Received: 28 June 2021 | Revised: 17 August 2021 | Accepted: 20 August 2021

DOI: 10.1002/jcp.30573

REVIEW ARTICLE

Journal of Cellular Physiology WILEY

Molecular mechanisms involved in DNA repair in human cancers: An overview of PI3k/Akt signaling and PIKKs crosstalk

Forough Alemi[1] | Aydin Raei sadigh[1] | Faezeh Malakoti[1] | Yusuf Elhaei[2] | Seyed Hamed Ghaffari[3] | Masomeh Maleki[1] | Zatollah Asemi[4] | Bahman Yousefi[1] | Niloufar Targhazeh[1] | Maryam Majidinia[5]

[1]Department of Biochemistry and Clinical Laboratories, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran

[2]Department of Clinical Biochemistry, Faculty of Medical Sciences, Tarbiat Modares University, Tehran, Iran

[3]Department of Orthopedics, Shohada Medical Research & Training Hospital, Tabriz University of Medical Sciences, Tabriz, Iran

[4]Research Center for Biochemistry and Nutrition in Metabolic Diseases, Kashan University of Medical Sciences, Kashan, Iran

[5]Solid Tumor Research Center, Urmia University of Medical Sciences, Urmia, Iran

Correspondence

Bahman Yousefi, Molecular Medicine Research Center, Tabriz University of Medical Sciences, Tabriz 5166/15731, Iran.
Email: yousefib@tbzmed.ac.ir

Niloufar Targhazeh, Anesthesiology Research Team, Tabriz University of Medical Sciences, Tabriz 5166/15731, Iran. Email: n.targhazeh@gmail.com

Maryam Majidinia, Solid Tumor Research Center, Urmia University of Medical Sciences, Urmia, Iran.
Email: majidinia.m@umsu.ac.ir

Abstract

The cellular genome is frequently subjected to abundant endogenous and exogenous factors that induce DNA damage. Most of the Phosphatidylinositol 3-kinase-related kinases (PIKKs) family members are activated in response to DNA damage and are the most important DNA damage response (DDR) proteins. The DDR system protects the cells against the wrecking effects of these genotoxicants and repairs the DNA damage caused by them. If the DNA damage is severe, such as when DNA is the goal of chemo-radiotherapy, the DDR drives cells toward cell cycle arrest and apoptosis. Some intracellular pathways, such as PI3K/Akt, which is overactivated in most cancers, could stimulate the DDR process and failure of chemo-radiotherapy with the increasing repair of damaged DNA. This signaling pathway induces DNA repair through the regulation of proteins that are involved in DDR like BRCA1, HMGB1, and P53. In this review, we will focus on the crosstalk of the PI3K/Akt and PIKKs involved in DDR and then discuss current achievements in the sensitization of cancer cells to chemo-radiotherapy by PI3K/Akt inhibitors.

KEYWORDS

DNA damage response, malignancy, PI3K/Akt, signaling pathway

1 | INTRODUCTION

On a daily basis, endogenous and exogenous stresses cause damage like single-strand breaks (SSB) and double-strand breaks (DSB) in the human DNA structure of body cells (Basu, 2018). Cells implement different strategies to identify and repair the damaged sites to maintain genome stability. Therefore, after a DNA lesion, DNA damage response (DDR) as a multicomplex repair mechanism is activated by a kinase-based signaling network to identify the damage in DNA structure and recruit repair factors to the damaged site to initiate repair pathways (Tian et al., 2015). There are several repair pathways depend on the type of damage: Homologous recombination (HR), Nonhomologous end joining (NHEJ), Base excision repair, nucleotide excision repair (NER), and DNA mismatch repair (Majidinia & Yousefi, 2017).

Phosphoinositide 3-kinase (PI3K) is responsible for initiating the PI3K/Akt/mammalian target of rapamycin (mTOR) prosurvival

Forough Alemi and Aydin Raei sadigh contributed equally to this study.

pathway, and its overactivation cause increases cancerous behavior in different cells. More importantly, this complex pathway has a significant role in the regulation of cell-cycle checkpoints and the tumor microenvironment (Wanigasooriya et al., 2020). Also, multiple studies have reported the expression of the PI3K/Akt signaling pathway has significant effects on the repair of DNA damage through the regulation of proteins that are involved in the DDR process like BRCA1, HMGB1, and P53 (Lange et al., 2008; Naderali et al., 2019; J. Wu et al., 2010). Furthermore, PI3K/Akt signaling inhibitors have become the center of attention in recent decades and open new avenues in offering combinational therapies with conventional chemotherapy regimens for cancer patients.

The PI3K-related kinase (PIKK) family is a large serine/threonine kinase family, with sequence similarity to PI3K, and phosphorylates proteins responsible for vital cellular processes such as cell cycle progression, DNA repair, apoptosis, and cellular senescence. The PIKK family consists of six members, including ataxia-telangiectasia mutated (ATM), ataxia- and Rad3-related (ATR), DNA-dependent protein kinase catalytic subunit (DNA-PKcs), mTOR, suppressor of morphogenesis in genitalia (SMG-1) and transformation/transcription domain-associated protein (TRRAP) (Lempiäinen & Halazonetis, 2009). These proteins as intracellular signal transducer enzymes have been proven to play a major role in the occurrence of the DDR process, cell cycle progression, and apoptosis (Lovejoy & Cortez, 2009). Here, we will bring a brief introduction to the PIKK family members and how they contribute to the DDR process. Then, we summarize the current understanding of the roles of the PI3K/Akt signaling cascade in DNA damage elimination, which causes the failure of DNA damage-based chemotherapies. Finally, we outline a recent understanding of targeting PI3K/Akt signaling as a new strategy to enhance chemotherapy and radiotherapy.

2 | PIKK FAMILY MEMBERS ARE ACTIVATED IN RESPONSE TO DNA DAMAGE

Members of the PIKK family (Table 1), including ATM, ATR, DNA-PKcs, mTOR, and SMG1, have a similar structure in the PI3K kinase domain (Shaik & Kirubakaran, 2020). In the N-terminal α-helical,

TABLE 1 PIKK family members and their roles in DNA damage/repair

Member(s)	Role	Reference(s)
ATM	• Regulation of cancer development and repair system upon DNA break • Phosphorylates hnRNP K and dissociates it from HDM2 • Enhancing RNAPII ubiquitination • Inhibitory effects on cell apoptosis • Contributes in chromatin remodeling	(M. H. Jin & D.-Y. Oh, 2019; Tanya T. Paull, 2015)
ATR	• Specifically recognize DNA damage • Mediates phosphorylation of TopBP1, RPA, Rad17, and CHK1, to function in regulation of fork progression, cell-cycle transitions, and DNA repair • ATR/CHK1 pathway inactivates CDC25 phosphatases function and also enhances G2/M cell cycle checkpoint • Inhibitory effects on cell apoptosis	(Karlene A. Cimprich & David Cortez, 2008; Alexandre Maréchal & Lee Zou, 2013; Miiko Sokka, Sinikka Parkkinen, Helmut Pospiech, & Juhani E. Syväoja, 2010)
DNA-PKcs	• Expression regulation of immune effectors, tumor suppressors and hormone receptors • NHEJ mediators phosphorylation • As a tether for end site of the damage has important role in ligation of the broken ends of DSB site of DNA to suppress further degradation	(Andrew N. Blackford & Stephen P. Jackson, 2017; Jonathan F. Goodwin & Karen E. Knudsen, 2014; Medová et al., 2020)
mTOR	• Cell growth and survival in response to genotoxic stress • mTORC1 signaling requires for G_1 transition to S phase in progression of cell-cycle and replication fork • mTOR has the capability to regulate p53/p21 pathway • Involves in DDR events in a FANCD2-dependent manner	(Sricharan Bandhakavi et al., 2010; Changxian Shen, Lancaster, et al., 2007; Stephan Wullschleger, Robbie Loewith, & Michael N. Hall, 2006)
SMG1	• Regulate the G1/S checkpoint • Enhances stabilization of p53 and suppresses p53 proteasomal degradation • Executes tumor-suppressive role through the regulation of CDK2 and Cdc25A • Responds to mRNA splicing errors through NMD facilitation	(Jennifer S. Gewandter, Bambara & O'Reilly, 2011; Evgenia Gubanova, Natalia Issaeva, Camilla Gokturk, Tatjana Djureinovic, & Thomas Helleday, 2013)

Abbreviations: ATM, ataxia-telangiectasia mutated; CDK, cyclin-dependent kinase; DNA-PKcs, DNA-dependent protein kinase catalytic subunit; mRNA, messenger RNA; mTOR, mammalian target of rapamycin; SMG-1, suppressor of morphogenesis in genitalia.

these kinases have a different structure in size and shape that enable them to interact with related DNA binding co-activator complexes, which are recruited to binding to the damaged site (Lovejoy & Cortez, 2009; Menolfi & Zha, 2020).

Most of the PIKKs exert their effect on the DDR pathway through P53 mediation. P53 is the most important tumor suppressor of the cell, which normally has multiple functions, including inducing cell death or senescence, cell cycle arrest, and DNA repair. Upon stress response, p53 is activated and halts the cell cycle to removes the DNA damage by initiating the DDR pathway, which finally suppresses cancer progression (Green & Kroemer, 2009; Malakoti et al., 2021). However, mutations, which occur regularly in most cancer cells, disturb the core DNA binding domain of p53, and inactivate this protein. Therefore, p53 loss of function enables cancer cells to escape cell cycle arrest, cell death and also increase genomic instability as well as induction of oncogenic pathways, which overall results in cancer progression and cell survival (Blagih et al., 2020). One of the vital genes that p53 activates its transcriptional status is p21. P21 is a cyclin-dependent kinase (CDK) inhibitor that has a significant role in the DDR process through different mechanisms, like cell arrest at the G1-phase by inhibiting cyclin/CDK complexes and inhibition of DNA replication through direct interaction and suppression of PCNA (Cazzalini et al., 2010).

2.1 | mTOR and SMG-1

mTOR as one of the PIKKs is a downstream kinase of the insulin/IGF-1-PI3K-Akt pathway that responds to environmental changes like nutrient and growth factor signals, cell growth, survival, and metabolism (Serej et al., 2018; Wullschleger et al., 2006). mTOR signaling is required for G1 transition to S phase and cell survival in response to genotoxic stress (Shen et al., 2007). Studies revealed that mTOR can regulate the p53/p21 pathway as an essential player in the DDR process (Jung et al., 2019). Analyses have shown that mTOR inhibition by rapamycin increases ATM activation and 53BP1/p53 interaction conducing DDR activation and reduces functional proteins responsible for chromosomal integrity (S. Bandhakavi et al., 2010).

SMG-1 is another member of the PIKK family (suppressor with a morphogenetic effect on genitalia), which can regulate the G1/S checkpoint in the p53-dependent or p53-independent pathway. SMG-1 enhances stabilization of p53 and suppresses p53 proteasomal degradation by its phosphorylation on Ser15 residue, which has a compromised role in G1/S checkpoint regulation during ionizing radiation (IR) exposure therapy (Gewandter et al., 2011). Experimental analysis shows that CDK2 as an oncogene provokes replication activity and enhances tumor growth. In the same way, cell division cycle 25 homolog A (Cdc25A), a common overexpressed component of cancerous cells, associated with poor prognosis. SMG-1 executes a p53-independent tumor-suppressive role through the regulation of CDK2 and Cdc25A. SMG-1 can phosphorylate and then inactivate CDK2 by implementing kinase activity. In contrast to this, Cdc25A phosphatase removes the inhibitory phosphate of CDK2 and facilitates the transition to the S phase and cell-cycle progression. To prevail Cdc25A phosphatase function, SMG-1 enables to phosphorylate and inhibit Cdc25A activation. Taken together, SMG-1 maintains genomic stability through inhibition of CDK2 and Cdc25A, conducing cell-cycle arrest (Gubanova et al., 2013). Meanwhile, there is a surveillance process in cells named nonsense-mediated messenger RNA (mRNA) decay (NMD), which is responsible for deleting potentially harmful transcripts. Upon genotoxic stress, SMG1 responds to mRNA splicing errors through NMD facilitation (McIlwain et al., 2010).

2.2 | ATM, ATR, and DNA-PKcs

HR and NHEJ are the two most essential repair pathways cells take to eliminate DNA lesions (Majidinia & Yousefi, 2017). PIKKs, including ATM, ATR, and DNA-PKcs, specifically recognize DNA damage, then orchestrate the kinase cascade, leading to DSB or SSB signaling amplification and DDR pathway facilitation (Jin & Oh, 2019).

ATM monomerization and autophosphorylation on Serine 1981 are two essential alterations for its activation. The MRN complex (Mre11, Rad50, and Nbs1) is one of the key components in DNA damage recognition and subsequently regulates HR or NHEJ repair pathways by activation of ATM (Qiu & Huang, 2021). Following DNA damage, the MRN complex monomerizes the inactive form of dimeric ATM and increases ATM's monomeric active form. Not only the MRN complex but also severe DNA breaks can monomerize and provoke ATM activation (T. T. Paull, 2015). Then, ATM plays specific roles in DDR cascade initiation and regulation of all phases of the cell cycle through phosphorylation and regulation of DDR main components, including histone H2AX, p53, checkpoint kinase 2 (CHK2), and BRCA1 (Bartek & Lukas, 2007; Maréchal & Zou, 2013; Shiloh, 2003). Phosphorylated-H2AX is responsible for recruiting DDR components like NBS1, 53BP1, and TopBP1to the damaged site (Sokka, Parkkinen, Pospiech, Syväoja 2010). CHK2 and p53 phosphorylation are vital for p53 stabilization at the nucleus to regulate the expression of genes involving in the DDR process in response to cell cycle arrest or apoptosis, depending on the severity of the damage (Vogelstein et al., 2000). HDM2 is a nonredundant paralogous protein, which downregulates p53 under normal cellular conditions. In addition, it has the capability to inhibit p53 activity by ubiquitination. During the DDR, ATM phosphorylates HDM2 and allow p53 activation by removing p53 inhibition (Medina-Medina et al., 2018).

