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RESEARCH ARTICLE

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Crosstalk between Phosphoinositide 3-kinase/Akt signaling pathway with DNA damage response and oxidative stress in cancer

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Abstract

The phosphatidylinositol 3-kinases (PI3K)/Akt signaling pathway is one of the well-characterized and most important signaling pathways activated in response to DNA damage. This review discusses the most recent discoveries on the involvement of PI3K/Akt signaling pathway in cancer development, as well as stimulation of some important signaling networks involved in the maintenance of cellular homeostasis upon DNA damage, with an exploration of how PI3K/Akt signaling pathway contributes to the regulation of modulators and effectors underlying DNA damage response, the intricate, protein-based signal transduction network, which decides between cell cycle arrest, DNA repair, and apoptosis, the elimination of irreparably damaged cells to maintain homeostasis. The review continues by looking at the interplay between cell cycle checkpoints, checking the repair of damage inflicted to the DNA before entering DNA replication to facilitate DNA synthesis, and PI3K/Akt signaling pathway. We then investigate the challenges the cells overcome to ameliorate damages induced by oxidative activities, for example, the recruitment of many pathways and factors to maintain integrity and hemostasis. Finally, the review provides a discussion of how cells use the PI3K/Akt signaling pathway to regulate the balance between these networks.

KEYWORDS

apoptosis, cell cycle, DNA damage and repair, oxidative stress, phosphatidylinositol 3-kinases (PI3K)/Akt signaling

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1 | INTRODUCTION

The serine/threonine kinase Akt/protein kinase B (PKB), plays an important role in a signaling pathway that controls multiple cellular processes such as proliferation, translation, cell growth, cell size, cell death as well as invasion, and angiogenesis via the process of phosphorylation.[1,2] A member of the ACG kinase family, this molecule has three conserved domains consisting of the N-terminal pleckstrin homology (PH) domain, a central kinase catalytic domain, and a regulatory hydrophobic motif domain. Akt has multiple isoforms with distinct functions in various signaling pathways, with Akt one being the most important and having functions in cell survival. Akt exists in the cytoplasm in an inactive state, and during activation, is relocated to the cell membrane.[1] The binding of many factors, such as cytokines, growth factors, and hormones to their receptors leads to phosphorylation of Akt at two regulatory residues, namely T308 and S473, mediated by phosphatidylinositol 3-kinases (PI3K) activation.[3] But further, it has been shown that Akt can be activated in a PI3K-independent manner, by a Ca^{2+}/Calmodulin-dependent protein kinase, severe heat, increased concentration of Ca^{2+}, and other signaling pathways.

PI3K located upstream Akt establishes PI3K/Akt signaling pathway, which phosphorylates inositol ring group in inositol phospholipid. Class 1A PI3Ks have a heterodimers structure consisted of a catalytic (p110α, p110β, and p110δ) and a regulatory subunit (p85α, p55α, p50α, p85β, and p55γ), the substrate for this class, as well as phosphatidylinositol-4,5-bisphosphate (PIP2) to generate the second messenger phosphatidylinositol-3,4,5-trisphosphate (PIP3) that promotes the activation of Akt for activation of downstream factors.[4,5] The messages received from activated tyrosine kinase receptors, G-protein coupled receptors, cytokine receptors, and activated rat sarcoma (RAS) lead to activation of PI3K and formation of PIP3.

This factor has two docking sites for proteins containing FYVE (Fab 1 [yeast orthologue of PIKfyve], YOTB, Vac 1 [vesicle transport protein], and EEA1) and PH domain. PH domains have been found in many proteins such as phosphoinositide-dependent kinase-1 (PDK1) and Akt/PKB.[6] Following PI3K activation, AKT is localized to the inner membrane via its PH domain. Phosphorylation of AKT in the activation loop (T308) by 3-phosphoinositide-dependent protein kinase-1 (PDK1) or in serine 473 by the mammalian target of rapamycin complex 2 (mTORC2) is essential for this translocation.[7] Phosphatase and tensin homolog (PTEN) is a tumor suppressor gene that works as lipid phosphatase whose activity removes phosphate group from phosphoinositide signaling molecules like PIP3.[8-10] Dephosphorylation of PIP3 occurs at position 3 on the inositol ring, which serves to inhibit signaling transduction by PI3K/Akt signaling pathway.[11]

mTOR is a prominent effector downstream of Akt that has an important function in this pathway, for activation of mTOR (mTORC1) by Akt, direct phosphorylation of tuberous sclerosis complex 2 (TSC2) needs to happen or else mTOR activity is inhibited. Tuberous sclerosis complex 1 (TSC1) together with TSC2 form a heterodimer complex and inhibit activation of Rheb, also known as Ras homolog enriched in brain, which is a small GTPase protein required for mTOR activation.[12] Upon activation of mTOR, protein synthesis, cell survival, cell growth, and proliferation are induced by phosphorylation of its effectors molecules such as elF4E-binding proteins and ribosomal S6 kinase (S6K1 and S6K2), which eventually lead to messenger RNA translation and accelerate tumorigenesis.[13] A preponderance of evidence has implicated hyperactivation of PI3K/Akt in various types of human cancer as it leads to phosphorylation or inactivation of proapoptotic agents such as Bcl-2-associated death promoter (BAD) and procaspase-9, inhibition of the cytochrome C releasing from mitochondria, and phosphorylation or inactivation of forkhead box O (FoxO)-3 which upregulates the expression of proapoptotic proteins such as Bim, FasL, and PUMA, as well as phosphorylation and localization of mouse double minute 2 homolog (MDM2), which results in the degradation of p53 and, thereby, the suppression of the inhibitory effects of p53 on cell cycle.[14] More importantly, it is said that the PI3K/Akt signaling pathway is also activated in cells upon DNA damage, which in turn stimulates some important signaling networks involved in the maintenance, as well as restoration of cellular homeostasis. Therefore, understanding the mechanisms by which PI3K/Akt signaling regulates DNA damage response (DDR) is essential to ascertain their function in initiation, progression, metastasis, and therapy of various types of cancers.[15] In this review, we will discuss the involvement of the PI3K/Akt signaling pathway in the regulation of DDR and discussing its interaction and crosstalk with three important parts of DDR including sensors, transducers, and effectors.

2 | DDR: AN INTRICATE NETWORK FOR SIMPLE PURPOSE

Subjection of DNA to tens of thousands of damages per day for each of ~10^{13} cells within the body is a hazardous threat to the integrity and stability of the genome, and the organism's viability, as well as being the hallmark of various

cancers.[16] Some of the most important DNA lesions with deleterious effects include single-strand breaks and double-strand breaks (DSBs) which are commonly induced by environmental hazards, such as ionizing radiation (IR), or camptothecin and etoposide, pyrimidine dimers and 6-4 photoproducts caused by IR and ultraviolet light, just to name a few.[17] To withstand all these threats to the DNA, a powerful system is very vital for all organisms a system which senses and detects any potential damages to DNA, transduces the damage signals to the downstream network, as well as processing the signal, and eliciting an appropriate proper response to the benefits of the cells.[18] That is, the system has to provide a condition for the cells so that they are capable of deciding their fate, by repairing the lesions and continuing life or entering the apoptotic phase and death.[19] The intricate network with this important responsibility in cells is called DDR. It is a protein based-signal transduction cascade operated by three key players, namely, sensors, transducers, and effectors, to decide between repair of DNA lesions, alterations in the cell cycle and apoptosis.[20] To maintain the genome health, DDR machinery does not function alone, but rather coordinates with other various complementary machines such as chromatin-remodeling mechanism, to provide the accessibility of the DNA repair components to the site of DNA damage within chromosomes, homologous recombination (HR), chromosome cohesion machinery, cell-cycle-checkpoint, and chromosome-segregation machinery.[21,22] The whole process of the DDR pathway takes place before the cell enters mitotic phase to ensure the passing of the intact complement of genetic material to daughter cells (Figure 1).[22]

