	Rittmeyer, et al, 2017 [394]
CheckMate 066	Melanoma	III	Nivolumab 3 mg/kg	Dacarbazine	Robert, et al, 2015 [395]
KEYNOTE-061	Gastric or gastroesophageal junction adenocarcinoma	III	Pembrolizumab 200 mg	Paclitaxel	Shitara, et al, 2018 [396]
CheckMate 037	Melanoma	III	Nivolumab 3 mg/kg	Investigator's choice	Weber, et al, 2015 [400]
CheckMate 078	Non-small-cell lung cancer	III	Nivolumab 3 mg/kg	Docetaxel	Wu, et al, 2019 [401]

B. Combination therapies in recent clinical trials

Clinical trial name	**Target cancer**	**Phase of study**	**Intervention and dose**	**Control treatment**	**Ref**
JASPAC 04	Resectable pancreatic ductal adenocarcinoma	II	IV Gemcitabine 1000 mg/m^2 + Oral S-1 50 mg	Chemoradiotherapy	Toyama, et al, 2020 [398]
SOBIC	Metastatic colorectal cancer	II	FL: S-1+ Oxaliplatin+ Bevacizumab (SOX+Bmab) SL: S-1+ Irinotecan+ Cetuximab (IRIS+Cmab)	None	Nakamoto, et al, 2020 [388]
SOPP	Metastatic or recurrent gastric cancer	III	S-1 80 mg/m^2 + Oxaliplatin 130 mg/m^2 (SOX)	S-1 80 mg/m^2 + Cisplatin 60 mg/m^2 (SP)	Lee, et al, 2021 [383]
No-name	Platinum-resistant recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer	II	IV Bevacizumab 15 mg/kg + IV Gemcitabine 1000 mg/m^2	Platinum-based	Nagao, et al, 2020 [387]
NRG-GI004/SWOG-S1610	Deficient DNA mismatch repair (dMMR) colorectal cancer	III	mFOLFOX6/ Bevacizumab, Atezolizumab monotherapy, or mFOLFOX6/Bevacizumab + Atezolizumab	Investigator's choice	Lee, et al., 2019 [382]
GOG-0213	Platinum-sensitive, recurrent ovarian cancer	III	Platinum-based combination chemotherapy (with or without Bevacizumab)	Investigator's choice	Coleman, et al., 2018 [370]
DESMOPAZ	Progressive desmoid tumor	II	Oral Pazopanib 800 mg per day or IV combined Methotrexate-Vinblastine (5 mg/m^2, 30 mg/m^2)	Investigator's choice	Toulmonde, et al., 2019 [397]

(*continued on next page*)

Table 2 (*continued*)

A. Immunotherapies Vs. Chemotherapies in recent clinical trials on solid tumors

Clinical trial name	Target cancer	Phase of study	Intervention and dose	Control treatment	Ref
PICCA	Advanced biliary tract cancer	II	cisplatin 25 mg/m^2 and gemcitabine 1000 mg/m^2 with or without Panitumumab 9 mg/kg	Investigator's choice	Vogel, et al, 2018 [399]
No-name	Advanced bone and soft tissue sarcomas	II	Gemcitabine 900 mg/m^2 + Docetaxel 70 mg/m^2	None	Hara, et al., 2019 [377]
POUT	Upper tract urothelial carcinoma	III	IV cisplatin or carboplatin 70 mg/m^2 + IV gemcitabine 1000 mg/m^2	Investigator's choice	Birtle, et al., 2020 [365]
CheckMate 016	Advanced or metastatic renal cell carcinoma	I	Nivolumab + Sunitinib (50 mg/day) or Nivolumab + Pazopanib (800 mg/day)	None	Amin, et al., 2018 [360]
TBCRC 022	HER-2-positive breast cancer with brain metastases	II	Oral Neratinib (240 mg/day) + Capecitabine (750 mg/m^2)	Lapatinib-naïve or Lapatinib-treated	Freedman, et al., 2019 [375]
LANDSCAPE	HER-2-positive breast cancer with brain metastases (not treated with WBRT)	II	Oral Lapatinib (1250 mg) + Capecitabine (2000 mg/m^2)	None	Bachelot, et al., 2013 [361]
No-name	HER-2-positive relapsed or metastatic breast cancer treated with taxanes, anthracyclines, trastuzumab	II	Capecitabine (1000 mg/m^2) + Pyrotinib (400 mg) or Lapatinib (1250 mg)	None	Ma, et al., 2019 [385]
BrighTNess	Stage-II or III-triple-negative breast cancer	III	Segment 1 regimen: IV Paclitaxel (80 mg/m^2) + IV Carboplatin (6 mg/ml per min) + oral Veliparib (go mg) Segment 2 regimen: Doxoru-bicin + Cyclophosphamide	paclitaxel plus carboplatin plus veliparib placebo, or paclitaxel plus carboplatin placebo plus veliparib placebo	Loibl, et al., 2018 [384]
No-name	ER-positive, HER-2-negative advanced breast cancer	III	Palbociclib (125 mg) + Letrozole (2.5 mg)	Placebo + Letrozole	Finn, et al., 2016 [373]

IV: intravenous, FL: first-line, SL: second line, HER-2: human epidermal growth factor-2, WBRT: whole brain radiotherapy, ER: estrogen receptor

it can assist in precision medicine [351]. For instance, Lee et al. have represented a promising approach in identifying molecular characteristics to develop more precise targeted therapies for acute myeloid leukemia (AML). To illustrate this, collecting genome-wide gene expression data, in-vitro investigation of the drug sensitivity of 160 chemotherapeutic drugs, as well as multi-omic computational algorithms, they were able to find SMARCA4 as a marker and driver of sensitivity to topoisomerase II inhibitors, mitoxantrone, and etoposide in AML [345].