ATR as a holoenzyme consists of two ATR and two ATRIP (ATR-interacting proteins). ATR mediates phosphorylation of some important proteins, including topoisomerase IIβ-binding protein 1 (TopBP1), replication protein A (RPA), Rad17, and CHK1, to function in the regulation of fork progression, cell-cycle transitions, and DNA repair. TopBP1 is introduced as a vital protein in protecting the stability of the genome (Sokka et al. 2010). In detail, TopBP1 as a protein scaffold is recruited by RAD9-RAD1-HUS1 (911) to enhance the interaction of ATR holoenzyme with other substrates through its ATR-activating domain (Maréchal & Zou, 2013). Additionally, RPA is

essential for recruiting and activating ATR on single-strand DNA by binding to the ATRIP subunit (Zou & Elledge, 2003). CHK1 improves cell cycle checkpoints and consequently causes cell cycle arrest that prepares cells to repair DNA damage. Also, it is confirmed that ATR phosphorylates its downstream substrate, CHK1. ATR/CHK1 pathway inactivates CDC25 phosphatases function and conduces cell to suppression of cell cycle progression, which gives cells time to incur repair process (Cimprich & Cortez, 2008; Dai & Grant, 2010).

Notably, ATM and ATR have a vulnerable crosstalk in the presence of DNA lesions. On this basis, experimental data revealed that ATM and ATR appear to phosphorylate each other and also positively influence activation and localization of each other at the site of the lesion (Jin & Oh, 2019). Not only ATM and ATR phosphorylate p53 at Ser15, but also they can phosphorylate and activate Chk2 and Chk1, which consequently phosphorylates p53 in Ser20. These phosphorylations are vital for p53 stabilization and activation (Enari et al., 2017).

DNA-PKcs, the largest member of PIKK (460kD), participated in different cellular paths by expression regulation of immune effectors, tumor suppressors, and hormone receptors (Blackford & Jackson, 2017; Goodwin & Knudsen, 2014). DNA-PKcs in association with Ku70/Ku80 complex makes the active form of the DNA-PK holoenzyme complex. Upon DSBs, two Ku70/80 complexes recruit two units of DNA-PKcs at the site of damage, the catalytic function of DNA-PK holoenzyme activates, leading to intermolecular autophosphorylation and subsequently NHEJ mediators phosphorylation. Moreover, DNA-PKcs as a tether for the end site of the damage has an important role in ligation of the broken ends of the DSB site of DNA to suppress further degradation (Goodwin & Knudsen, 2014).

DNA-PKcs not only involves in NHEJ but also functions in the HR process. P53-RPA interaction has been proven to function in the efficiency of HR repair (Serrano et al., 2013). Indeed, in response to inaccurate spontaneous HR pathway, DNA-PKcs mediates RPA32 hyperphosphorylation at Ser4/Ser8 residues, and also ATM/ATR is directly causing a rise in p53 phosphorylation. These two phosphorylation statuses improve dissociation of the p53-RPA complex, resulting in HR repression and G2/M arrest (Ashley et al., 2014; Serrano et al., 2013). In this regard, DNA-PKcs require restraining accumulation of DNA damage in post-mitotic cells (Enriquez-Rios et al., 2017). It is not surprising that the loss of DNA-PKcs aberrantly impairs DNA repair and enhances cell cycle progression (Ashley & Kemp, 2018).

3 | PI3k/Akt SIGNALING ROLES IN DNA DAMAGE REPAIR

PI3k/Akt signaling pathway has critical roles in cellular processes such as cell growth, survival, etc. (Rodon et al., 2013), and its regulating effects in DDR (Karimian et al., 2019) attracts the attention of researchers in this field. This pathway also is one of the main signaling pathways involved in tumorigenesis (Jiang et al., 2020). Its components and regulators (e.g., phosphatase and tensin homolog [PTEN]) are mutated or epigenetically modified in many human cancers, and thereby we observe aberrant functions of this pathway in cancer cells (Engelman et al., 2006). PI3K, accompanied by its main lipid product, PIP_3, is responsible for Akt activation as a downstream substrate. In detail, after stimulation of receptor tyrosine kinases or G protein-coupled receptors or cellular stress, PI3K is recruited and activated in the plasma membrane, and then, it produces some lipid products like PIP_3. After that, PIP3 initiates Akt activation directly and indirectly through phosphorylation (Manning & Toker, 2017).

This activated-Akt has different functions in the cell. Akt plays an antiapoptotic role by suppressing apoptosis mediators like the Bcl-2 family and forkhead box (FOX) family. Bcl-2 family is essential to cell fate. This family has both antiapoptotic and proapoptotic members. To prepare cells for apoptosis, proapoptotic members of the Bcl-2 family, Bax, and Bak induce caspases activation, mitochondrial outer membrane permeabilization, and also cytochrome c secretion conducting to cell-dead (Tsujimoto, 1998). Also, there is a superfamily named FOX that has a compromised role in the regulation of apoptosis and cell cycle modulation at both G1/S and G2/M transition phases (J. Wang et al., 2018).

Cyclin/CDKs play an imperative role in phosphorylation and activation of essential components involved in cycle progression. P21 and p27 as CDK inhibitors appear to suppress the different types of cyclin/CDKs. Akt also induces phosphorylation of p21 and p27 at different Ser and Thr residues to export them from the nucleus to the cytoplasm to inhibit their function in cell cycle arrest (Xu et al., 2012). Besides this, P21 and p27 expression are positively regulated by the FOX family. The PI3K/Akt pathway inactivates FOX that leads to inhibition of p21 and p27 and subsequently cell cycle progression (Van der Vos & Coffer, 2011).

Furthermore, Mdm2 (murine double minute 2) as an oncoprotein binds to p53 and facilitates p53 ubiquitination and degradation to inhibit p53 function in DDR. Akt mediates activation of Mdm2 by phosphorylation of Ser166 and Ser186. Thus, it has been proposed that Akt has prosurvival properties. On this basis, after stress, ATM, ATR, and DNA-PKcs induce Akt activation. Akt has a remarkable positive effect on activation of DNA-PKcs and consequently NHEJ repair. In opposition to this, Akt impairs the HR signaling pathway by inhibition of HR major components like RPA, BRCA1, Rad51, CtIP, and CHK1 (Xu et al., 2012).

A set of studies has suggested a close relation between hypoxia and epidermal growth factor receptor (EGFR) and PI3K/Akt/mTOR signaling cascade. Trans-membrane protein EGFR in both physiological and pathophysiological conditions stimulates the PI3K-Akt-mTOR signaling pathway, which is responsible for the modulation of proliferation, differentiation, migration, and inflammation. Moreover, activation and translocation of EGFR into the nucleus enhances DNA-PKcs functional activity and subsequently DDR process progression (Horn et al., 2015). Hypoxic cells show more resistance to radiation compares with normal somatic cells. Hypoxia and EGFR stimulate expression of transcriptional activator hypoxia-inducible factor 1 (HIF-1), which enhances expression and activation of vascular endothelial growth factor (VEGF) and PI3K/Akt signaling.

More importantly, PI3K/Akt signaling amplifies VEGF overexpression by HIF-1. As a result, HIF-1 and VEGF contribute to tumor-angiogenesis, aggressiveness, and radio-resistance in a PI3K/Akt-dependent manner (Chang et al., 2015).

Many cancer treatment procedures such as chemotherapeutic drugs and radiotherapy focused on DNA damage as a mechanism of action. Several studies reported that DNA damage activates the PI3K/Akt pathway in cancer cells, and diverse effects such as DNA repair regulation and apoptosis prevention provide a form of cancer cells that are resistant to treatment (Q. Liu et al., 2014). It is also reported that abnormally hyperactivated Akt participates in DNA damage accumulation because it impairs nonhomologous end-joining repair in cancer cells (P. Liu et al., 2015). In normal cells such as animal-derived oocytes, inhibition of PTEN (as the main inhibitor of the PI3K/Akt pathway) elevates DNA damage and diminishes DDR protein expression (Maidarti et al., 2019). These reports generally indicate that dysregulated PI3K/Akt pathway in association with DNA damage adversely affects the cells. Downstream proteins of the PI3K/Akt signaling pathway and their regulators interact with various factors such as DDR proteins and cell cycle checkpoints when the cells undergo DNA damage (Figure 1). These interactions affect tumorigenesis and may influence the efficiency of cancer therapeutic approaches. However, the research findings in this context may be contradictory, but we should consider the sophisticated nature of the pathway and its different interactions with other molecules. In the following, we will discuss the main ones of such interactions and their roles in DDR and cancer.

3.1 | PTEN

PTEN as a phosphatase can reverse the activity of PI3K on phosphatidylinositol 4,5 bisphosphate and therefore inhibits the whole pathway activation (Martini et al., 2014). PTEN also has a

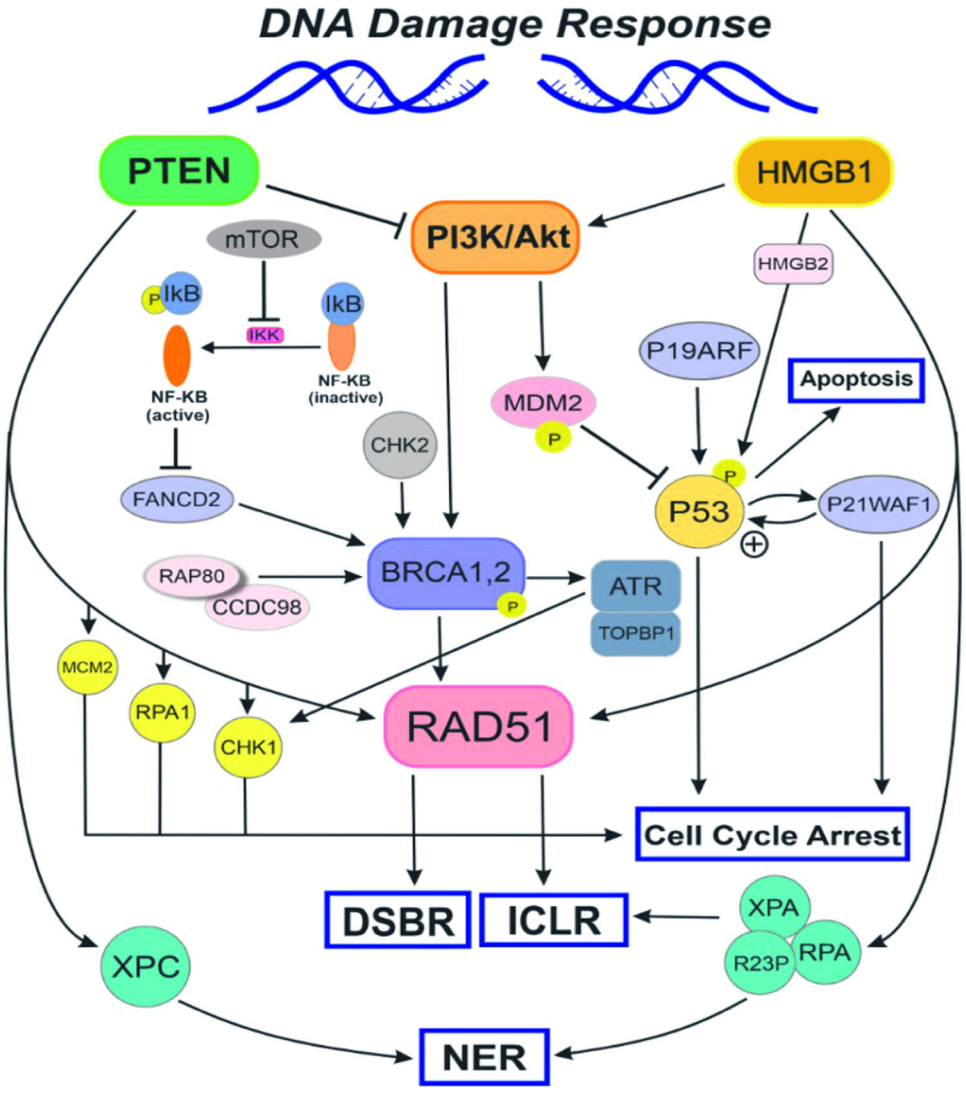

FIGURE 1 A schematic diagram depicting the effect of PI3K signaling on the DNA damage response. DSBR sys, double-strand break repair system; ICLR, interstrand cross-link repair; NER, nucleotide excision repair