3 | PI3K/Akt SIGNALING PATHWAY IN DDR

3.1 | Crosstalk between PI3K/Akt signaling and DDR sensors/transducers

To maintain the integrity of the DNA content of cells, any damage to DNA structure and composition must be recognized and signaled to downstream molecules for an appropriate response (Figure 2). There are two major sensor complexes; Mre11-Rad50-Nbs1 (MRN) mediator complex and proliferating cell nuclear antigen (PCNA)-related Rad9-Rad1-Hus1 complex, also known as the 9-1-1 complex. The MRN complex is involved in the recognition of DSBs, the most common and dangerous DNA damage. Previous studies have noted the overexpression of Nbs1, part of the MRN complex, results in the process of cancer progression and distant metastasis, which is mediated by the activation of PI3K/Akt.[23] Nbs1 interacts, through its conserved C-terminal motif, with the p110α catalytic subunit of PI3K (with its N-terminal domain), hence stimulating PI3K activity.[23] It is suggested that overexpression of Nbs1 may

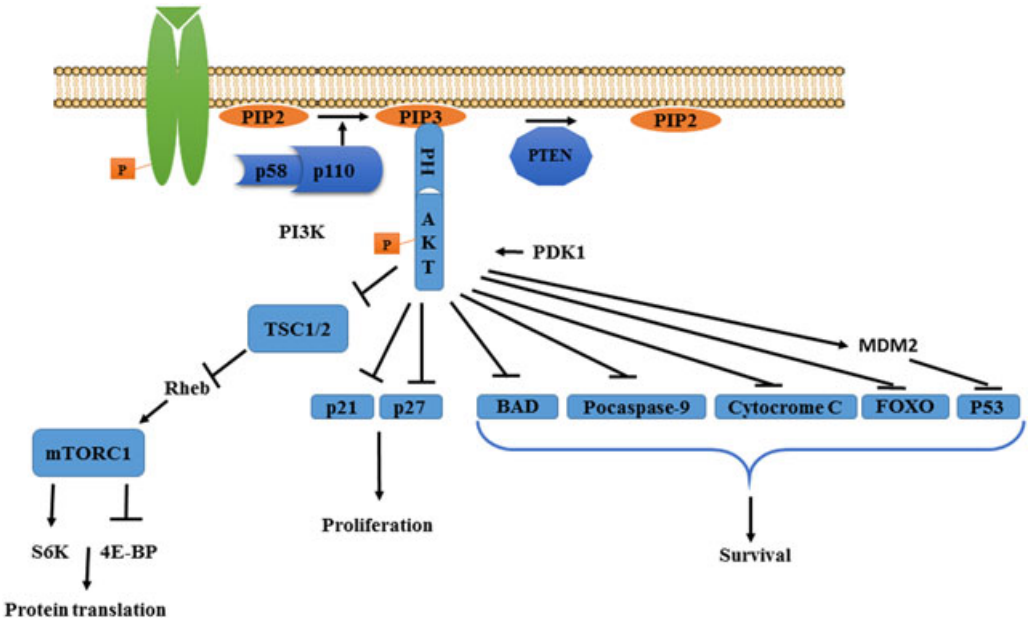

FIGURE 1 The general overview of PI3K/Akt signaling pathway. PI3K consists of the catalytic subunit, p110, and the regulatory subunit, p85. PI3K phosphorylates PIP2 and produces PIP3. PIP3 then activates PDK1 and its major downstream effector, Akt. Phosphorylation of Akt promotes cell proliferation, survival, migration, and differentiation through targeting various genes. PTEN dephosphorylates PIP3 and inhibits activation of Akt by PIP3. Phosphorylation of Akt induces the activation of one of the major downstream effectors, mTOR. mTOR, mammalian target of rapamycin; PDK1, 3-phosphoinositide-dependent kinase 1; PIP2, phosphatidylinositol 3, 4-bisphosphate; PIP3, phosphatidylinositol 3,4,5-trisphosphate; PI3K, phosphatidylinositol 3-kinases; PTEN, phosphatase and tensin

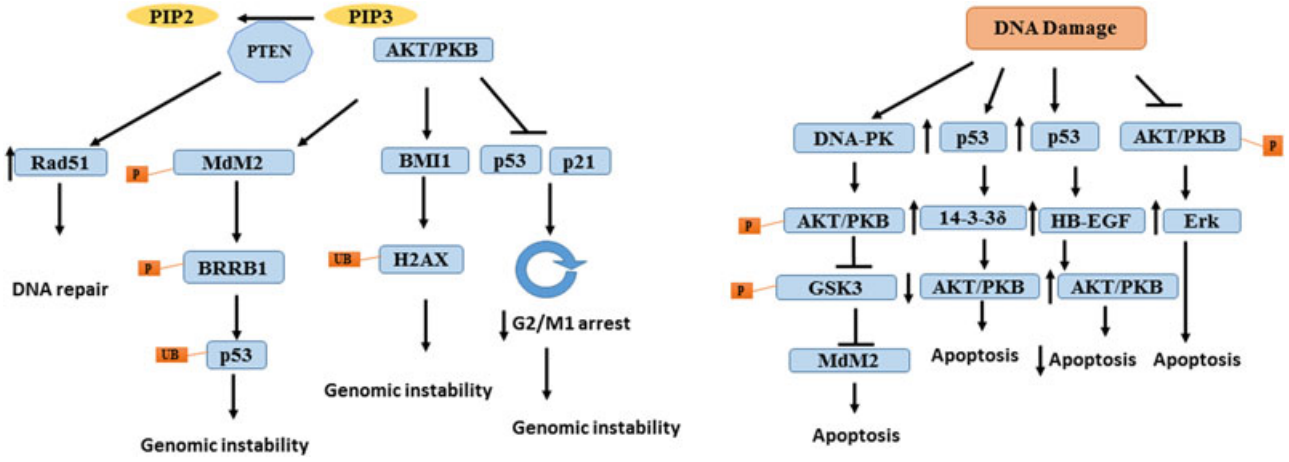

FIGURE 2 This schematic representation shows the relationship between the PI3K/Akt signaling pathway, DNA damage and cancer progression. There is a mutual interaction between PI3K/Akt and DDR, in which DDR targets key components of PI3K/Akt signaling and vice versa. DDR, DNA damage response; PI3K, phosphatidylinositol 3-kinases

mediate its role in the cell, namely the cytoplasm by interacting with p110α to activate PI3K, which is an oncogenic signaling pathway with aberrant expression in various cancers. In addition, it was shown that increased Nbs1 expression is a surrogate marker of aggressive squamous cell carcinoma in the head and neck, and is also correlated with the function of the PI3K/Akt pathway in cancer cell lines. In fact, the oncogenic characteristic of Nbs1 overexpression and its role in the cancer is exerted indirectly by PI3K/Akt pathway.[24] Sagan et al noted an increased radiosensitivity in $Nbs1^{-/-}$ cells accompanied by enhanced γ-radiation-induced apoptosis in a p53 independent manner but required caspase-8 activity, in addition to the observation that γ-radiation-induced CD95 clustering in γ-irradiated $Nbs1^{-/-}$ cells was caused by a disturbance of the PI3K/Akt pathway. The authors concluded that Nbs1 suppressed the CD95 death receptor-dependent apoptotic pathway following γ-irradiation by effecting the PI3K/Akt survival pathway.[25]

Upon detection of DNA damage, MRN complex recruits Ataxia-telangiectasia mutated (ATM) to break DNA molecules.[26] A study by Lee et al found that the coexistence of the MRN complex and DNA molecules led to the activation of the previously inactive ATM dimers, which itself led to further activation and recruitment of downstream molecules such as checkpoint kinase 2 (Chk2), p53, and breast cancer susceptibility gene 1 (BRCA1), which have important roles in translating ATM signaling into tangible effects. It was suggested in this study that the MRN complex was necessary for ATM activation and function, as it also took part in unwinding DNA ends.[27] The MRN complex might also recruit substrates to ATM.[27] ATM along with ATR (ATM- and Rad3-related) and DNA-PKcs comprise three important members of phosphoinositide-3-kinase-related kinases, the most meticulously studied transducers of DDR. There are a variety of other proteins involved in ATM activation,[28] such as PP5 phosphatase and the histone acetyltransferase, Tip60.