Finding predictive and specific biomarkers have impacted the chemotherapy approaches for ovarian cancer patients as well. There are specific molecular characteristics even within a particular histological subtype of ovarian cancer. Therefore, treating ovarian cancer has altered from one-size-fits-all to a precise methodology, including surgery, chemotherapy, and targeted therapy. Moreover, the progressions in NGS hope to find various distinct biomarkers and variations in genomics, which altogether assist in developing new approaches for each ovarian cancer patient [352].

Immunotherapy is another approach that has been accepted to benefit cancer cases; nonetheless, one major disadvantage is that they give rise to unnecessary inflammatory responses and autoimmune diseases by the upregulation of the immune system [353]. Having said that, their applications and clinical trials are expanding due to their increased survival rate in advanced cancers [354]. Tumor mutational burden (TMB) is a robust approach for predicting specific biomarkers in the context of personalized medicine. Non-small-cell lung cancer is an example regarding the application of precision medicine, that numerous FDA-approved targeted therapies, such as immune-checkpoint inhibitors, have been developed based on identified biomarkers, like EGFR, ALK, ROS1, and BRAF. TMB can be assessed using NGS and whole-exome sequencing (WES), although NGS is more affordable globally. Shreds of evidence have lent support to the application of TMB in the selection of possible personalized immune-checkpoint-inhibitor treatments [355].

Moreover, the treatment of head and neck squamous cell carcinoma (HNSCC) is a sophisticated procedure due to loads of mutations without any specifications. Although surgery and radiation are the established therapy against HNSCC, administration of checkpoint inhibitors, targeted immunotherapy, including anti-PD-L1 and anti-CTLA-4, as well as precision medicine, can shed light on developing novel and more effective approaches against HNSCC [356].

Promising chemotherapeutic drugs, immunotherapies, and related clinical trials

Currently, numerous chemotherapeutic and immunotherapeutic candidates are under clinical trials. Numerous reports have indicated their responses, and some provided a comprehensive comparison between the application of them either alone or in combination [353]. In this regard, we have summarized some of the recent clinical trials regarding the comparison between immunotherapies and chemotherapies (Table 2.A) [353], and combination therapies (Table 2.B), as well as their target cancer and study phase. Table 2.

Conclusion

Although numerous chemotherapeutic drugs have been introduced and increased the life expectancy of cancer patients, chemoresistance

and tumor relapse have limited their application. Mutations seem to be one of the game-changer criteria in this regard. Stochastic mutations allow tumor cells to become resistant and continue growing, expanding, and invading, despite the chemotherapy in some cases [357]. Therefore, malignant cells have found their ways to proliferate and adapt themselves in most cases [358].

Despite all the prosperities in chemotherapeutic drugs, it is assumed that tumor cells are one step ahead. Tumors either through acquired mutations or exploiting the vital resources essential for our normal cells, immune cells, in particular, aggressively proliferate and survive even under stressful circumstances, such as hypoxia, malnutrition, and low pH, to say the least [359].

Since single chemotherapies have represented less satisfactory outcomes, combination chemotherapies have absorbed the attention of scientists to improve the chemotherapy responses. As discussed earlier, although they have had disappointing results in some cases, promising responses in the rest of cancers have shed light on developing novel regimens for various cancers.

Moreover, the role of precision medicine should be appreciated. Genomic and proteomic screenings have become easier due to the recent progressions and availabilities in highthrouput technologies such as omics, NGS, and WES. Therefore, using big data extracted from the aforementioned technologies will probably facilitate developing personalized chemotherapy regimens based on the genetic variations in the human population.

Finally, our aim must be to evaluate and study the exact mechanisms, including intracellular signaling and molecular interactions in both resistance and cell-death. We should also utilize highthrouput technologies to investigate the distinct variations that influence the response in different cancer cases. This way, we might develop potential drugs, enhance life-expectancy, and improve the quality of life in patients suffering from cancers.

Declaration of Competing Interest

The authors declare no conflict of interest.

CRediT authorship contribution statement

Mojtaba Mollaei: Project administration, Supervision, Writing – original draft, Writing – review & editing, Investigation, Validation, Conceptualization. **Zuhair Mohammad Hassan:** Writing – review & editing, Investigation, Validation, Conceptualization. **Fatemeh Khorshidi:** Writing – review & editing, Investigation, Validation. **Ladan Langroudi:** Writing – review & editing.

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