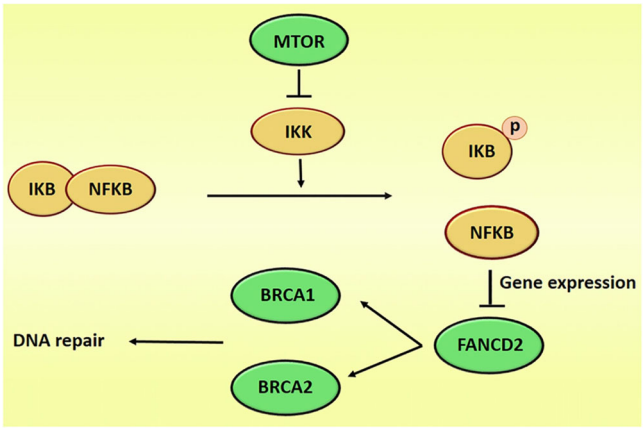

FIGURE 2 A chart describing the relationship between BRCA1, mTOR, and FANCD2. mTOR, mechanistic target of rapamycin

SUMOylated form that can translocate into the nucleus and protect cells against DNA damage, especially by influencing the HR repair system. The fact that PTEN deficient cells are much sensitive to DNA damage, gives rise to the idea of the combination of the chemo-radiotherapy and PI3K inhibitors for more effective cancer treatment (Bassi et al., 2013). Furthermore, it is reported that PTEN phosphorylation is essential for it to interact with chromatin and trigger DNA repair through RAD51 recruitment when cells are subjected to IR (J. Ma et al., 2019). Although the PTEN has a critical role in DNA repair, loss of PTEN diminishes DNA repair and induces genomic instability that leads to deteriorated cancer treatment (Ming & He, 2012). PTEN is involved in many genomic repair systems as it can regulate Rad51 expression, the key protein of the DSB repair system (Shen et al., 2007), also it regulates XPC expression, the important protein of the NER system (Ming et al., 2011). PTEN has a genomic protecting role not only in interphase but also in other cell cycle phases. For example, in the S phase, PTEN interacts (directly or indirectly) with DNA replication proteins such as MCM2 (Minichromosome Maintenance Complex Component 2) (J. Feng et al., 2015), and RPA1 (G. Wang et al., 2015) and checkpoint proteins such as CHK1 (Puc et al., 2005), and provides an efficient and authentic DNA replication and prevents genomic instability caused by replication stress (Hou et al., 2017).

3.2 | BRCA1

BRCA1 is a tumor suppressor that is involved in many DNA damage repair systems and regulates a variety of cell cycle checkpoints. Mutation and loss of function of BRCA1 observed in many cancers (especially breast and ovarian cancers) may indicate that BRCA1 deficiency leads to DNA damage accumulation and tumorigenesis (Chiou et al., 2010; B. Ma et al., 2020). BRCA1 can translocate to DNA damage sites and interact with DNA repair proteins (e.g., RAD51) (Scully et al., 1997). BRCA1 phosphorylation and nuclear localization are regulated by PI3k/Akt pathway. Phosphorylation of BRCA1 by Akt prevents BRCA1 proteasomal degradation, and also Akt cooperates with BRCA1 to reduce DNA damage susceptibility (Nelson et al., 2010). Phosphorylation of BRCA1 by other regulators such as CHK2 is important to BRCA1 functions for selectively enhancing the HR system than the non-homologous one (J. Zhang et al., 2004). BRCA1 deficiency makes cells susceptible to DNA damage accumulation when cells are subjected to external stimuli (such as hormones) and triggers ATM and nuclear factor kappa B (NF-κB) signaling that induces aberrant proliferation (Sau et al., 2016). Furthermore, it has been proven that there is a close relation between three molecules, NF-κB, FANCD2 (Fanconi anemia group D2 protein), and mTOR at the DDR process. In this regard, in the cytoplasm, inhibitor κB (IkB) binds to NF-κB and inhibits its activity. IKK (IkB kinase) is a protein kinase complex that phosphorylates and removes IkB inhibitory effect on NF-κB, leading to NF-κB activation and nucleus localization (Aliyari et al., 2015; Grondona et al., 2018). Also, FANCD2 was introduced as an essential protein for the maintenance of chromosomal stability and DNA repair. Activated-FANCD2 protein is in association with BRCA1 and BRCA2. In fact, NF-κB binds to four binding sites on the promoter region of the FANCD2 gene and suppresses its gene expression. On the other hand, mTOR deactivates the IKKa subunit of the IKK complex, which causes to decrease NF-κB active form and leads to the removal of the negative regulatory effect of NF-κB in FANCD2 gene expression. Thereby, mTOR involves in DDR events in a FANCD2-dependent manner (Garcia-Higuera et al., 2001; F. Guo et al., 2013) (Figure 2).

BRCA also interacts with other proteins such as RAP80 (Receptor-associated protein 80) and CCDC98 (Coiled-coil domain-containing protein 98) to localize DNA damage sites and control the G2/M checkpoint (H. Kim, Chen, et al., 2007; Z. Liu et al., 2007). The recruitment of BRCA1 in DNA damage sites is through the ubiquitin-interacting motif of RAP80 when it interacts with ubiquitinated histones. In case of inhibition of histone ubiquitination, BRCA1 recruitment is diminished, and DNA damage may be increased (J. Wu et al., 2009). BRCA1 not only participates in the regulation of HR DNA repair proteins (e.g., RAD51) but also regulates the NER system by enhancing its related gene expression, such as XPC (Hartman & Ford, 2002). BRCA1 and DDR factors have functioned more than in DNA repair because it is reported that BRCA1 enhances DDR factors such as ATR and TOPBP1 accumulation on sexual unsynapsed chromosomes leading to proper morphogenesis of these chromosomes and meiosis progression (Broering et al., 2014).

3.3 | HMGB1

HMGB1 is a DNA binding protein with vast effects such as induction of cell proliferation and cell cycle proteins (e.g., cyclin D1) by interacting with NF-KB and PI3K/Akt pathways (X.-J. Feng et al., 2014). In a cell line study, it is reported that when HMGB1 is knocked down, the DNA damage increased, and DNA damage repair proteins such as RAD51 decreased in the presence of chemotherapeutic agents (X. Guo et al., 2018). HMGB1 is a critical protein in chromatin

structural remodeling and can recruit the NER system proteins such as XPA, RPA, and R23P to the damaged sites. In the case of HMGB1 omission, the risk of mutagenesis and the sensitivity to ultraviolet irradiation-induced DNA damage elevated (Lange et al., 2008). However, HMGB1 is an important molecule in the induction of DDR pathways, but cancer cells lacking HMGB1 showed resistance to chemotherapeutic agents. This phenomenon may be explained by the fact that in DNA damage, HMGB1 and its associated proteins such as HMGB2 drive DDR and also trigger P53 phosphorylation that may induce apoptosis (Krynetskaia et al., 2009). Another cooperation between HMGB1 and XPA is observed in DNA interstrand crosslinks repair. In lacking both HMGB1 and XPA, the mutagenesis induced by DNA interstrand crosslinks is enhanced (A. Mukherjee & Vasquez, 2016). Nuclear HMGB1 has a regulatory effect on DDR as it is recently reported that overexpression of HMGB1 reduced DNA damage and also DDR because it inhibits ATM activation and subsequent induction of extracellular signal-regulated kinase 1/2 (ERK 1/2) and NF-κB signaling pathways and therefore diminishes heart failure pathogenesis (Takahashi et al., 2019). Posttranslational modifications such as phosphorylation and acylation in HMGB1 enhance interaction with chemotherapeutic agents-induced DNA damage sites and with DDR proteins such as P53 that may drive cells to DNA damage repair or apoptosis (He et al., 2015).

3.4 | PI3K/Akt pathway triggers p19ARF/p53/p21WAF1

p19ARF/p53/p21WAF1 is a signaling pathway that has been known for its roles in tumor suppression, apoptosis, and cell cycle arrest that causes senescence (Sugihara et al., 2001; Symonds et al., 1994). When cells are subjected to IR, the p19ARF/p53/p21WAF1 pathway elevates, which may be acting in cell cycle arrest. Although, it is reported that the resistance of hepatic cancer cells toward senescence is independent of the deficiency in p19ARF/p53/p21WAF1 pathway (Obata et al., 2001). p19ARF, the upstream regulator of the p53/p21WAF1 pathway, has a role in sustained (but not acute) DDR and senescence induction (Bieging-Rolett et al., 2016). p19ARF/p53/p21WAF1 pathway is involved in cell responses to genotoxic agents, and each factor of this pathway interacts with other elements in a precise and complicated manner. In this context, it is reported that p21WAF1 has positive feedback on the transcription and induction of P53 in response to DNA damage (Pang et al., 2011). P53, by its critical functions, prevents the proliferation of cells harboring DNA damage that may develop cancers. P53 levels in cells are reversed by MDM2, the oncogenic protein that ubiquitinated P53 and subjected it to proteasome degradation (Moll & Petrenko, 2003). PI3K/Akt pathway phosphorylates MDM2 that is required for its nuclear localization and subsequent degradation of P53. Hence, upregulated PI3K/Akt pathway decreased the P53 level and its tumor suppressiveness activity in the cells (Mayo & Donner, 2001). PI3K/Akt pathway inhibition upregulates P53, and on the other hand causes upregulation and phosphorylation of PTEN, which has a positive effect on P53 level elevation through stabilizing it (Naderali et al., 2019). This evidence and others that reported the overexpression of PTEN causes P53 overexpression (Li et al., 2019) indicates the positive correlation between the two tumor suppressors in protection against cancer development. However, it is reported that inhibition of the PI3K/Akt pathway, reduced P53 activation and disrupted DNA damage-induced apoptosis (Bar et al., 2005). However in some reports, it is shown that PTEN inactivation, just like PI3K/Akt pathway activation leads to P53 and its target genes upregulation, but this may be due to the P53 balancing effect in regulating cell proliferation and countering oncogenic PI3K/Akt pathway hyperactivation (J.-S. Kim, Lee, et al., 2007). The complicated relationship between the PI3K/Akt pathway and p19ARF/p53/p21WAF1 pathway that are both important signaling pathways in cell cycle, cell proliferation, and other main cellular events and also the results obtained from different cell models and different conditions, may help interpret the variance between reports in this field.

3.5 | Epigenetic, PI3K, and DNA damage/repair

PI3K/Akt pathway-dependent epigenetic effects participate in oncogenesis. Phosphorylation of many substrates by Akt noticeably activates transcription processes and promotes oncogenesis through precise mechanisms such as DNA hypomethylation induction and histone acetylation enhancement. So that, developing new cancer therapies according to these effects of the PI3K/Akt pathway on the epigenome seems to be worthwhile (Spangle et al., 2017). In hepatocellular carcinoma (HCC), the formiminotransferase cyclodeaminase gene is downregulated by its promoter hypermethylation, and when it is overexpressed in the HCC cells, it leads to PI3K/Akt pathway suppression and induces DNA damage and apoptosis (J. Chen et al., 2019). Dual inhibition of histone deacetylases and PI3K favorably sensitizes glioma cells to radiation by inducing cell cycle arrest and impairing DDR through diminishing the activity of DDR-related factors such as NF-κB and FOXM1 (Pal et al., 2018). It is recently reported that aberrant hypermethylation of GADD45A (Growth arrest and DNA-damage-inducible protein 45 alpha), a gene related to DDR, is mediated by PI3K/Akt pathway, which leads to radioresistance in cervical cancer (Lou et al., 2021).

3.6 | PI3K/Akt pathway, MAPKs, and DNA damage/repair

The PI3K/Akt pathway interacts with other signaling cascades such as MAPK (mitogen-activated protein kinase) to regulate cellular events such as proliferation and apoptosis. ERK1/2, one of the known MAPK, which positively correlated with DNA damage-induced apoptosis, could be suppressed by activated Akt (Lee et al., 2006). P53-induced heparin-binding EGF-like growth factor upregulation protects cells from apoptosis by activation of both MAPK and PI3K/Akt pathways. When these pathways are inhibited,

the overall cell survival diminished markedly following DNA damage (Fang et al., 2001). A study on the mechanism of the dual inhibition of MAP/ERK kinase and PI3K on the melanoma cells cytotoxicity revealed that many proteins especially those related to DDR, significantly phosphorylated and when DDR kinases such as ATM and PRKDC (protein kinase, DNA-activated, catalytic subunit) were inhibited, the cytotoxicity mediated by dual inhibition of the pathways enhanced (Kirkpatrick et al., 2013).

3.7 | Importance of other DNA damage-related molecules crosstalk with Pi3K pathway

Expression of X-ray repair cross-complementing group 1 (XRCC1), a protein involved in DNA-damage repair, especially base excision and DSB repair, is regulated by signaling pathways such as MAP/ERK1/2 kinases and PI3K/Akt pathways in human cancer cells (Toulany et al., 2008). The PI3K/Akt pathway significantly participated in an immunomodulator-induced XRCC1 upregulation, and this phenomenon may involve chemotherapeutic resistance in colorectal cancer (CRC). When this pathway is blocked, the CRC cells become more sensitive to DNA damage and cell death (P. Zhang et al., 2017). In regards to γ-H2AX (the indicator of DSB and essential protein in the DDR), it is reported that PI3K/Akt pathway inhibition promotes unrepaired DNA damage after irradiation as inferred by the persistence of γ-H2AX foci in the glioma cells. These results are useful for studies on enhancing the efficiency of irradiation therapy of cancer (Kao et al., 2007). A recent study revealed that the PI3K/Akt pathway inhibition increased γ-H2AX level and decreased RAD51 level and its colocalization with γ-H2AX foci. Consequently, these events led to impaired DDR and enhanced the cytotoxicity of chemotherapeutic agents in several cancer cells (Boichuk et al., 2020).