Single strand DNAs (SSDs) emergence is commonly detected by the replication protein A[29] protein complex, with two substantial functions in DDR: first, like sensors in the DSB pathway, is the recruitment of a transducer, ATR by effecting a subunit of this molecule known as ATR interacting protein (ATRIP), and second, the recruitment and subsequent activation of Rad17 which then attaches to the PCNA-related 911 (Rad9-Rad1-Hus1) complex and facilitates interaction with the damaged DNA molecule. It is noteworthy to mention that Rad17 is shown to act as a clamp loader in DDR.[30] Thereafter, ATR phosphorylates and interacts with upstream DNA damage sensors, which is necessary for optimal ATR signaling. Downstream of the cascade, ATR phosphorylates Chk1 kinases, and TopBP1, which again transit the signal generated by the sensors to DDR effectors.

TopBP1 is a key molecule regarding the function of ATR.[31] TopBP1 is a substrate for both ATR and ATM, and its phosphorylation initiates its function in checkpoint signaling.[32] It has a unique ability of binding to the 911 complex and the ATRIP subunit of ATR. This gives TopBP1 the ability to regulate the function of ATR. A study by Liu et al showed that the PI3K/Akt signaling pathway had a regulatory effect on the function of TopBP1. They showed that Akt was able to phosphorylase TopBP1 and induce oligomerization in this molecule. This was necessary for the regulatory function which TopBP1 exerts on E2F-1, a molecule involved in the regulation of apoptosis. the authors concluded that the PI3K-Akt-TopBP1 signaling cascade had parallel roles to cyclin-Cdk-Rb in regulating apoptosis.[33]

DNA-PKcs are induced upon recognition of DSBs, and subsequently autophosphorylate themselves, as well as phosphorylating other mediator substrates. DNA-PKcs plays a unique role in DNA repair by promoting nonhomologous end joining (NHEJ).[34] The major transducer molecules of DDR belong to PI3K-like kinase (PI3KK) family, the interactions, as well as crosstalk between PI3KK and PI3K/Akt signaling pathways, have been intensively investigated in recent years. Mukherjee et al assessed whether NVP-BEZ235, a dual PI3K/mTOR inhibitor, could radiosensitize human GBM cells by inhibiting the functions of ATM and DNA-PKcs, the two major kinases responding to DSBs induced by irradiation. They found that NVP-BEZ235 could sensitize cells to radiation, and compared with KU55933 (ATM inhibitor, 10 μM) and NU7026 (DNA-PKcs inhibitor, 10 μM), the amount of sensitization to radiation was significantly greater. As expected, KU55933 and NU7026 treatments resulted in weakened DSB repair, consistent with the important functions of DNA-PKcs regarding promoting NHEJ and the role of ATM in facilitating HR and heterochromatic DNA repair. Interestingly, NVP-BEZ235 treatment resulted in a repair defect that was much graver than that was seen with either of the earlier mentioned agents (NU7026 or KU55933). Furthermore, treatment with NVP-BEZ235 affected both "early" and "late" phases of DSB repair, with almost 70% of breaks remaining unattended after exposure to radiation. It was also shown that NVP-BEZ235 decreased radiation-induced activation of ATM and DNA-PKcs, similar to the specific inhibitors NU7026 or KU55933. In addition, phosphorylation of important ATM substrates downstream effectors such as SMC1 (Ser966), Chk2 (Thr68), KAP-1 (Ser824), p53 (Ser15), and H2AX (Ser139) was reduced by pretreatment with NVP-BEZ235, similar to what was witnessed with KU55933.[35] Alcazar et al[36] reported the same results in glioblastoma, in which NVP-BEZ235 aggressively effected both DNA-PKcs and ATM kinases and reduced the appropriate repair of radiation-induced DNA damage in cancerous tumors. In another study, Toulany et al[37] investigated whether small-molecule inhibitors of epidermal growth factor receptor (EGFR) tyrosine kinase (BIBX1382BS), PI3K activity (BIBX1382BS), or Akt (API-59CJ-OH), as well as Akt 1 small interfering RNA (siRNA), were able to effect irradiation induced activation and localization of multiple proteins involved in the process of DNA repair. The authors demonstrated that radiation-induced autophosphorylation of DNA-PKcs was only blocked in K-RAS-mutated A549 bronchial carcinoma cells by BIBX1382BS, BIBX1382BS, and Akt 1 siRNA transfection. However, the inhibitors did not alter the phosphorylation of ATM. They concluded, therefore, that targeting of PI3K-Akt signaling initiated by EGFR activation in K-RAS-mutated A549 cells significantly affected survival after radiation by altering the activation of DNA-PKcs, resulting in an attenuated DSB repair capacity in the cells.[37] Burrows et al studied the effects of PI3K and PIKK signaling on the radiosensitivity of thyroid carcinomas. To do so, they examined the effects of PI3K-inhibition achieved by administrating GDC-0941 to ATC (8505c) and FTC (FTC-133) cell lines. They noticed that GDC-0941 was able to inhibit the activation of ATM, ATR, and DNA-PKcs after exposure to radiation. They also noticed that these series of molecules were not activated in PTEN-reconstituted FTC cells, showing a link between inhibition of DDR transducers and PI3K signaling. Interestingly, the authors found that the effects of PI3K inhibition were greater in anoxia, as inhibition of PI3K was only able to reduce survival in anoxic, not normoxic conditions. Another observation was made regarding the effects of GDC-0941 in inhibiting the function of PIKKs. It was shown that the inhibitory effects of PI3K inhibition on PIKKs were able to significantly increase the time which was needed for tumors to triple in size. This result was particularly important as overactivation of PIKKs is commonly seen in thyroid cancers.[38] It has also been reported that ATM-mediated PTEN activation increases translocation of PTEN into the nucleus and also results in increased autophagy in response to DNA-damaging agents in cancer cells.[39] More importantly, Topotecan or cisplatin-activated ATM phosphorylated, in turn, PTEN at serine 113 and further regulated PTEN nuclear translocation in A549 and HeLa cells. After nuclear translocation, PTEN induces autophagy in response to topotecan (TPT), which is associated with the activation of the p-JUN-SESN2/AMPK pathway.[39] In another study conducted by Biechonski et al the effects of Quercetin, a polyphenol compound with wide-ranging effects on PI3K signaling on DDR was assessed. They found that this molecule exerted its genotoxic effects by inhibiting Topoisomerase II, causing DNA damage and also inhibiting NHEJ and HR in mixed lineage leukemia cell lines. The authors found that these effects were mediated partly by PI3K signaling inhibition and a decrease in the expression of DDR genes. One important DDR players affected by Quercetin was ATM. Quercetin decreased the expression of ATM, although a transient increase was seen because of the implicated DNA damage. This resulted in the impaired HR, which was mentioned earlier.[40] In a study done by Viniegra et al it was shown that the relation between ATM and Akt further extended. They found that optimal activation of PKB/Akt signaling in response to radiation or insulin was dependent on the function of ATM. ATM had the ability to bind to Akt but came short of directly phosphorylating it, evidence

suggested that other downstream kinases related to ATM could have phosphorylated and activated Akt.[41] Other studies found that the counterpart of ATM, ATR could have roles in directly activating Akt. In a study by Caporali et al it was shown that ATR, directly phosphorylated Akt on Ser473 in response to temozolomide, and that using siRNAs to disrupt the function of ATR, abolished the phosphorylation of Akt.[42] At this point, it would also seem reasonable to propose that ATR mediates stimulation of other kinases such as DNA-PKcs to phosphorylate Akt. DNA-PKcs plays important functions in Akt activation in response to DNA damage resulted by IR and doxorubicin.[43] A study by Bozulic et al found that DNA-PKcs were the upstream molecules of PKBalpha/Akt 1 signaling. They showed that PKB, a molecule responsible for orchestrating prosurvival signals was dependent on the functions of PDK1 and DNA-PKcs. It was witnessed that after DNA damage PKB would localize to the damage site and interact with DNA-PKcs and that it was inversely associated with the rate of apoptosis in cells undergoing radiation. Furthermore, PKB was able to promote survival by regulating the transcription of p21, an important DDR effector.[43]