4 | TARGETING THE PI3k/Akt SIGNALING AND DDR AS A THERAPEUTIC STRATEGY

Radiotherapy remains a neo-adjuvant, adjuvant, or palliative therapeutic strategy for multiple kinds of cancers like head and neck squamous cell carcinoma (HNSCC), HCC, glioblastoma, prostate cancer. IR is the main cause of highly toxic DNA damage production or stimulation of reactive oxygen species in target cancer cells, and then free radicals interact with oxygen molecules and lead to stabilization of DNA damage. Now, depending on the severity of the damage, target cells can choose between repair pathways and cell apoptosis. Radio-resistant malignant cells escape the apoptosis strategy (Ashley & Kemp, 2018; Brown & Wilson, 2004). As a result, radio-resistance (intrinsic or acquired) is a major obstacle in today's cancer therapy.

On this basis, evidence shows that during radiation, the PI3K/Akt pathway activates and frequently expresses in malignant cells, which conduces to initiation of repair response of radiation-induced DSBs and subsequently radio-resistance development in various types of cancer cells (Park et al., 2017). In other words, DSB repair inhibition improves the accumulation of DNA damage leading to radiosensitization. A considerable number of studies have proven that targeting the PI3K/Akt pathway by specific repressors in association with radiation appears to enhance radiosensitization (Wanigasooriya et al., 2020) (Figure 3). Inhibition of PI3K signaling induces DNA damage by dysregulation of HR and NHEJ pathways and depleting deoxynucleoside triphosphates (dNTP). It has been proposed that dNTP as a survival factor helps cells to repair broken DNA (Juvekar et al., 2016; Y. Ma et al., 2018). In vitro and in vivo investigations demonstrated that a dual combination of PARP and PI3K inhibitors induce synthetic lethality in breast, prostate, and ovarian cancer cells and represents a promising preclinical antitumor effect. The United

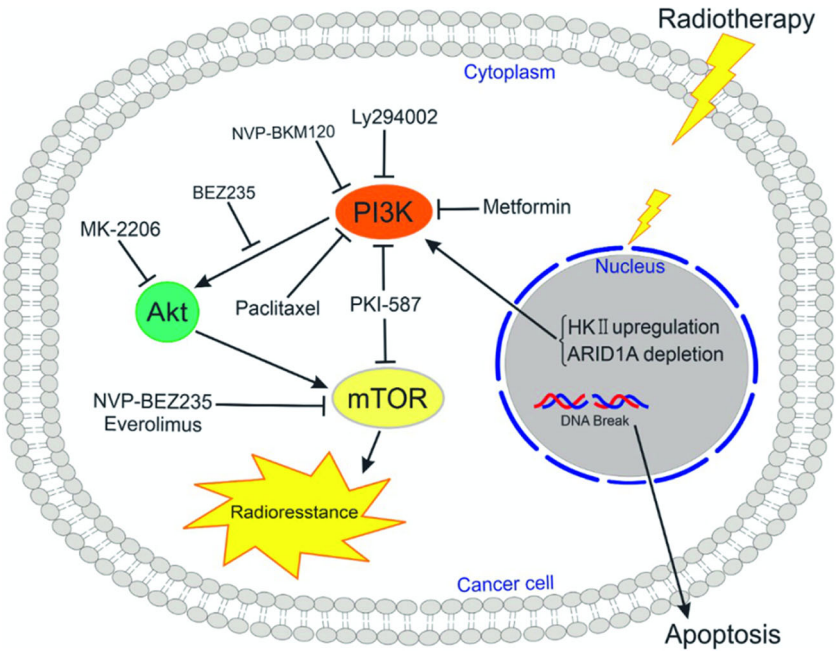

FIGURE 3 Potential effects of the PI3K/Akt/mTOR deactivation in reducing radio-resistance by inhibitors. mTOR, mechanistic target of rapamycin

States Food and Drug Administration has approved Several PI3K pathway inhibitors, such as buparlisib (BKM120), for various cancers. Investigations showed that BKM120 leads to the appearance of DNA damage (significantly increased) and attenuated HR repair by down-regulating BRCA2 or RAD51 (Huang et al., 2020; Landry et al., 2020; Pons-Tostivint et al., 2017).

Chromatin remodeling gene ARID1A (AT-rich interactive domain-containing protein 1A), which plays a cell-cycle regulatory function through modulation of three transcriptional factors E2F1, CCNE1, and c-MYC, has been reported to be frequently mutated in cancer cells. Mechanistically, ARID1A depletion increases the radio-resistance behavior of cancer cells due to apoptosis suppression, cell-cycle progression, DDR development, and PI3K/Akt signaling stimulation of activation. It has been suggested that implementing LY294002 as a PI3K repressor or MK-2206 as an Akt repressor sensitizes ARID1A-depleted-pancreatic cancer cells to radiotherapy (Yang et al., 2018). As such, another in-vitro and in-vivo study released the same results for ARID1A-depleted gastric cancer (GC) cell sensitization to radiotherapy (Q. Zhang et al., 2016).

More importantly, experimental *in vivo* and *in vitro* studies demonstrated that NVP-BEZ235 not only inhibits PI3K (IC_{50} = 4–75 nM) and mTOR (IC_{50} = 20 nM) (Maira et al., 2008) but also has an inhibitory effect on two chief components of DNA repair, including DNA-PKcs and ATM because of homology in the catalytic domain between them (B. Mukherjee et al., 2012). Irradiation in mouse models shows that DSB load in tumor areas was more than normal areas, which opens a new therapeutic window in combinational therapy. It is noteworthy that NVP-BEZ235 can cross the blood-brain barrier and plays a role in anti-DDR activity leading to radio-sensitization in intracranial tumors (Gil del Alcazar et al., 2014). In a recent study, 50 nM of BEZ235 (Dactolisib) appears to abrogate phosphorylation and activation of Akt in both endogenous and exogenous stimuli and also suppresses irradiation-induced DNA-PKcs activation, which overall impairs both repair pathways, resulting in improvement of radiosensitivity of HNSCC cells in-dependent to human papillomavirus status (Schötz et al., 2020).

Hexokinase II (HKII) has promising roles in aerobic glycolysis and ATP production, which provides energy for the DNA damage repair process. Thereby, it has been illustrated that HKII overexpression in multiple myeloma cell lines is correlated with genotoxic stress resistance and cell survival (Pedersen et al., 2002; Pelicano et al., 2006). The co-treatment of Akt and PI3K/mTOR inhibitors, including MK-2206 and BEZ235, with topoisomerase inhibitors (doxorubicin, etoposide, topotecan) disturbs HKII functional activity and synergistically decrease glucose metabolism, and potentially increases apoptosis in multiple myeloma cells (Demel et al., 2015). Indeed, there is evidence to show that topoisomerase activates the PI3K/Akt/mTOR signaling pathway, and in this way, promotes cancer cell growth and invasiveness (Lyu et al., 2020). Furthermore, topoisomerase inhibitors could induce p-Akt downregulation at early time points after treatment (Miyata et al., 2015).

Polymer nanoparticles (NPs) are an ideal approach to deliver drugs accompanied by less toxic side effects (Alemi et al., 2020). NP-BEZ235-Ab improves the γ-ray effect on DNA and reduces the expression level of the pDNA-PKcs enzyme, subsequently inhibits DDR process and conducts cell to apoptosis more efficiently than single-drug BEZ235 (Tang et al., 2020).

Moreover, EGFRmAb–AuNPs + NIR as a new strategy for hypopharyngeal carcinoma treatment upregulates mRNA expression level of DSB factors ATM, and BRCA1 indicating loss of genomic integrity, and downregulates the PI3K/Akt/mTOR pathway, which overall provokes apoptosis (Y. Zhang et al., 2018). Although paclitaxel (PTX) is one of the primary drug choices for advanced GC, acquired resistance to PTX happens in different ways, including drug efflux, microtubule dynamics, and epithelial-mesenchymal transition as well as activation of PI3K/Akt/mTOR and MAPK signaling cascade (Duran et al., 2017; Kavallaris, 2010). Dual blocking of PI3K/Akt/mTOR signaling by BEZ235 is one of the validated strategies to improve the antitumor effectiveness of PTX in GC patients (D. Chen et al., 2018). Twenty four hours after implementing oxaliplatin therapy for HCC patients, the PI3K/Akt/mTOR pathway activates and leads to oxaliplatin resistance and consequently reduces HCC patient survival rate. In this regard, PKI-587 inactivates upregulation of PI3K/Akt/mTOR pathway and suppresses both DNA repair pathways, which sensitizes cell to oxaliplatin-caused-DNA damage and then leads to cell cycle arrest at G0/G1 state and finally cell death. Recent in vivo experimental data have shown that PI3K/mTOR inhibition by PKI-587 in association with oxaliplatin decreases >55% of xenograft tumor size compared to solo oxaliplatin therapy. However, Y. Zhang et al. (2019) demonstrated that implementing PKI-587 alone did not have a remarkable effect on the reduction of tumor size.

Caspases are known as the main mediators of apoptosis. The cooperation between caspase-8 and pro-caspase 3 leads to caspase-3 activation and mediation of programmed cell death. This process can be inhibited by antiapoptotic members of the Bcl-2 family (Hengartner, 2000). A study revealed that the combination of PI3K/Akt repressor and Bcl2 family repressor activate caspase-8 and -3, and also PARP, resulting in cell-death in glioma cell lines in-dependent to PTEN status (Jane et al., 2014).

Maturation of Akt and survivin as oncogenic proteins depends on heat shock protein 90 that can be inhibited by BIIB021 (CNF2024) (Lundgren et al., 2009; Pearl & Prodromou, 2006). Additionally, Triptolide is used for treating inflammatory diseases (B. J. Chen, 2001). Taken collectively, using these two drugs together play a cytotoxic role in thyroid carcinoma cells depending on alteration in some cellular mechanisms like suppression of PI3K/Akt/mTOR and NF-kB signaling pathways and also a significant reduction in the level of survivin, xIAP (X-linked inhibitor of apoptosis protein) and cIAP (cellular inhibitor of apoptosis protein) and finally enhancement of p-p53, and cleaved caspase-3 (S. H. Kim et al., 2016).

Everolimus (Eve) and PTX are widely used alone to treat different kinds of neoplasms like breast cancer (Houghton, 2010; Scripture et al., 2006). Additionally, a study evaluated the co-treatment effect of these two drugs on cervical cancer. In this study, evidence shows that Eve and PTX synergistically inhibit the PI3K/Akt/mTOR pathway

TABLE 2 Targeting PI3K/AKT signaling with specific drugs in combination with other drugs enhances tumor therapy

Combinational therapy	Cell lines	Concentration	Molecular effects	Cellular effects	Reference(s)
LY294002 or MK-2206 with radiotherapy	PANC-1 and SW1990		PI3K/AKT signaling↓	Radiosensitization of ARID1A-depleted-pancreatic and gastric cancer cells	(Yang et al., 2018)
NVP-BEZ235 with radiotherapy	six GBM lines	100 nM	PI3K, mTOR, DNA-PKcs and ATM↓	Radio sensitization glioblastoma	(B. Mukherjee et al., 2012)
NVP-BEZ235 with radiotherapy	U87MG cells	150 mg/kg	ATM and DNA-PKcs↓	The inhibition of DNA repair, Radio sensitization and Improving glioblastoma therapy	(Gil del Alcazar et al., 2014)
NVP-BEZ235 with radiotherapy	ten HNSCC cell lines	50 nM	DNA-PKcs, Akt↓	Radio sensitization of squamous cell carcinoma of the head and neck (HNSCC) both HPV negative and positive	(Schötz et al., 2020)
NP-BEZ235-Ab with radiotherapy	Human HCC HepG2 cell line	10 nM BEZ235	ATM and BRCA1, RAD51, PI3K/mTOR↓	The inhibition of DNA repair, Radio sensitization, improving tumor-cell apoptosis	(Tang et al., 2020)
MK-2206 and BEZ235 with topoisomerase inhibitors	OPM-2 cell line	1 μM + 200 nM + doxorubicin (5 nM–51.2 μM), etoposide (0.5 μM–1.024 mM), topotecan (25 nM-25.6 μM)	Akt, PI3K/mTOR and HKII ↓	Reduction of glucose metabolism and multiple myeloma cells apoptosis	(Demel et al., 2015)
BEZ235 with PTX	PTX-resistant GC cells	(45 mg/kg/d, by gavage) + (10 mg/kg/weekly, by ip)	PI3k/Akt/mTOR↓	Improvement of antitumor effectiveness	(D. Chen et al., 2018)
PKI-587 with oxaliplatin	HCC cell line HepG2 cells and SK-Hep1	0.01, 0.03, and 0.1 μmol/L + 2 μmol/L and 4 μmol/L	PI3K/mTOR↓	chemosensitization, cell-cycle arrest and apoptosis	(Y. Zhang et al., 2019)
NVP-BKM120 with ABT-737	glioma cell lines U87		PI3K/Akt and Bcl-2 family ↓	The inhibition of DNA repair and cell growth, induction of glioma cell apoptosis	(Jane et al., 2014)
BIIB021 and Triptolide	8505C and TPC-1 human thyroid carcinoma cells	1–10mM + 4–40 nM or 1–10 nM	PI3K/Akt/mTOR and NF-kB signaling↓	enhancement of p-p53, and cleaved caspase-3	(S. H. Kim et al., 2016)
Eve and Pac	cell lines HeLa (HPV 18þ) and SiHa (HPV 16þ)	100 nM + 100 nM	PI3K/AKT/mTOR↓	Inhibition of cell proliferation and increase apoptosis	(Dong et al., 2018)

that conduces cervical cancer cells apoptosis and suppression cell proliferation (Dong et al., 2018).

As we mentioned before, damage activates the DDR process to save cells and maintain genome integrity, but a high level of damage is associated with growth arrest, cell death, and suppression of tumorigenesis in different cancers like breast cancer. Cyclin E as an oncoprotein is frequently overexpressed in cancers and mediates resistance of cancer cells to the treatment (Chu et al., 2021). Cyclin E provokes DNA damage and inhibits Akt-mTOR at transcriptional and posttranslational levels, leading to suppression of tumor progression and cell death (Bhardwaj et al., 2014).

It is demonstrated that metformin, as an oral drug that is widely prescribed for diabetes treatment, targets mTORC1 (mTOR complex 1). Thus, metformin plays a tumor-suppressive role in cervical cancer by upregulation of p53 signaling and downregulation of PI3K/Akt pathway (Xia et al., 2020). This signaling cascade has an essential role in the glucose and lipid metabolism function of IGF1. Thus, knockdown of PI3K/Akt/mTOR signaling by inhibitors raises the risk of hyperglycemia in patients, specifically by diabetes mellitus background. A study has reported that mTOR inhibition, in addition to PI3K suppression, can enhance insulin signaling through its effect on the phosphorylation status of insulin receptor substrate-1, while another study has investigated that dual repression of PI3K and mTOR increases hyperglycemia (Khan et al., 2016; Um et al., 2006). Therefore, targeting the PI3K/Akt/mTOR signaling pathway in combination with chemo-radiotherapy is an attractive strategy in the development of tumor therapy (Table 2) (Asati et al., 2016).

5 | CONCLUSION

The PI3K pathway plays a crucial role in cell growth and survival, and its overactivation is one of the most important reasons for cancer occurrence. ATM, ATR, DNA-PKcs, mTOR, and SMG1 are members of the PIKK family, which are involved in DDR signaling mostly with P53 mediatory. PI3K/Akt pathway phosphorylates MDM2 that subsequently destroys P53, and upregulation of this pathway decreases the tumor-suppressive activity of the cells by P53 level decline. Overactivation of DDR is one of the well-known obstacles in chemo-radiotherapy success due to repairing the damage done to DNA by these treatments. Studies show PI3K signaling overactivation in cancer cells has diverse effects such as DNA repair activation and apoptosis prevention, which provides a form of cancer cells that are resistant to treatment. As radiotherapy activates the PI3K/Akt pathway and initiates repair response of radiation-induced DSBs and subsequently radio-resistance development in cancer cells, targeting this pathway is considered as a complementary treatment approach. BKM120, LY294002, BEZ235, and PKI-587 are some of the recent inhibitors of PI3K, of which their combinations with chemo-radiotherapy have shown promising results in conducing cancer cells to apoptosis. Despite efforts to inhibit PI3K and DDR pathways to increase the sensitivity of cancer cells to treatment, more studies are needed to pave the way for clinical use of PI3K inhibitors in combination with chemo-radiotherapy in the near future.

ACKNOWLEDGMENTS

The authors would like to thank Shohada Clinical Research Development Unit, Shohada Hospital, Tabriz University of Medical Science, Tabriz, Iran

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ORCID

Forough Alemi http://orcid.org/0000-0003-2055-1961
Yusuf Elhaei http://orcid.org/0000-0001-5977-4324
Zatollah Asemi http://orcid.org/0000-0001-5265-4792
Bahman Yousefi http://orcid.org/0000-0002-4220-1527
Maryam Majidinia http://orcid.org/0000-0001-9776-5816

REFERENCES

Alemi, F., Zarezadeh, R., Sadigh, A. R., Hamishehkar, H., Rahimi, M., Majidinia, M., Asemi, Z., Ebrahimi-Kalan, A., Yousefi, B., & Rashtchizadeh, N. (2020). Graphene oxide and reduced graphene oxide: Efficient cargo platforms for cancer theranostics. *Journal of Drug Delivery Science and Technology*, *60*, 101974.

Aliyari, Z., Alemi, F., Brazvan, B., Taye fi Nasrabadi, H., & Charoudeh, H. N. (2015). $Cd26^{+}$ cord blood mononuclear cells significantly produce B, T, and Nk cells. *Iranian Journal of Immunology*, *12*(1), 16–26.

Asati, V., Mahapatra, D. K., & Bharti, S. K. (2016). PI3K/Akt/mTOR and Ras/Raf/MEK/ERK signaling pathways inhibitors as anticancer agents: Structural and pharmacological perspectives. *European Journal of Medicinal Chemistry*, *109*, 314–341. https://doi.org/10.1016/j.ejmech.2016.01.012

Ashley, A. K., & Kemp, C. J. (2018). DNA-PK, ATM, and ATR: PIKKing on p53. *Cell Cycle*, *17*(3), 275–276. https://doi.org/10.1080/15384101.2017.1412147

Ashley, A. K., Shrivastav, M., Nie, J., Amerin, C., Troksa, K., Glanzer, J. G., Liu, S., Opiyo, S. O., Dimitrova, D. D., Le, P., Sishc, B., Bailey, S. M., Oakley, G. G., & Nickoloff, J. A. (2014). DNA-PK phosphorylation of RPA32 Ser4/Ser8 regulates replication stress checkpoint activation, fork restart, homologous recombination and mitotic catastrophe. *DNA Repair (Amst)*, *21*, 131–139. https://doi.org/10.1016/j.dnarep.2014.04.008

Bandhakavi, S., Kim, Y. M., Ro, S. H., Xie, H., Onsongo, G., Jun, C. B., Kim, D. H., & Griffin, T. J. (2010). Quantitative nuclear proteomics identifies mTOR regulation of DNA damage response. *Molecular & Cellular Proteomics*, *9*(2), 403–414. https://doi.org/10.1074/mcp.M900326-MCP200

Bar, J., Lukaschuk, N., Zalcenstein, A., Wilder, S., Seger, R., & Oren, M. (2005). The PI3K inhibitor LY294002 prevents p53 induction by DNA damage and attenuates chemotherapy-induced apoptosis. *Cell Death & Differentiation*, *12*(12), 1578–1587.

Bartek, J., & Lukas, J. (2007). DNA damage checkpoints: From initiation to recovery or adaptation. *Current Opinion in Cell Biology*, *19*(2), 238–245. https://doi.org/10.1016/j.ceb.2007.02.009

Bassi, C., Ho, J., Srikumar, T., Dowling, R. J., Gorrini, C., Miller, S. J., Mak, T. W., Neel, B. G., Raught, B., & Stambolic, V. (2013). Nuclear

PTEN controls DNA repair and sensitivity to genotoxic stress. *Science*, *341*(6144), 395–399.

Basu, A. K. (2018). DNA damage, mutagenesis and cancer. *International Journal of Molecular Sciences*, *19*(4):970. https://doi.org/10.3390/ijms19040970

Bhardwaj, A., Rosen, D., Liu, M., Liu, Y., Hao, Q., Ganesan, N., Etzel, C. J., Gullett, A., Albarracin, C. T., & Bedrosian, I. (2014). Suppression of Akt-mTOR pathway-a novel component of oncogene induced DNA damage response barrier in breast tumorigenesis. *PLoS One*, *9*(5), e97076. https://doi.org/10.1371/journal.pone.0097076

Bieging-Rolett, K. T., Johnson, T. M., Brady, C. A., Beaudry, V. G., Pathak, N., Han, S., & Attardi, L. D. (2016). P19 Arf is required for the cellular response to chronic DNA damage. *Oncogene*, *35*(33), 4414–4421.

Blackford, A. N., & Jackson, S. P. (2017). ATM, ATR, and DNA-PK: The trinity at the heart of the DNA damage response. *Molecular Cell*, *66*(6), 801–817. https://doi.org/10.1016/j.molcel.2017.05.015

Blagih, J., Buck, M. D., & Vousden, K. H. (2020). p53, cancer and the immune response. *Journal of Cell Science*, *133*(5), jcs237453. https://doi.org/10.1242/jcs.237453

Boichuk, S., Bikinieva, F., Nurgatina, I., Dunaev, P., Valeeva, E., Aukhadieva, A., Sabirov, A., & Galembikova, A. (2020). Inhibition of AKT-signaling sensitizes soft tissue sarcomas (STS) and gastrointestinal stromal tumors (GIST) to doxorubicin via targeting of homology-mediated DNA repair. *International Journal of Molecular Sciences*, *21*(22), 8842.

Broering, T. J., Alavattam, K. G., Sadreyev, R. I., Ichijima, Y., Kato, Y., Hasegawa, K., Camerini-Otero, R. D., Lee, J. T., Andreassen, P. R., & Namekawa, S. H. (2014). BRCA1 establishes DNA damage signaling and pericentric heterochromatin of the X chromosome in male meiosis. *Journal of Cell Biology*, *205*(5), 663–675.

Brown, J. M., & Wilson, W. R. (2004). Exploiting tumour hypoxia in cancer treatment. *Nature Reviews Cancer*, *4*(6), 437–447. https://doi.org/10.1038/nrc1367

Cazzalini, O., Scovassi, A. I., Savio, M., Stivala, L. A., & Prosperi, E. (2010). Multiple roles of the cell cycle inhibitor p21(CDKN1A) in the DNA damage response. *Mutation Research/DNA Repair*, *704*(1-3), 12–20. https://doi.org/10.1016/j.mrrev.2010.01.009

Chang, L., Graham, P. H., Ni, J., Hao, J., Bucci, J., Cozzi, P. J., & Li, Y. (2015). Targeting PI3K/Akt/mTOR signaling pathway in the treatment of prostate cancer radioresistance. *Critical Reviews in Oncology/Hematology*, *96*(3), 507–517. https://doi.org/10.1016/j.critrevonc.2015.07.005

Chen, B. J. (2001). Triptolide, a novel immunosuppressive and anti-inflammatory agent purified from a Chinese herb Tripterygium wilfordii Hook F. *Leukemia and Lymphoma*, *42*(3), 253–265. https://doi.org/10.3109/10428190109064582

Chen, D., Lin, X., Zhang, C., Liu, Z., Chen, Z., Li, Z., Wang, J., Li, B., Hu, Y., Dong, B., Shen, L., Ji, J., Gao, J., & Zhang, X. (2018). Dual PI3K/mTOR inhibitor BEZ235 as a promising therapeutic strategy against paclitaxel-resistant gastric cancer via targeting PI3K/Akt/mTOR pathway. *Cell Death & Disease*, *9*(2), 123. https://doi.org/10.1038/s41419-017-0132-2

Chen, J., Chen, Z., Huang, Z., Yu, H., Li, Y., & Huang, W. (2019). Formiminotransferase cyclodeaminase suppresses hepatocellular carcinoma by modulating cell apoptosis, DNA damage, and phosphatidylinositol 3-kinases (PI3K)/Akt signaling pathway. *Medical Science Monitor*, *25*, 4474–4484. https://doi.org/10.12659/msm.916202

Chiou, S. H., Wang, M. L., Chou, Y. T., Chen, C. J., Hong, C. F., Hsieh, W. J., Chang, H. T., Chen, Y. S., Lin, T. W., Hsu, H. S., & Wu, C. W. (2010). Coexpression of Oct4 and Nanog enhances malignancy in lung adenocarcinoma by inducing cancer stem cell-like properties and epithelial-mesenchymal transdifferentiation. *Cancer Research*, *70*(24), 10433–10444. https://doi.org/10.1158/0008-5472.can-10-2638

Chu, C., Geng, Y., Zhou, Y., & Sicinski, P. (2021). Cyclin E in normal physiology and disease states. *Trends in Cell Biology*, *31*, 732–746.

Cimprich, K. A., & Cortez, D. (2008). ATR: An essential regulator of genome integrity. *Nature Reviews Molecular Cell Biology*, *9*(8), 616–627. https://doi.org/10.1038/nrm2450

Dai, Y., & Grant, S. (2010). New insights into checkpoint kinase 1 in the DNA damage response signaling network. *Clinical Cancer Research*, *16*(2), 376–383. https://doi.org/10.1158/1078-0432.ccr-09-1029

Demel, H. R., Feuerecker, B., Piontek, G., Seidl, C., Blechert, B., Pickhard, A., & Essler, M. (2015). Effects of topoisomerase inhibitors that induce DNA damage response on glucose metabolism and PI3K/Akt/mTOR signaling in multiple myeloma cells. *American Journal of Cancer Research*, *5*(5), 1649–1664.