3.2 | Crosstalk between PI3K/Akt signaling and DDR mediators

Mediators promote interactions between transducers and their downstream effector molecules (Figure 2).[44] They also have indisputable functions in recruiting other molecules involved in DDR and act as platforms onto which molecular complexes are assembled on to.[45] After DNA damage, the two DDR transducers ATR, ATM, and DNA PK phosphorylate H2AX on Ser139 and recruit Mdc1 to further facilitate H2AX phosphorylation, possibly by tethering ATM or inhibiting the dephosphorylation of H2AX.[46] The combined action of H2AX and Mdc1 also facilitates the recruitment of other mediator and non-mediator proteins to the sites of DNA damage, causing irradiation-induced foci to exist. If you recall, the PI3K/Akt pathway plays a critical role in increasing survival in cancer cells, and, therefore, malfunction of this signaling pathway imposed by specific inhibitors such as BKM120, and its combination with radiation, may contribute to the enhanced sensitivity of liver cancer cell lines to irradiation. Liu et al demonstrated that BKM120 inhibition of PI3K resulted in the retention of the γ-H2AX foci at DSBs following irradiation, leaving the DNA damage unrepaired. In other words, the combined effect of BKM120 and irradiation abrogated the activation of Akt by radiation causing an increase in apoptosis and suppression of repair of DNA defects in hepatocellular carcinoma cells. As such, one may postulate that the final signaling output of the PI3K/Akt pathway increases resistance to radiation or chemotherapies and that theoretically, synthetic PI3K inhibitors radiosensitize cancer cells.[47] In a study by Gwak et al the effects of silencing miRNA-21, a prominent onco-miRNA with roles in radiosensitivity in gliomas was discussed. In this study, anti-miRNA-20 was used to reverse the effects of miRNA, in glioma cells. This resulted in an increased rate of autophagosome formation, and formation of sustained gamma-H2AX foci. Furthermore, it was shown that the expression of Akt phosphorylated on ser473 significantly decreased, after irradiation.[48] In another study, it was reported that inhibition of the PI3K/Akt pathway by induction of PTEN led to increased sensitivity to radiation in glioblastoma cells.[49] Kao et al found that PTEN deficient U251 glioblastoma cells had a relatively high basal Akt activation rates. Induction of PTEN in these cells would decrease Akt activity and was coupled with increased sensitization to radiation. Furthermore, induction of PTEN significantly delayed the rate at which gamma-H2AX foci decreased. Interestingly, PI3K signaling inhibitors delayed this process. The results of this study suggested that a crucial link existed between PI3K signaling and DDR and that this link could be targeted to increase radio-sensitivity.[49] Along these lines, Pappas et al demonstrated that pretreating non–small-cell lung carcinoma (NSCLC) cell lines with an adenoviral-mediated PTEN-expressing vector sensitized cells to radiation, compared with controls.[50] In that study, H2AX DNA foci formation was increased and the repair of radiation-induced breaks was halted, consistent with previous studies and the radiosensitizing properties of the used vector.

Afterward, 53BP1 is recruited to the damage site, in an H2AX- and Mdc1-dependent manner.[51] An E3 ubiquitin ligase, Ubc13-Rnf8, is recruited by activated Mdc1, and subsequently ubiquitinates H2AX and other important molecules involved in DDR. The combined action leads to the recruitment of other important mediators, such as 53-binding protein-1, which itself is a link to further signaling cascades, and a centerpiece of DDR mediatory function, the BRCA1 "A complex."[52-54] The function of Ubc13, Rnf8, and BRCA1 is necessary for optimal foci formation, with the last one being a ubiquitin ligase itself.[55] Furthermore, other studies have shown that the BRCA1-CtBP interacting protein had functions in using MRN complex action. This importance was highlighted in a study by Ibrahim et al where PI3K inhibition was used to impair HR in triple negative breast cancer cells proficient in BRCA-1. PI3K inhibition led to increased DNA damage, downregulation of BRCA1, and sensitization to poly (ADP-ribose) polymerase (PARP) inhibitors.

It is noteworthy to mention that MEK1/ERK signaling was also involved in BRCA1 downregulation after PI3K inhibition.[56] In conclusion, this study found that co-treatment with BKM120 and Olaparib, which are PI3K and PARP inhibitors; significantly improved response to treatment and reduced the growth of the tumors.[56] Phosphorylation of BRCA1 inherently alters its function. Activation of the Akt oncogenic pathway is an example of BRCA1 malfunction.[57] A study by Xiang et al found that BRCA1 had negative regulatory effects on Akt. They showed that silencing BRCA1 significantly increased the phosphorylation of Akt, thus increasing its activity, and increasing its signaling output. This malfunction of BRCA1 also causes the disruption of functions of FOXO3a, which is a target of Akt signaling. Further investigation by the authors elicited that BRCA1, have a tendency to bind to phosphorylated Akt, and leading to its degradation by the ubiquitin-proteasome pathway.[57] PI3K/Akt signaling also enhances nuclear localization and transcriptional activity of BRCA1.[58] Altiok et al introduced a signaling pathway by which heregulin, a combinatorial ligand for the EGFR family, induced cell cycle-independent phosphorylation of BRCA1.[59] This was done via Akt in the Thr-509 residue of BRCA1, in T47D human breast cancer cells. Furthermore, the introduction of PI3K/Akt signaling inhibitors to the medium reversed the effects of heregulin. The authors also found that the ectopic expression of active subunits of PI3K was able to mimic the effects of heregulin, suggesting that extracellular pathways such as PI3K/Akt can directly affect the functional status of DDR mediators in human cancer cell lines.