Dong, P., Hao, F., Dai, S., & Tian, L. (2018). Combination therapy Eve and Pac to induce apoptosis in cervical cancer cells by targeting PI3K/AKT/mTOR pathways. *Journal of Receptor and Signal Transduction Research*, *38*(1), 83–88. https://doi.org/10.1080/10799893.2018.1426610

Duran, G. E., Wang, Y. C., Moisan, F., Francisco, E. B., & Sikic, B. I. (2017). Decreased levels of baseline and drug-induced tubulin polymerisation are hallmarks of resistance to taxanes in ovarian cancer cells and are associated with epithelial-to-mesenchymal transition. *British Journal of Cancer*, *116*(10), 1318–1328. https://doi.org/10.1038/bjc.2017.102

Enari, M., Matsushima-Hibiya, Y., Miyazaki, M., & Otomo, R. (2017). Studies of ATM kinase activity using engineered ATM sensitive to ATP Analogues (ATM-AS). *Methods in Molecular Biology*, *1599*, 145–156. https://doi.org/10.1007/978-1-4939-6955-5_11

Engelman, J. A., Luo, J., & Cantley, L. C. (2006). The evolution of phosphatidylinositol 3-kinases as regulators of growth and metabolism. *Nature Reviews Genetics*, *7*(8), 606–619. https://doi.org/10.1038/nrg1879

Enriquez-Rios, V., Dumitrache, L. C., Downing, S. M., Li, Y., Brown, E. J., Russell, H. R., & McKinnon, P. J. (2017). DNA-PKcs, ATM, and ATR Interplay maintains genome integrity during neurogenesis. *Journal of Neuroscience*, *37*(4), 893–905. https://doi.org/10.1523/jneurosci.4213-15.2016

Fang, L., Li, G., Liu, G., Lee, S. W., & Aaronson, S. A. (2001). p53 induction of heparin-binding EGF-like growth factor counteracts p53 growth suppression through activation of MAPK and PI3K/Akt signaling cascades. *EMBO Journal*, *20*(8), 1931–1939. https://doi.org/10.1093/emboj/20.8.1931

Feng, J., Liang, J., Li, J., Li, Y., Liang, H., Zhao, X., Mcnutt, M. A., & Yin, Y. (2015). PTEN controls the DNA replication process through MCM2 in response to replicative stress. *Cell Reports*, *13*(7), 1295–1303.

Feng, X.-J., Liu, S.-X., Wu, C., Kang, P.-P., Liu, Q.-J., Hao, J., Li, H. B., Li, F., Zhang, Y. J., Fu, X. H., Zhang, S. B., & Zuo, L. F. (2014). The PTEN/PI3K/Akt signaling pathway mediates HMGB1-induced cell proliferation by regulating the NF-κB/cyclin D1 pathway in mouse mesangial cells. *American Journal of Physiology-Cell Physiology*, *306*(12), C1119–C1128.

Garcia-Higuera, I., Taniguchi, T., Ganesan, S., Meyn, M. S., Timmers, C., Hejna, J., Grompe, M., & D'Andrea, A. D. (2001). Interaction of the Fanconi anemia proteins and BRCA1 in a common pathway. *Molecular Cell*, *7*(2), 249–262. https://doi.org/10.1016/s1097-2765(01)00173-3

Gewandter, J. S., Bambara, R. A., & O'Reilly, M. A. (2011). The RNA surveillance protein SMG1 activates p53 in response to DNA double-strand breaks but not exogenously oxidized mRNA. *Cell Cycle*, *10*(15), 2561–2567. https://doi.org/10.4161/cc.10.15.16347

Gewandter, J. S., Bambara, R. A., & O'Reilly, M. A. (2011). The RNA surveillance protein SMG1 activates p53 in response to DNA

double-strand breaks but not exogenously oxidized mRNA. *Cell Cycle*, *10*(15), 2561–2567.

Gil del Alcazar, C. R., Hardebeck, M. C., Mukherjee, B., Tomimatsu, N., Gao, X., Yan, J., Xie, X. J., Bachoo, R., Li, L., Habib, A. A., & Burma, S. (2014). Inhibition of DNA double-strand break repair by the dual PI3K/mTOR inhibitor NVP-BEZ235 as a strategy for radiosensitization of glioblastoma. *Clinical Cancer Research*, *20*(5), 1235–1248. https://doi.org/10.1158/1078-0432.ccr-13-1607

Goodwin, J. F., & Knudsen, K. E. (2014). Beyond DNA repair: DNA-PK function in cancer. *Cancer Discov*, *4*(10), 1126–1139. https://doi.org/10.1158/2159-8290.cd-14-0358

Green, D. R., & Kroemer, G. (2009). Cytoplasmic functions of the tumour suppressor p53. *Nature*, *458*(7242), 1127–1130. https://doi.org/10.1038/nature07986

Grondona, P., Bucher, P., Schulze-Osthoff, K., Hailfinger, S., & Schmitt, A. (2018). NF-κB activation in lymphoid malignancies: Genetics, signaling, and targeted therapy. *Biomedicines*, *6*(2):38. https://doi.org/10.3390/biomedicines6020038

Gubanova, E., Issaeva, N., Gokturk, C., Djureinovic, T., & Helleday, T. (2013). SMG-1 suppresses CDK2 and tumor growth by regulating both the p53 and Cdc25A signaling pathways. *Cell Cycle*, *12*(24), 3770–3780. https://doi.org/10.4161/cc.26660

Guo, F., Li, J., Du, W., Zhang, S., O'Connor, M., Thomas, G., Kozma, S., Zingarelli, B., Pang, Q., & Zheng, Y. (2013). mTOR regulates DNA damage response through NF-κB-mediated FANCD2 pathway in hematopoietic cells. *Leukemia*, *27*(10), 2040–2046. https://doi.org/10.1038/leu.2013.93

Guo, X., He, D., Zhang, E., Chen, J., Chen, Q., Li, Y., Yang, L., Yang, Y., Zhao, Y., Wang, G., He, J., & Cai, Z. (2018). HMGB1 knockdown increases MM cell vulnerability by regulating autophagy and DNA damage repair. *Journal of Experimental & Clinical Cancer Research*, *37*(1), 205.

Hartman, A.-R., & Ford, J. M. (2002). BRCA1 induces DNA damage recognition factors and enhances nucleotide excision repair. *Nature Genetics*, *32*(1), 180–184.

He, Y., Ding, Y., Wang, D., Zhang, W., Chen, W., Liu, X., Qin, W., Qian, X., Chen, H., & Guo, Z. (2015). HMGB1 bound to cisplatin–DNA adducts undergoes extensive acetylation and phosphorylation in vivo. *Chemical Science*, *6*(3), 2074–2078.

Hengartner, M. O. (2000). The biochemistry of apoptosis. *Nature*, *407*(6805), 770–776. https://doi.org/10.1038/35037710

Horn, D., Hess, J., Freier, K., Hoffmann, J., & Freudlsperger, C. (2015). Targeting EGFR-PI3K-AKT-mTOR signaling enhances radiosensitivity in head and neck squamous cell carcinoma. *Expert Opinion on Therapeutic Targets*, *19*(6), 795–805. https://doi.org/10.1517/14728222.2015.1012157

Hou, S. Q., Ouyang, M., Brandmaier, A., Hao, H., & Shen, W. H. (2017). PTEN in the maintenance of genome integrity: From DNA replication to chromosome segregation. *BioEssays*, *39*(10), 1700082.

Houghton, P. J. (2010). Everolimus. *Clinical Cancer Research*, *16*(5), 1368–1372. https://doi.org/10.1158/1078-0432.ccr-09-1314

Huang, T. -T., Lampert, E. J., Coots, C., & Lee, J.-M. (2020). Targeting the PI3K pathway and DNA damage response as a therapeutic strategy in ovarian cancer. *Cancer Treatment Reviews*, *86*, 86.

Jane, E. P., Premkumar, D. R., Morales, A., Foster, K. A., & Pollack, I. F. (2014). Inhibition of phosphatidylinositol 3-kinase/AKT signaling by NVP-BKM120 promotes ABT-737-induced toxicity in a caspase-dependent manner through mitochondrial dysfunction and DNA damage response in established and primary cultured glioblastoma cells. *Journal of Pharmacology and Experimental Therapeutics*, *350*(1), 22–35. https://doi.org/10.1124/jpet.114.212910

Jiang, N., Dai, Q., Su, X., Fu, J., Feng, X., & Peng, J. (2020). Role of PI3K/AKT pathway in cancer: The framework of malignant behavior. *Molecular Biology Reports*, *47*(6), 4587–4629. https://doi.org/10.1007/s11033-020-05435-1

Jin, M. H., & Oh, D.-Y. (2019). ATM in DNA repair in cancer. *Pharmacology and Therapeutics*, *203*, 107391. https://doi.org/10.1016/j.pharmthera.2019.07.002

Jung, S. H., Hwang, H. J., Kang, D., Park, H. A., Lee, H. C., Jeong, D., Lee, K., Park, H. J., Ko, Y. G., & Lee, J. S. (2019). mTOR kinase leads to PTEN-loss-induced cellular senescence by phosphorylating. *Oncogene*, *38*(10), p531639–1650.

Juvekar, A., Hu, H., Yadegarynia, S., Lyssiotis, C. A., Ullas, S., Lien, E. C., Bellinger, G., Son, J., Hok, R. C., Seth, P., Daly, M. B., Kim, B., Scully, R., Asara, J. M., Cantley, L. C., & Wulf, G. M. (2016). Phosphoinositide 3-kinase inhibitors induce DNA damage through nucleoside depletion. *Proceedings of the National Academy of Sciences*, *113*(30), E4338–E4347.

Kao, G. D., Jiang, Z., Fernandes, A. M., Gupta, A. K., & Maity, A. (2007). Inhibition of phosphatidylinositol-3-OH kinase/Akt signaling impairs DNA repair in glioblastoma cells following ionizing radiation. *Journal of Biological Chemistry*, *282*(29), 21206–21212. https://doi.org/10.1074/jbc.M703042200

Karimian, A., Mir, S. M., Parsian, H., Refieyan, S., Mirza-Aghazadeh-Attari, M., Yousefi, B., & Majidinia, M. (2019). Crosstalk between Phosphoinositide 3-kinase/Akt signaling pathway with DNA damage response and oxidative stress in cancer. *Journal of Cellular Biochemistry*, *120*(6), 10248–10272. https://doi.org/10.1002/jcb.28309

Kavallaris, M. (2010). Microtubules and resistance to tubulin-binding agents. *Nature Reviews Cancer*, *10*(3), 194–204. https://doi.org/10.1038/nrc2803

Khan, K. H., Wong, M., Rihawi, K., Bodla, S., Morganstein, D., Banerji, U., & Molife, L. R. (2016). Hyperglycemia and phosphatidylinositol 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/AKT/mTOR) inhibitors in phase I trials: Incidence, predictive factors, and management. *The oncologist*, *21*(7), 855–860. https://doi.org/10.1634/theoncologist.2015-0248

Kim, H., Chen, J., & Yu, X. (2007). Ubiquitin-binding protein RAP80 mediates BRCA1-dependent DNA damage response. *Science*, *316*(5828), 1202–1205.

Kim, J.-S., Lee, C., Bonifant, C. L., Ressom, H., & Waldman, T. (2007). Activation of p53-dependent growth suppression in human cells by mutations in PTEN or PIK3CA. *Molecular and Cellular Biology*, *27*(2), 662–677.

Kim, S. H., Kang, J. G., Kim, C. S., Ihm, S. H., Choi, M. G., Yoo, H. J., & Lee, S. J. (2016). Synergistic cytotoxicity of BIIB021 with triptolide through suppression of PI3K/Akt/mTOR and NF-κB signal pathways in thyroid carcinoma cells. *Biomedicine & Pharmacotherapy*, *83*, 22–32. https://doi.org/10.1016/j.biopha.2016.06.014

Kirkpatrick, D. S., Bustos, D. J., Dogan, T., Chan, J., Phu, L., Young, A., Friedman, L. S., Belvin, M., Song, Q., Bakalarski, C. E., & Hoeflich, K. P. (2013). Phosphoproteomic characterization of DNA damage response in melanoma cells following MEK/PI3K dual inhibition. *Proceedings of the National Academy of Sciences*, *110*(48), 19426–19431.

Krynetskaia, N. F., Phadke, M. S., Jadhav, S. H., & Krynetskiy, E. Y. (2009). Chromatin-associated proteins HMGB1/2 and PDIA3 trigger cellular response to chemotherapy-induced DNA damage. *Molecular Cancer Therapeutics*, *8*(4), 864–872.

Landry, M., DuRoss, A., Neufeld, M., Hahn, L., Sahay, G., Luxenhofer, R., & Sun, C. (2020). Low dose novel PARP-PI3K inhibition via nanoformulation improves colorectal cancer immunoradiotherapy. *Materials Today Bio*, *8*, 100082.

Lange, S. S., Mitchell, D. L., & Vasquez, K. M. (2008). High mobility group protein B1 enhances DNA repair and chromatin modification after DNA damage. *Proceedings of the National Academy of Sciences of the United States of America*, *105*(30), 10320–10325. https://doi.org/10.1073/pnas.0803181105

Lee, E. R., Kim, J. Y., Kang, Y. J., Ahn, J. Y., Kim, J. H., Kim, B. W., Choi, H. Y., Jeong, M. Y., & Cho, S. G. (2006). Interplay between PI3K/Akt and MAPK signaling pathways in DNA-damaging drug-induced apoptosis. *Biochimica et Biophysica Acta/General Subjects*, *1763*(9), 958–968. https://doi.org/10.1016/j.bbamcr.2006.06.006

Lempiäinen, H., & Halazonetis, T. D. (2009). Emerging common themes in regulation of PIKKs and PI3Ks. *The EMBO Journal*, *28*(20), 3067–3073.