3.3 | Crosstalk between PI3K/Akt signaling pathway and DDR effectors

As mentioned before, DDR is composed of numerous molecules, which are activated after ATM and ATR perform their enzymatic function. These are the molecules which directly mediate how cells are altered in response to DDR.[60,61] As noted, one important function of DDR is promoting DNA repair where and when it is needed.[45] In addition, the critical role of DDR in controlling the cell cycle has significant importance in human pathologies such as cancer. The next major effector pathway of DDR is apoptosis, which has important physiologic roles in development and also an important antioncogenic function. All these multiple functions are both regulated by integrated signaling in DDR and also by other signaling pathways. One of the most important being PI3K signaling. The next paragraphs will aim to demonstrate how exactly PI3Ks effects endpoints of DDR signaling.[62]

3.3.1 | Apoptosis

Following any deleterious irreparable damage to DNA integrity, the cells enter the apoptotic phase. Apoptosis can be induced through two distinct pathways, the extrinsic death receptors or the intrinsic mitochondrial pathway to diminish corrupted cells that cannot maintain themselves or cells with irreparable DNA damage, to maintain homeostasis. The PI3K/Akt signaling pathway is probably one of the well-characterized and most prominent pathways involving in the transmission of apoptotic signals in cell survival. For example, Jeyamohan et al investigated the effect of Parthenolide on HeLa cervical cancer cell lines and found that this agent-induced apoptosis and autophagy by downregulating mTOR signaling and inhibiting PI3K signaling. This downregulation in PI3K signaling was secondary to PTEN activation.[63] Bai et al study the effects of (1β,3β,5β,25S)-spirostan-1,3-diol1-[α-L-rhamnopyranosyl-(1→2)-β-D-xylopyranoside] (RCE-4) on cervical cancer cells and found that this agent increased apoptosis via the mitochondrial pathway. This effect was mediated by downregulation of PI3K/Akt/mTOR and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling, which was shown by reduced levels of PI3K, Akt, and NF-κBp65. Furthermore, mRNA levels of important interleukins involved in inflammatory processes such as interleukin-1 beta (IL-1β) and interleukin-6 (IL-6) were reduced, showing a prompt anti-inflammatory effect. Study of apoptosis mediators revealed that the balance between proapoptotic and antiapoptotic molecules changed to favor apoptosis.[64] Moreover, PI3K/Akt signaling pathway crosstalk with MAPK signaling pathway in DNA-damaging drug-induced apoptosis was demonstrated in a study by Lee et al[65] They used Doxorubicin on NIH3T3 cells and examined its effect on the aforementioned signaling pathways. Inhibition of PI3K signaling and p38-mitogen-activated protein kinase (MAPK) pathway caused an increase in apoptosis, but ERK inhibition caused a decline in apoptosis. Furthermore, affecting PI3K/Akt signaling using LY294002 or Akt mutants significantly modulated ERK1/2 function, and sustained activation of PI3K and ERK together were associated with apoptosis induced by etoposide. A study by Hao et al investigated the effects of Licochalcone A on human gastric cancer cells.[66] Licochalcone A is a polyphenol, from the flavonoid subgroup. This agent had effects on the function of PI3K/Akt and MAPK signaling, and also increased the formation of reactive oxygen species (ROS), which caused an increase in apoptosis. Furthermore, these effects were coupled with an activation of JNK, p38 MAPK, and ERK. This agent suppressed the activation of PI3K signaling and

decreased the function of PI3K and Akt, causing a decrease in cellular proliferation.

In an interesting investigation by Demel et al the relation between DDR, PI3K signaling and glucose metabolism was discussed. For this purpose, OPM-2 multiple myeloma cells were treated with topoisomerase inhibitors, bortezomib, vincristine, inhibitors of ATM, DNA-PKcs, and inhibitors of PI3K signaling. After treatment, [18F]-fluorodeoxyglucose (FDG) uptake was monitored using a positron emission tomography (PET) scan. It was witnessed that treatment with topoisomerase inhibitors alone increased the uptake of [18F]-FDG, signaling an increase in survival. But combining these agents with inhibitors of PIKK and PI3K signaling decreased [18F]-FDG uptake and increased rates of apoptosis. This study showed that targeting DDR and other signaling pathways affecting its function such as PI3K/Akt signaling could be beneficial in cancer treatment.[67]

One of the most important and central components in DDR involved in the induction of apoptosis is the tumor suppressor p53.[68] P53 is released under controlling effect of MDM2, and accumulates in the cell and induces expression of the target gene,[69] in response to DNA damage. In effect, ATM phosphorylates Chk2 and subsequently p53 at serine 20, which leads to an increase in p53 levels. In addition, ATM phosphorylates MDM2 and releases p53 from its control.[70] The interplay between p53 and PI3K/Akt signaling pathway was investigated in a number of studies detailed in the Table 1.

3.3.2 | Cell cycle checkpoints

Cell-cycle status is an important factor which determines the response to DNA damage. Furthermore, there are multiple crosslinks between multiple effectors and mediators of DDR and cell cycle checkpoint molecules.[93] For example, ATM, p53, and CHK2 regulate the G1/S checkpoint, which is an important time period for ensuring that the DNA content of the cell is suitable for replication. Repair in the G1 phase is dependent on NHEJ.[94,95] The S phase checkpoint is upheld by DDR proteins such as ATR, DNAPK, WEE1, and CHK1, which can delay replication initiation, so that undesired alterations of the DNA do not cause cell death responses or are not passed to the next generation of cells.[96] MYT1, CHK1, and WEE1 contribute to the G2/M arrest by increasing phosphorylated CDK1 and delaying mitotic entry. These examples show the complicated role of DDR in maintaining the genomic integrity, both by promoting repair and affecting the cell cycle. This has caused many scholars to investigate agents to target DDR and its functional outcomes in cancer.[96] It is important to note that many signaling pathways such as PI3K control DDR. The stimulatory effects of PI3k/Akt signaling on the cell cycle progression have been established in various studies as being involved in the regulation of the function of multiple substrates related to the G1/S and G2/M transitions. Table 2 enlists the studies which investigated the interplay between cell cycle checkpoints, DDR molecules and the PI3K/Akt signaling pathway.

3.3.3 | DNA repair

On the basis of the characteristics of the damage imposed on the DNA, DNA damages can be repaired by multiple distinct mechanisms, including nucleotide excision repair (NER), base excision repair (BER) and mismatch repair (MMR).[17,119,120] NER is mainly required to repair transcription blocking and helix sorting lesions which might happen when pyrimidine dimers and intrastrand crosslinks occur.[121] BER functions by correcting chemical modifications of DNA or single nucleotides which have been altered as the result of processes such as oxidation,[122] and MMR corrects mistakes during the DNA synthesis or replication process.[120] NHEJ or HR are two additional repair mechanisms used in DSBs to remove the most frequent toxic and difficult-to-repair DNA damages. NHEJ is an error-prone process activated during G0 and G1 phases of the cell cycle and is active in rejoining broken ends of the DNA. HR is active in the S phase or replication phase of the cell cycle and requires a homologous DNA template sequence, leading to an error-free repair process.[123] Some key players of these DNA repair machinery are modulated by PI3K/Akt signaling pathway. An intestinal-secreted neurotrophic factor, glucagon-like peptide-1 (GLP-1), for example, this molecule is implicated in neuronal survival and neurite outgrowth, as well as protecting synaptic plasticity from age driven β-amyloids[124] and ameliorating the oxidative DNA damage to neurons. Research has shown that binding of GLP-1 to its receptor (GLP-1R) initiates a signaling cascade which promotes DNA repair, namely BER, by increasing the expression of apurinic/apyrimidinic endonuclease 1 (APE1) which is an enzyme active in BER. This is mediated in part by activating the cAMP response element binding protein (CREB).[125] More so, inhibition of the PI3K signaling by LY294002 resulted in the significant downregulation of the APE1 expression. In addition, administration of exendin-4, an analog of GLP-1, was shown to promote rates of DNA repair in neuronal brain cells of rats undergoing ischemia. Accordingly, these studies suggest that a novel function of GLP-1 is to induce DNA repair mechanisms by promoting the expression of APE1, which is regulated by the PI3K pathway. One study has implicated PI3K-Akt signaling in the regulation of basal rates of expression of X-ray repair cross-complementing group 1 protein (XRCC1), which is involved in BER.[126]

TABLE 1 The interplay between p53 and PI3K/Akt signaling pathway

Targets	Therapeutic agent	PI3K inhibitor	Major effects	Ref.
A29 Ovarian cancer	Apigenin	LY294002	Apigenin inhibited VEGF transcriptional activation through the PI3K/AKT/p70S6K1 and HDM2/p53 pathway. LY294002 inhibited phosphorylation of AKT and HDM2 and induction of p53 expression. PI3K/AKT signaling plays an important role in regulating HDM2 and p53 expression.	[71]
MCF7 Breast cancer	Mitomycin C	LY294002	Treatment with mitomycin C increased the level of phospho-Akt, which was blocked by pre-incubation of the PI3K inhibitor LY294002. Akt activation in response to p53 accumulation was mediated through PI3K. p53 activates PI3K/Akt signaling through induction of heparin-binding EGF-like growth factor.	[72]
Human Jurkat cells	Morphine	LY294002	Morphine-induced apoptosis is dependent on FADD. Suppression of p53 expression considerably attenuated the morphine-induced apoptosis. Morphine-induced apoptosis is dependent on the activation of PI3K, as PI3K inhibition by the PI3K inhibitor enhanced morphine-induced apoptosis. Inhibition of Akt or NF-κB expression increased morphine-induced apoptosis. Morphine induces cell apoptosis through FADD/p53, antiapoptotic PI3K/Akt and NF-κB pathways.	[73]
Promyelocytic leukemia-derived cells and gastric cancer cell lines	Arsenic trioxide (ATO)	LY294002	ATO-induced G2/M phase arrest and p53 degradation. LY294002 significantly increased the amount of p53 protein and ATO-induced apoptosis. ATO upregulated the expression of Cbl proteins Inhibition of Cbl decreased apoptosis and increased the G2/M phase arrest, and it also prolonged the activation of PI3K/Akt by ATO. Inhibition of PI3K/Akt signaling by Cbl is involved in both ATO-induced apoptosis.	[74]

(Continues)

TABLE 1 (Continued)

Targets	Therapeutic agent	PI3K inhibitor	Major effects	Ref.
Intestinal stem cells	Radiation	LY294002	IGF-I and bFGF reduced radiation-induced PUMA and p53 expression in the intestinal crypts. Growth factors protected against radiation-induced apoptosis through the PI3K/Akt pathway in vitro. The levels of p-Akt were significantly elevated by IGF-1 or bFGF treatment. A constitutive active form of Akt suppressed PUMA and p53 induction by radiation. Growth factor-mediated suppression of radiation-induced apoptosis was blocked by either LY294002.	[75]
Renal cell carcinoma cell lines	9-Aminoacridine (9-AA)	shRNA against p110γ	9AA treatment results in selective downregulation of a specific catalytic subunit of the PI3K family, p110γ. 9AA inhibits AKT/mTOR activity. 9AA affects p53 and NF-kB activity at least partially through inhibition of AKT.	[76]
Bovine aortic vascular endothelial cells	H_2O_2	Wortmannin	H_2O_2 caused increases of DNA fragmentation, p53 expression, Bax/Bcl-2 ratio, and the activities of caspases 3 and 9. The potentiating effect of wortmannin on the apoptosis was not due to an alteration of Ca^{2+}. H_2O_2 increased the levels of PI3K activity and Akt phosphorylation.	[77]
U87MG/PTEN glioblastoma cells	Etoposide	LY294002	PTEN protects p53 from survival signals, permitting p53 to function as a guardian of the genome. PTEN regulates the cellular localization and levels of Mdm2. PTEN can sensitize tumor cells to chemotherapy that relies on p53 activity.	[78]
Ovarian cancer OV2008 cells	Cisplatin	–	Xiap and Akt can modulate cisplatin sensitivity individually but that Xiap requires Akt for its full function. Cisplatin increased p53, decreased Xiap content, and induced apoptosis in OV2008 cells but not in the resistant counterpart (C13*). p53 function is required for sensitization to cisplatin through suppression of Akt activity. Akt2 may be an important regulator of both Xiap and p53 contents after cisplatin challenge.	[79]

(Continues)

TABLE 1 (Continued)

Targets	Therapeutic agent	PI3K inhibitor	Major effects	Ref.
Ovarian cancer OV2008 and A2780s cells	Cisplatin	–	Akt inhibits cisplatin-induced mitochondrial Smac release and apoptosis in ovarian cancer cells. Akt suppresses p53 accumulation at mitochondria. Akt inhibits cisplatin-induced, p53-mediated mitochondrial Smac release.	[80]
p53-deficient M1 acute myeloid leukemia cells	Cisplatin	Wortmannin and LY294002	Direct inhibition of PI3K/Akt in G2-arrested cells by wortmannin or LY294002 strongly enhanced the cytotoxicity of cisplatin without influencing the G2 checkpoint. Inhibition of PI3K/Akt was accompanied by rapid apoptotic cell death during G2, whereas cells underwent mitotic transit and cell division followed by cell death during G1 when both checkpoint and survival signaling were inhibited.	[81]
B-cell precursor acute lymphoblastic leukemia	Bortezomib and HDACi	LY294002, MK-2206	Bortezomib and HDACi resulted in the upregulation of caspases and TNFaR and downregulation of BCL2. treatment with PI3K/AKT inhibitors did not induce apoptosis in leukemia cells, but the triple combination showed a decrease of apoptosis.	[82]
Human gastric SGC-7901 cells	Dracorhodin perchlorate	Wortmannin	Dracorhodin perchlorate-induced apoptosis is mediated via upregulation of p53, inhibiting the activation of PI3K/Akt, and NF-κB, thereby decreasing the expression of the antiapoptotic proteins, Bcl-2 and Bcl-XL. Dracorhodin perchlorate dramatically enhanced the wortmannin- and TNF-induced apoptosis.	[83]
HeLa cells	Chelidonine	–	Chelidonine inhibited proliferation and induced apoptosis through generation of ROS, cell cycle arrest at sub-G1 and G0/G1 stage, change in mitochondrial membrane potential and fragmentation of DNA. Chelidonine could efficiently induce apoptosis through upregulation of expressions of p38, p53 and other proapoptotic genes and downregulation of expressions of AKT, PI3K, JAK3, STAT3, E6, E7, and other antiapoptotic genes.	[84]
Hepatocellular carcinoma HA22T cell	Diosmin	–	Diosmin showed strong HA22T cell viability inhibition. Diosmin significantly reduced the cell proliferative proteins as well as inducing cell cycle arrest in the G2/M phase through p53 activation and PI3K-Akt-MDM2 signaling pathway inhibition.	[85]

(Continues)

TABLE 1 (Continued)

Targets	Therapeutic agent	PI3K inhibitor	Major effects	Ref.
			Protein phosphatase 2A (PP2A) siRNA or PP2A inhibitor totally reversed the diosmin effects. The HA22T-implanted nude mice model confirmed that diosmin inhibited HA22T tumor cell growth and down regulated the PI3K–Akt–MDM2 signaling and cell cycle regulating proteins, as well as activating PP2A and p53 proteins.	
Prostate and breast cancer cells	β-caryophyllene oxide (CPO)	Wortmannin and AKT inhibitor IV	CPO inhibited the constitutive activation of PI3K/AKT/mTOR/S6K1 signaling cascade. CPO induced increased ROS generation from mitochondria, induction of apoptosis, loss of mitochondrial membrane potential, release of cytochrome c, activation of caspase-3, and cleavage of PARP. CPO downregulated the expression of cyclin D1, bcl-2, bcl-xL, survivin, IAP-1, and IAP-2, COX-2, VEGF, and increased the expression of p53 and p21. CPO can significantly potentiate the apoptotic effects of various PI3K/AKT inhibitors when used in combination in tumor cells.	86
Cervical (HeLa, Caski, and C33A) and endometrial (HEC-1-A and KLE) cancer cells	Thioridazine	Wortmannin and LY294002	Thioridazine increased early- and late-stage apoptotic fraction. Thioridazine induced the downregulation of cyclin D1, cyclin A and CDK4, and the induction of p21 and p27, a cyclin-dependent kinase inhibitor. Thioridazine inhibited phosphorylation of Akt, phosphorylation of 4E-BP1 and phosphorylation of p70S6K. Thioridazine increased expression level of p53 and Bax and decreased expression of antiapoptotic protein Bcl-2 and Bcl-xL	87
Hepatocellular carcinoma cells	Glycyrrhiza polysaccharide (GPS)	–	GPS inhibited the tumorigenicity of hepatocellular carcinoma cells in nude mice. GPS increased the number of apoptotic cells. GPS increased p53 and downregulated p-PI3K and p-AKT protein expressions.	88