Li, B., Zhang, J., Su, Y., Hou, Y., Wang, Z., Zhao, L., Sun, S., & Fu, H. (2019). Overexpression of PTEN may increase the effect of pemetrexed on A549 cells via inhibition of the PI3K/AKT/mTOR pathway and carbohydrate metabolism. *Molecular Medicine Reports*, *20*(4), 3793–3801.

Liu, P., Gan, W., Guo, C., Xie, A., Gao, D., Guo, J., Zhang, J., Willis, N., Su, A., Asara, J. M., Scully, R., & Wei, W. (2015). Akt-mediated phosphorylation of XLF impairs non-homologous end-joining DNA repair. *Molecular Cell*, *57*(4), 648–661. https://doi.org/10.1016/j.molcel.2015.01.005

Liu, Q., Turner, K. M., Alfred Yung, W. K., Chen, K., & Zhang, W. (2014). Role of AKT signaling in DNA repair and clinical response to cancer therapy. *Neuro-oncology*, *16*(10), 1313–1323. https://doi.org/10.1093/neuonc/nou058

Liu, Z., Wu, J., & Yu, X. (2007). CCDC98 targets BRCA1 to DNA damage sites. *Nature Structural & Molecular Biology*, *14*(8), 716–720.

Lou, M., Li, R., Lang, T. Y., Zhang, L. Y., Zhou, Q., & Li, L. (2021). Aberrant methylation of GADD45A is associated with decreased radiosensitivity in cervical cancer through the PI3K/AKT signaling pathway. *Oncology Letters*, *21*(1), 8. https://doi.org/10.3892/ol.2020.12269

Lovejoy, C. A., & Cortez, D. (2009). Common mechanisms of PIKK regulation. *DNA Repair (Amst)*, *8*(9), 1004–1008. https://doi.org/10.1016/j.dnarep.2009.04.006

Lundgren, K., Zhang, H., Brekken, J., Huser, N., Powell, R. E., Timple, N., Busch, D. J., Neely, L., Sensintaffar, J. L., Yang, Y. C., McKenzie, A., Friedman, J., Scannevin, R., Kamal, A., Hong, K., Kasibhatla, S. R., Boehm, M. F., & Burrows, F. J. (2009). BIIB021, an orally available, fully synthetic small-molecule inhibitor of the heat shock protein Hsp90. *Molecular Cancer Therapeutics*, *8*(4), 921–929. https://doi.org/10.1158/1535-7163.mct-08-0758

Lyu, W. J., Shu, Y. J., Liu, Y. B., & Dong, P. (2020). Topoisomerase II alpha promotes gallbladder cancer proliferation and metastasis through activating phosphatidylinositol 3-kinase/protein kinase B/mammalian target of rapamycin signaling pathway. *Chin Med J (Engl)*, *133*(19), 2321–2329. https://doi.org/10.1097/cm9.0000000000001075

Ma, B., Guo, W., Shan, M., Zhang, N., Ma, B., & Sun, G. (2020). BRCA1 subcellular localization regulated by PI3K signaling pathway in triple-negative breast cancer MDA-MB-231 cells and hormone-sensitive T47D cells. *Open Life Sciences*, *15*(1), 501–510. https://doi.org/10.1515/biol-2020-0054

Ma, J., Benitez, J. A., Li, J., Miki, S., Ponte de Albuquerque, C., Galatro, T., Orellana, L., Zanca, C., Reed, R., Boyer, A., Koga, T., Varki, N. M., Fenton, T. R., Nagahashi Marie, S. K., Lindahl, E., Gahman, T. C., Shiau, A. K., Zhou, H., DeGroot, J., Furnari, F. B. (2019). Inhibition of nuclear PTEN tyrosine phosphorylation enhances glioma radiation sensitivity through attenuated DNA repair. *Cancer Cell*, *35*(3), 504–518. e507.

Ma, Y., Vassetzky, Y., & Dokudovskaya, S. (2018). mTORC1 pathway in DNA damage response. *Biochimica et Biophysica Acta (BBA)-Molecular Cell Research*, *1865*(9), 1293–1311.

Maidarti, M., Clarkson, Y. L., McLaughlin, M., Anderson, R. A., & Telfer, E. E. (2019). Inhibition of PTEN activates bovine non-growing follicles in vitro but increases DNA damage and reduces DNA repair response. *Human Reproduction*, *34*(2), 297–307. https://doi.org/10.1093/humrep/dey354

Maira, S. M., Stauffer, F., Brueggen, J., Furet, P., Schnell, C., Fritsch, C., Brachmann, S., Chène, P., De Pover, A., Schoemaker, K., Fabbro, D., Gabriel, D., Simonen, M., Murphy, L., Finan, P., Sellers, W., & García-Echeverría, C. (2008). Identification and characterization of NVP-BEZ235, a new orally available dual phosphatidylinositol 3-kinase/mammalian target of rapamycin inhibitor with potent in vivo antitumor activity. *Molecular Cancer Therapeutics*, *7*(7), 1851–1863. https://doi.org/10.1158/1535-7163.mct-08-0017

Majidinia, M., & Yousefi, B. (2017). DNA repair and damage pathways in breast cancer development and therapy. *DNA Repair (Amst)*, *54*, 22–29. https://doi.org/10.1016/j.dnarep.2017.03.009

Malakoti, F., Alemi, F., Younesi, S., Majidinia, M., Yousefi, B., Morovat, P., Khelghati, N., Maleki, M., Karimian, A., & Asemi, Z. (2021). The cross-talk between signaling pathways, noncoding RNAs and DNA damage response: Emerging players in cancer progression. *DNA Repair (Amst)*, *98*, 103036. https://doi.org/10.1016/j.dnarep.2020.103036

Manning, B. D., & Toker, A. (2017). AKT/PKB signaling: Navigating the network. *Cell*, *169*(3), 381–405. https://doi.org/10.1016/j.cell.2017.04.001

Maréchal, A., & Zou, L. (2013). DNA damage sensing by the ATM and ATR kinases. *Cold Spring Harbor Perspectives in Biology*, *5*(9), https://doi.org/10.1101/cshperspect.a012716

Martini, M., De Santis, M. C., Braccini, L., Gulluni, F., & Hirsch, E. (2014). PI3K/AKT signaling pathway and cancer: An updated review. *Annals of Medicine*, *46*(6), 372–383.

Mayo, L. D., & Donner, D. B. (2001). A phosphatidylinositol 3-kinase/Akt pathway promotes translocation of Mdm2 from the cytoplasm to the nucleus. *Proceedings of the National Academy of Sciences*, *98*(20), 11598–11603.

McIlwain, D. R., Pan, Q., Reilly, P. T., Elia, A. J., McCracken, S., Wakeham, A. C., Itie-Youten, A., Blencowe, B. J., & Mak, T. W. (2010). Smg1 is required for embryogenesis and regulates diverse genes via alternative splicing coupled to nonsense-mediated mRNA decay. *Proceedings of the National Academy of Sciences of the United States of America*, *107*(27), 12186–12191. https://doi.org/10.1073/pnas.1007336107

Medina-Medina, I., Martínez-Sánchez, M., Hernández-Monge, J., Fahraeus, R., Muller, P., & Olivares-Illana, V. (2018). p53 promotes its own polyubiquitination by enhancing the HDM2 and HDMX interaction. *Protein Science*, *27*(5), 976–986.

Medová, M., Medo, M., Hovhannisyan, L., Maldonado, C. M., Aebersold, D. M., & Zimmer, Y. (2020). DNA-PK in human malignant disorders: Mechanisms and implications for pharmacological interventions. *Pharmacology & Therapeutics*, *215*, 107617.

Menolfi, D., & Zha, S. (2020). ATM, ATR and DNA-PKcs kinases-the lessons from the mouse models: Inhibition ≠ deletion. *Cell & Bioscience*, *10*, 8. https://doi.org/10.1186/s13578-020-0376-x

Ming, M., Feng, L., Shea, C. R., Soltani, K., Zhao, B., Han, W., Smart, R. C., Trempus, C. S., & He, Y. Y. (2011). PTEN positively regulates UVB-induced DNA damage repair. *Cancer Research*, *71*(15), 5287–5295.

Ming, M., & He, Y.-Y. (2012). PTEN in DNA damage repair. *Cancer Letters*, *319*(2), 125–129.

Miyata, S., Fukuda, Y., Tojima, H., Matsuzaki, K., Kitanaka, S., & Sawada, H. (2015). Mechanism of the inhibition of leukemia cell growth and induction of apoptosis through the activation of ATR and PTEN by the topoisomerase inhibitor 3EZ, 20Ac-ingenol. *Leukemia Research*, *39*(9), 927–932. https://doi.org/10.1016/j.leukres.2015.06.006

Moll, U. M., & Petrenko, O. (2003). The MDM2-p53 interaction. *Molecular Cancer Research*, *1*(14), 1001–1008.

Mukherjee, A., & Vasquez, K. M. (2016). HMGB1 interacts with XPA to facilitate the processing of DNA interstrand crosslinks in human cells. *Nucleic Acids Research*, *44*(3), 1151–1160.

Mukherjee, B., Tomimatsu, N., Amancherla, K., Camacho, C. V., Pichamoorthy, N., & Burma, S. (2012). The dual PI3K/mTOR inhibitor NVP-BEZ235 is a potent inhibitor of ATM- and DNA-PKCs-mediated

DNA damage responses. *Neoplasia*, *14*(1), 34–43. https://doi.org/10.1593/neo.111512

Naderali, E., Valipour, B., Khaki, A. A., Soleymani Rad, J., Alihemmati, A., Rahmati, M., & Nozad Charoudeh, H. (2019). Positive effects of PI3K/Akt signaling inhibition on PTEN and P53 in prevention of acute lymphoblastic leukemia tumor cells. *Advanced Pharmaceutical Bulletin*, *9*(3), 470–480. https://doi.org/10.15171/apb.2019.056

Nelson, A. C., Lyons, T. R., Young, C. D., Hansen, K. C., Anderson, S. M., & Holt, J. T. (2010). AKT regulates BRCA1 stability in response to hormone signaling. *Molecular and Cellular Endocrinology*, *319*(1-2), 129–142.

Obata, M., Imamura, E., Yoshida, Y., Goto, J., Kishibe, K., Yasuda, A., & Ogawa, K. (2001). Resistance of primary cultured mouse hepatic tumor cells to cellular senescence despite expression of p16Ink4a, p19Arf, p53, and p21Waf1/Cip1. *Molecular Carcinogenesis: Published in cooperation with the University of Texas MD Anderson Cancer Center*, *32*(1), 9–18.

Pal, S., Kozono, D., Yang, X., Fendler, W., Fitts, W., Ni, J., Alberta, J. A., Zhao, J., Liu, K. X., Bian, J., Truffaux, N., Weiss, W. A., Resnick, A. C., Bandopadhayay, P., Ligon, K. L., DuBois, S. G., Mueller, S., Chowdhury, D., & Haas-Kogan, D. A. (2018). Dual HDAC and PI3K inhibition abrogates NFκB- and FOXM1-mediated DNA damage response to radiosensitize pediatric high-grade gliomas. *Cancer Research*, *78*(14), 4007–4021. https://doi.org/10.1158/0008-5472.can-17-3691

Pang, L. Y., Scott, M., Hayward, R. L., Mohammed, H., Whitelaw, C. B. A., Smith, G. C., & Hupp, T. R. (2011). p21WAF1 is component of a positive feedback loop that maintains the p53 transcriptional program. *Cell Cycle*, *10*(6), 932–950.

Park, J. H., Jung, K. H., Kim, S. J., Fang, Z., Yan, H. H., Son, M. K., Kim, J., Kang, Y. W., Lee, J. E., Han, B., Lim, J. H., & Hong, S. S. (2017). Radiosensitization of the PI3K inhibitor HS-173 through reduction of DNA damage repair in pancreatic cancer. *Oncotarget*, *8*(68), 112893–112906. https://doi.org/10.18632/oncotarget.22850

Paull, T. T. (2015). Mechanisms of ATM activation. *Annual Review of Biochemistry*, *84*, 711–738.

Pearl, L. H., & Prodromou, C. (2006). Structure and mechanism of the Hsp90 molecular chaperone machinery. *Annual Review of Biochemistry*, *75*, 271–294. https://doi.org/10.1146/annurev.biochem.75.103004.142738

Pedersen, P. L., Mathupala, S., Rempel, A., Geschwind, J. F., & Ko, Y. H. (2002). Mitochondrial bound type II hexokinase: A key player in the growth and survival of many cancers and an ideal prospect for therapeutic intervention. *Biochimica et Biophysica Acta/General Subjects*, *1555*(1-3), 14–20. https://doi.org/10.1016/s0005-2728(02)00248-7

Pelicano, H., Martin, D. S., Xu, R. H., & Huang, P. (2006). Glycolysis inhibition for anticancer treatment. *Oncogene*, *25*(34), 4633–4646. https://doi.org/10.1038/sj.onc.1209597

Pons-Tostivint, E., Thibault, B., & Guillermet-Guibert, J. (2017). Targeting PI3K signaling in combination cancer therapy. *Trends in Cancer*, *3*(6), 454–469.