(Continues)

TABLE 1 (Continued)

Targets	Therapeutic agent	PI3K inhibitor	Major effects	Ref.
Prostate cancer cell lines	Polyinosinic-polycytidylic acid [poly(I:C)]	LY294002 and AKT1/2i	Poly(I:C) significantly reduced the viability of cancer cells. Poly(I:C) induced cell cycle arrest and apoptosis. Poly(I:C)-induced apoptosis and growth arrest depended on the PI3K/Akt pathway. Poly(I:C) treatment increased the protein expression of p53 and NOXA, but increased the expression of the antiapoptotic molecule XIAP.	89
Hepatoblastoma HepG2 cells	Isoorientin (ISO)	LY294002	ISO induced apoptosis by activating the Fas receptor-mediated apoptotic pathway, increasing p53 levels and blocking the nuclear translocation of NF-κB. LY294004 increased the expression of Beclin-1 and LC3-II. LY294004 decreased caspase-8 levels and increased PARP cleavage levels. LY294004 inhibited the phosphorylation of IκB and the nuclear translocation of NF-κB. Activation of p53 induced apoptosis.	90
Renal carcinoma Caki cells	Curcumin	NVP-BEZ235	Curcumin induced apoptosis in NVP-BEZ235-treated cells via downregulation of Bcl-2. Combined treatment with NVP-BEZ235 and curcumin induces apoptosis through p53-dependent Bcl-2 mRNA downregulation.	91
Dalton's lymphoma mice	Quercetin		Hyperactivation of PI3K signaling in ascite cells of Dalton's lymphoma mice led to activation of AKT1 and inactivation of p53. Quercetin regresses dalton's lymphoma growth via suppression of PI3K/AKT signaling leading to upregulation of p53 and decrease in energy metabolism.	92

Abbreviations: ATP, arsenic trioxide; bFGF, basic fibroblast growth factor; COX-2, cyclooxygenase-2; EGF, epidermal growth factor; FADD, Fas-associated death domain; GPS, glycyrrhiza polysaccharide; IAP, inhibitor of apoptosis; IGF-1, insulin-like growth factor-1; JAK3, janus kinase 3; MDM2, mouse double minute 2 homolog; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PI3K, phosphatidylinositide 3-kinase; PTEN, phosphatase and tensin homolog; ROS, reactive oxygen species; shRNA, short hairpin RNA; VEGF, vascular endothelial growth factor; siRNA, small interfering RNA; STAT3, signal transducer and activator of transcription 3; TNFaR, tumor necrosis factor receptor 1; XIAP, X-linked inhibitor of apoptosis protein.

TABLE 2 The interplay between cell cycle checkpoints, DDR molecules and the PI3K/Akt signaling pathway

Target	DNA damaging agent	PI3K inhibitor	Cell cycle arrest	Upregulated genes	Downregulated genes	Major finding	Ref.
Human Chondrosarcoma Cell Line	Berberine	LY294002 and SB203580	G2/M Arrest	p53, p21,	cyclin B1, cdc2, cdc25c	Berberine phosphorylated pRb expression. Berberine stimulated phosphorylation of Akt and p38 kinase. LY294002 and SB203580 decreased berberine-induced p53 and p21 expression and restored cell proliferation and expression of cyclin B1, cdc2, cdc25c, and pRb cell cycle progression proteins. Berberine-induced inhibition of cell proliferation by cell cycle arrest at the G2/M phases was regulated through PI3K/Akt and p38 kinase pathways.	97
Human esophageal squamous cell carcinoma cell line	MicroRNA-126	–	G2/M arrest	Myt1 and p-Cdc2	PIK3R2, AKT, Cdc2	Overexpression of miR-126 resulted in a significant decrease in cell proliferation, colon formation, and migration. miR-126 repressed PI3K/AKT signaling pathway by targeting PIK3R2 Overexpression of miR-126 suppressed G2/M transition. miR-126 functions as a potential tumor suppressor in ESCC progression via regulating PI3K/AKT signaling pathway partly by targeting PIK3R2	98
Activated hepatic stellate cells	Arctigenin	LY294002, PHT-427	G0/G1 arrest	$p27^{Kip1}$	CDK4/6, CDK2, cyclin D1,	The expression level of p27Kip1 and the formation of the CDK2-p27Kip1 complex were increased. p27Kip1 silencing attenuated the effect of arctigenin, including cell cycle arrest and suppression of proliferation. Arctigenin suppressed PDGF-BB-induced phosphorylation of Akt and its downstream FOXO3a, decreased binding of FOXO3a to 14-3-3 protein, and stimulated nuclear translocation of FOXO3a. Knockdown of FOXO3a expression attenuated arctigenininduced upregulation of p27Kip1.	99

(Continues)

TABLE 2 (Continued)

Target	DNA damaging agent	PI3K inhibitor	Cell cycle arrest	Upregulated genes	Downregulated genes	Major finding	Ref.
						Arctigenin could increase the levels of p27Kip1 protein through inhibition of Akt and improvement of FOXO3a activity, in turn, inhibited the CDK2 kinase activity, and eventually caused an overall inhibition of cell proliferation.	
Pancreatic cancer PANC-1 cells	Sulforaphane	Akt Inh-IV	G0/G1 arrest	$p21^{/WAF1/CIP1}$, $p27^{/KIP1}$, PTEN	cyclin D1, Akt	Sulforaphane inhibited cell proliferation and colony formation, and induced apoptosis through caspase-3 activation. The inhibition of PI3K/AKT pathways activated FOXO transcription factors. Sulforaphane inhibited phosphorylation of AKT and ERK, and activated FOXO transcription factors, leading to cell cycle arrest and apoptosis.	100
Lung cancer A549 cells	Osthole	–	G2/M arrest	Bax	Cyclin B1, p-Cdc2, and Bcl-2	Osthole inhibited the cell growth by inducing G2/M arrest and apoptosis. Inhibition of PI3K/Akt signaling pathway was observed after treating A549 cells with Osthole. The levels of p-Akt are dose-dependently decreased in response to Osthole	101
Hepatocarcinoma HepG2 cell	*Lonicera japonica* Thunb extraction	LY294002	G2/M arrest	caspase-3, Bak	CDK1, CDC25C, cyclin B1, pro-caspases-3 and -9, Bcl-xL, PARP	Polyphenolic extract affected cell viability by inhibiting cell cycle progression and inducing apoptosis. LY294002 enhanced polyphenolic extract on the suppression of procaspase-3 and increase of cleaved PARP. The Akt pathway is related to the induction of apoptosis, and G2/M cell cycle arrest mechanism caused by polyphenolic extract.	102
PC12 cells and primary neurons	Berberine	LY294002, Akti	G0/G1 arrest	p-Bad	p53 and cyclin D1, caspase 3	Berberine could protect PC12 cells from oxygen–glucose deprivation damage and reduce the rate of cell death LY294002 decreased the cell survival, but cyclin D1 inhibitor CDKi enhanced cell survival.	103

(Continues)

TABLE 2 (Continued)