Puc, J., Keniry, M., Li, H. S., Pandita, T. K., Choudhury, A. D., Memeo, L., Mansukhani, M., Murty, V. V., Gaciong, Z., Meek, S. E., Piwnica-Worms, H., Hibshoosh, H., & Parsons, R. (2005). Lack of PTEN sequesters CHK1 and initiates genetic instability. *Cancer Cell*, *7*(2), 193–204.

Qiu, S., & Huang, J. (2021). MRN complex is an essential effector of DNA damage repair. *Journal of Zhejiang University-SCIENCE B*, *22*(1), 31–37.

Rodon, J., Dienstmann, R., Serra, V., & Tabernero, J. (2013). Development of PI3K inhibitors: Lessons learned from early clinical trials. *Nature Reviews Clinical Oncology*, *10*(3), 143–153. https://doi.org/10.1038/nrclinonc.2013.10

Sau, A., Lau, R., Cabrita, M. A., Nolan, E., Crooks, P. A., Visvader, J. E., & Pratt, M. A. (2016). Persistent activation of NF-κB in BRCA1-deficient mammary progenitors drives aberrant proliferation and accumulation of DNA damage. *Cell Stem Cell*, *19*(1), 52–65. https://doi.org/10.1016/j.stem.2016.05.003

Schötz, U., Balzer, V., Brandt, F. W., Ziemann, F., Subtil, F., Rieckmann, T., Köcher, S., Engenhart-Cabillic, R., Dikomey, E., Wittig, A., & Arenz, A. (2020). Dual PI3K/mTOR inhibitor NVP-BEZ235 enhances radiosensitivity of head and neck squamous cell carcinoma (HNSCC) cell lines due to suppressed double-strand break (DSB) repair by non-homologous end joining. *Cancers (Basel)*, *12*(2), 467. https://doi.org/10.3390/cancers12020467

Scripture, C. D., Figg, W. D., & Sparreboom, A. (2006). Peripheral neuropathy induced by paclitaxel: Recent insights and future perspectives. *Current Neuropharmacology*, *4*(2), 165–172. https://doi.org/10.2174/157015906776359568

Scully, R., Chen, J., Ochs, R. L., Keegan, K., Hoekstra, M., Feunteun, J., & Livingston, D. M. (1997). Dynamic changes of BRCA1 subnuclear location and phosphorylation state are initiated by DNA damage. *Cell*, *90*(3), 425–435. https://doi.org/10.1016/s0092-8674(00)80503-6

Serej, F. A., Pourhassan-Moghaddam, M., Kalan, M. E., Mehdipour, A., Serej, Z. A., & Ebrahimi-Kalan, A. (2018). Targeting the PI3K/Akt/mTOR signaling pathway: Applications of nanotechnology. *Crescent Journal of Medical and Biological Sciences. 5*, 7–13.

Serrano, M. A., Li, Z., Dangeti, M., Musich, P. R., Patrick, S., Roginskaya, M., Cartwright, B., & Zou, Y. (2013). DNA-PK, ATM and ATR collaboratively regulate p53-RPA interaction to facilitate homologous recombination DNA repair. *Oncogene*, *32*(19), 2452–2462. https://doi.org/10.1038/onc.2012.257

Shaik, A., & Kirubakaran, S. (2020). Evolution of PIKK family kinase inhibitors: A new age cancer therapeutics. *Front Biosci (Landmark Ed.)*, *25*, 1510–1537.

Shen, C., Lancaster, C. S., Shi, B., Guo, H., Thimmaiah, P., & Bjornsti, M.-A. (2007). TOR signaling is a determinant of cell survival in response to DNA damage. *Molecular and Cellular Biology*, *27*(20), 7007–7017. https://doi.org/10.1128/mcb.00290-07

Shen, W. H., Balajee, A. S., Wang, J., Wu, H., Eng, C., Pandolfi, P. P., & Yin, Y. (2007). Essential role for nuclear PTEN in maintaining chromosomal integrity. *Cell*, *128*(1), 157–170.

Shiloh, Y. (2003). ATM and related protein kinases: Safeguarding genome integrity. *Nature Reviews Cancer*, *3*(3), 155–168. https://doi.org/10.1038/nrc1011

Sokka, M., Parkkinen, S., Pospiech, H., & Syväoja, J. E. (2010). Function of TopBP1 in genome stability. *Sub–Cellular Biochemistry*, *50*, 119–141. https://doi.org/10.1007/978-90-481-3471-7_7

Sokka, M., Parkkinen, S., Pospiech, H., & Syväoja, J. E. (2010). Function of TopBP1 in genome stability. *Genome Stability and Human Diseases*, *50*, 119–141.

Spangle, J. M., Roberts, T. M., & Zhao, J. J. (2017). The emerging role of PI3K/AKT-mediated epigenetic regulation in cancer. *Biochimica et Biophysica Acta, Reviews on Cancer*, *1868*(1), 123–131. https://doi.org/10.1016/j.bbcan.2017.03.002

Sugihara, T., Kaul, S. C., Kato, J.-Y, Reddel, R. R., Nomura, H., & Wadhwa, R. (2001). Pex19p dampens the p19ARF-p53-p21WAF1 tumor suppressor pathway. *Journal of Biological Chemistry*, *276*(22), 18649–18652.

Symonds, H., Krall, L., Remington, L., Saenz-Robles, M., Lowe, S., Jacks, T., & Van Dyke, T. (1994). p53-dependent apoptosis suppresses tumor growth and progression in vivo. *Cell*, *78*(4), 703–711.

Takahashi, T., Shishido, T., Kinoshita, D., Watanabe, K., Toshima, T., Sugai, T., Narumi, T., Otaki, Y., Tamura, H., Nishiyama, S., Arimoto, T., Takahashi, H., Miyamoto, T., Watanabe, T., Woo, C. H., Abe, J., Takeishi, Y., Kubota, I., & Watanabe, M. (2019). Cardiac nuclear high-mobility group box 1 ameliorates pathological cardiac hypertrophy

by inhibiting DNA damage response. *JACC: Basic to Translational Science*, *4*(2), 234–247.

Tang, X., Li, A., Xie, C., Zhang, Y., Liu, X., Xie, Y., Wu, B., Zhou, S., Huang, X., Ma, Y., Cao, W., Xu, R., Shen, J., Huo, Z., Cai, S., Liang, Y., & Ma, D. (2020). The PI3K/mTOR dual inhibitor BEZ235 nanoparticles improve radiosensitization of hepatoma cells through apoptosis and regulation DNA repair pathway. *Nanoscale Research Letters*, *15*(1), 63. https://doi.org/10.1186/s11671-020-3289-z

Tian, H., Gao, Z., Li, H., Zhang, B., Wang, G., Zhang, Q., Pei, D., & Zheng, J. (2015). DNA damage response—a double-edged sword in cancer prevention and cancer therapy. *Cancer Letters*, *358*(1), 8–16. https://doi.org/10.1016/j.canlet.2014.12.038

Toulany, M., Dittmann, K., Fehrenbacher, B., Schaller, M., Baumann, M., & Rodemann, H. P. (2008). PI3K-Akt signaling regulates basal, but MAP-kinase signaling regulates radiation-induced XRCC1 expression in human tumor cells in vitro. *DNA Repair*, *7*(10), 1746–1756.

Tsujimoto, Y. (1998). Role of Bcl-2 family proteins in apoptosis: Apoptosomes or mitochondria? *Genes to Cells*, *3*(11), 697–707. https://doi.org/10.1046/j.1365-2443.1998.00223.x

Um, S. H., D'Alessio, D., & Thomas, G. (2006). Nutrient overload, insulin resistance, and ribosomal protein S6 kinase 1, S6K1. *Cell Metabolism*, *3*(6), 393–402. https://doi.org/10.1016/j.cmet.2006.05.003

Vogelstein, B., Lane, D., & Levine, A. J. (2000). Surfing the p53 network. *Nature*, *408*(6810), 307–310. https://doi.org/10.1038/35042675

Van der Vos, K. E., & Coffer, P. J. (2011). The extending network of FOXO transcriptional target genes. *Antioxidants & Redox Signaling*, *14*(4), 579–592. https://doi.org/10.1089/ars.2010.3419

Wang, G., Li, Y., Wang, P., Liang, H., Cui, M., Zhu, M., Guo, L., Su, Q., Sun, Y., McNutt, M. A., & Yin, Y. (2015). PTEN regulates RPA1 and protects DNA replication forks. *Cell Research*, *25*(11), 1189–1204.

Wang, J., Li, W., Zhao, Y., Kang, D., Fu, W., Zheng, X., Pang, X., & Du, G. (2018). Members of FOX family could be drug targets of cancers. *Pharmacology and Therapeutics*, *181*, 183–196. https://doi.org/10.1016/j.pharmthera.2017.08.003

Wanigasooriya, K., Tyler, R., Barros-Silva, J. D., Sinha, Y., Ismail, T., & Beggs, A. D. (2020). Radiosensitising cancer using phosphatidylinositol-3-Kinase (PI3K), protein kinase B (AKT) or mammalian target of rapamycin (mTOR) inhibitors, *Cancers (Basel) 12*(5). https://doi.org/10.3390/cancers12051278

Wu, J., Huen, M. S., Lu, L.-Y., Ye, L., Dou, Y., Ljungman, M., Chen, J., & Yu, X. (2009). Histone ubiquitination associates with BRCA1-dependent DNA damage response. *Molecular and Cellular Biology*, *29*(3), 849–860.

Wu, J., Lu, L. Y., & Yu, X. (2010). The role of BRCA1 in DNA damage response. *Protein & Cell*, *1*(2), 117–123. https://doi.org/10.1007/s13238-010-0010-5

Wullschleger, S., Loewith, R., & Hall, M. N. (2006). TOR signaling in growth and metabolism. *Cell*, *124*(3), 471–484. https://doi.org/10.1016/j.cell.2006.01.016

Xia, C., Liu, C., He, Z., Cai, Y., & Chen, J. (2020). Metformin inhibits cervical cancer cell proliferation by modulating PI3K/Akt-induced major histocompatibility complex class I-related chain A gene expression. *Journal of Experimental and Clinical Cancer Research*, *39*(1), 127. https://doi.org/10.1186/s13046-020-01627-6

Xu, N., Lao, Y., Zhang, Y., & Gillespie, D. A. (2012). Akt: A double-edged sword in cell proliferation and genome stability. *Journal of Oncology*, *2012*, 951724. https://doi.org/10.1155/2012/951724

Yang, L., Yang, G., Ding, Y., Dai, Y., Xu, S., Guo, Q., Xie, A., & Hu, G. (2018). Inhibition of PI3K/AKT signaling pathway radiosensitizes pancreatic cancer cells with ARID1A deficiency in vitro. *Journal of Cancer*, *9*(5), 890–900. https://doi.org/10.7150/jca.21306

Zhang, J., Willers, H., Feng, Z., Ghosh, J. C., Kim, S., Weaver, D. T., Chung, J. H., Powell, S. N., & Xia, F. (2004). Chk2 phosphorylation of BRCA1 regulates DNA double-strand break repair. *Molecular and Cellular Biology*, *24*(2), 708–718.

Zhang, P., Chen, Z., Ning, K., Jin, J., & Han, X. (2017). Inhibition of B7-H3 reverses oxaliplatin resistance in human colorectal cancer cells. *Biochemical and Biophysical Research Communications*, *490*(3), 1132–1138.

Zhang, Q., Yan, H. B., Wang, J., Cui, S. J., Wang, X. Q., Jiang, Y. H., Feng, L., Yang, P. Y., & Liu, F. (2016). Chromatin remodeling gene AT-rich interactive domain-containing protein 1A suppresses gastric cancer cell proliferation by targeting PIK3CA and PDK1. *Oncotarget*, *7*(29), 46127–46141. https://doi.org/10.18632/oncotarget.10060

Zhang, Y., Cong, L., He, J., Wang, Y., Zou, Y., Yang, Z., Hu, Y., Zhang, S., & He, X. (2018). Photothermal treatment with EGFRmAb-AuNPs induces apoptosis in hypopharyngeal carcinoma cells via PI3K/AKT/mTOR and DNA damage response pathways. *Acta Biochim Biophys Sin (Shanghai)*, *50*(6), 567–578. https://doi.org/10.1093/abbs/gmy046

Zhang, Y., Xie, C., Li, A., Liu, X., Xing, Y., Shen, J., Huo, Z., Zhou, S., Liu, X., Xie, Y., Cao, W., Ma, Y., Xu, R., Cai, S., Tang, X., & Ma, D. (2019). PKI-587 enhances chemosensitivity of oxaliplatin in hepatocellular carcinoma through suppressing DNA damage repair pathway (NHEJ and HR) and PI3K/AKT/mTOR pathway. *American Journal of Translational Research*, *11*(8), 5134–5149.

Zou, L., & Elledge, S. J. (2003). Sensing DNA damage through ATRIP recognition of RPA-ssDNA complexes. *Science*, *300*(5625), 1542–1548. https://doi.org/10.1126/science.1083430

How to cite this article: Alemi, F., Raei Sadigh, A., Malakoti, F., Elhaei, Y., Ghaffari, S. H., Maleki, M., Asemi, Z., Yousefi, B., Targhazeh, N., & Majidinia, M. (2021). Molecular mechanisms involved in DNA repair in human cancers: An overview of PI3k/Akt signaling and PIKKs crosstalk. *Journal of Cellular Physiology*, 1–16. https://doi.org/10.1002/jcp.30573