Target	DNA damaging agent	PI3K inhibitor	Cell cycle arrest	Upregulated genes	Downregulated genes	Major finding	Ref.
						Berberine inhibited apoptosis. The neural protective effect of berberine was suppressed by the inhibitors of PI3K and Akt.	
Human colon cancer cells	Methyl 3, 5-dicaffeoyl quinate (MDQ)	–	G0/G1 arrest	p27	cyclin D1 and p53	MDQ inhibited proliferation and induced apoptosis. MDQ treatment resulted in increase in PARP cleavage and the cytosolic release of cytochrome c from mitochondria. MDQ treatment resulted in a collapse in the mitochondrial membrane potential and a decreased Bcl-2/Bax ratio. MDQ also inhibited the phosphorylation of PI3K/Akt and ERK; significantly reduced NF-κB.	104
Radioresistant prostate cancer cells	Radiation	BKM120, BEZ235, or PI103	G0/G1 and S arrest	p-CDK1, p-Chk1, p-Chk2, and p-Rb	Ki67, p-p53, p21,	PI3K/Akt/mTOR inhibitors combined with radiation greatly improved treatment efficacy by repressing colony formation, inducing more apoptosis, leading to the arrest of the G2/M phase, increased double-strand break levels and less inactivation of cell cycle checkpoint, autophagy and NHEJ/HR repair pathway proteins in radioresistant cells. Combination of dual PI3K/Akt/mTOR inhibitors (BEZ235 or PI103) with radiotherapy is a promising modality for the treatment of CaP to overcome radioresistance.	105
HeLa cells	Chelidonine	–	sub-G1 and G0/G1 arrest	p38, p53	AKT, PI3K, JAK3, STAT3, E6, E7	Chelidonine inhibited proliferation and induced apoptosis s through the generation of ROS, cell cycle arrest at sub-G1 and G0/G1 stage, change in mitochondrial membrane potential and fragmentation of DNA. Chelidonine efficiently induced apoptosis in HeLa cells through possible alteration of p38-p53 and AKT/PI3 kinase signaling pathways	84

(Continues)

TABLE 2 (Continued)

Target	DNA damaging agent	PI3K inhibitor	Cell cycle arrest	Upregulated genes	Downregulated genes	Major finding	Ref.
Glioblastoma cells	Proteasome inhibitor MG132	–	G2/M arrest	p21WAF1, JNK, and p38	bcl-xL	MG132 markedly inhibited GBM cells growth irrespective of the p53 or PTEN mutational status of the cells. MG132 promoted mitochondrial depolarization. MG132 markedly inhibited NF-kB and PI3K/Akt survival pathways.	[106]
Prostate cancer cell lines	–	Akt- specific siRNA	G1 arrest	cyclin G2, RBL2	Cdc25a, E2F2	Induced expression of PTEN inhibited cell proliferation. Blocking of Akt signaling inhibited E2F2 and Cdc25a mRNA expression, and upregulate the FOXO target cyclin G2.	[107]
Breast cancer cells	Alisertib (ALS)	Wortmannin	G2/M arrest	p21 Waf1/Cip1, p27 Kip1, and p53, Bax, PUMA, caspases -3, -9, LC3 and beclin 1	CDK1/ CDC2, CDK2, cyclin B1, Bcl-2	ALS induced mitochondria-mediated apoptosis. ALS induced the inhibition of the PI3K/Akt/mTOR and MAPK signaling pathway. Treatment with wortmannin markedly downregulated ALS-induced p38 MAPK activation and LC3 conversion. ALS promotes cellular apoptosis and autophagy via modulation of p38 MAPK/Akt/mTOR pathways.	[108]
Pancreatic cancer cells	Plumbagin	Wortmannin	G2/M arrest	CDK1/CDC2, p21 Waf1/Cip1, p27 Kip1, and p53, PTEN, beclin, E-cadherin	Sirt1, N-cadherin	Plumbagin induced the inhibition of the PI3K/Akt/mTOR and MAPK signaling pathway. Wortmannin enhanced Plumbagin-induced autophagy, indicating the roles of PI3K mediated signaling pathways in Plumbagin-induced autophagic cell death. Plumbagin significantly inhibited epithelial to mesenchymal transition phenotype.	[109]
Tongue squamous cell carcinoma cells	Plumbagin	Wortmannin	G2/M arrest	p21 Waf1/Cip1, p27 Kip1, p53, Bax	Cdc2, cyclin B1, Bcl-2, Bcl-xl,	Plumbagin exerted potent inducing effects on cell cycle arrest, apoptosis, and autophagy. Plumbagin induced the inhibition of the PI3K/Akt/mTOR, GSK3β, and MAPK signaling pathway. Wortmannin enhanced Plumbagin -induced autophagy	[110]

(Continues)

TABLE 2 (Continued)

Target	DNA damaging agent	PI3K inhibitor	Cell cycle arrest	Upregulated genes	Downregulated genes	Major finding	Ref.
RAT1, NIH-3T3 and HeLa cells	UVB irradiation, adriamycin	LY294002	G1 arrest	–	–	14-3-3η as a gene that inhibits Miz1 function through interaction with its DNA binding domain. Binding of 14-3-3η to Miz1 depends on phosphorylation by Akt and regulates the recovery of cells from arrest after DNA damage. Miz1 is required for upregulation of a large group of genes. Miz1 represses the expression of many genes in response to DNA damage in an Akt- and 14-3-3-η-regulated manner	111
Prostate cancer cells	Nimbolide	–	G0/G1 arrest	–	PCNA, c-Myc, CDK4/6-cyclin D, survivin	The effects of nimbolide were associated with PI3K/Akt/mTOR signaling pathway suppression.	112
Gastric cancer MGC803 cells	Resveratrol	PTEN- specific siRNA	G0/G1 arrest	–	p-GSK3β, cyclin D1, p-PTEN, p-PI3K, p-PKB/Akt	Resveratrol inhibited the progression of the cell cycle in MGC803 cells by repressing p-PI3K and p-Akt expression Resveratrol did not decrease the phosphorylation level of Akt when the PTEN gene expression was knocked down by a siRNA.	113
Breast cancer cell lines	Etoposide	PTEN- specific shRNA	G2/M arrest	Chk2,	CDC25C, H2AX, P53	Etoposide induces G2/M via activation of ATM, followed by the activation of Chk2 that subsequently inactivates CDC25C. knockdown of PTEN strongly antagonized ATM activation in response to etoposide treatment. PTEN plays a unique role in etoposide-induced G2/M arrest by facilitating the activation of the ATM pathway, and PTEN was required for the proper activation of checkpoints in response to DNA damage.	114
Glioblastoma and colon carcinoma cells	NVP-AUY922, irradiation	PI-103	G1-arrest, G2/M arrest	–	–	PI-103 exerted a radiosensitizing effect, also strongly enhanced the radiosensitization by NVP-AUY922. A downregulation of PI3K and ERK pathways during or directly after irradiation, increased residual DNA damage and strong G2/M arrest, were also observed.	115

(Continues)

TABLE 2 (Continued)

Target	DNA damaging agent	PI3K inhibitor	Cell cycle arrest	Upregulated genes	Downregulated genes	Major finding	Ref.
Hepatoma cancer cells	CCT128930	CCT128930	G1-arrest	p21, p27, p53, caspase-3, caspase-9, PARP, LC3-II and Beclin-1	cyclinD1 and Cdc25A	CCT128930 triggered cell apoptosis and autophagy Treatment with CCT128930 increased phosphorylation of ERK and JNK in HepG2 cells. CCT128930 activated DNA damage response of HepG2 cell characterized by phosphorylation of H2AX, ATM, Chk1 and Chk2	116
Rat embryo fibroblasts	6-Thioguanine (6-TG), gamma irradiation	–	G2/M arrest	–	–	Activated Akt overrides a G2/M cell cycle checkpoint induced by 6-TG and gamma irradiation. The ability of activated Akt to override G2/M arrest is independent of p53 status and cannot be reestablished by coexpression of Myc and Bcl-2. $PTEN^{-/-}$ ES cells are deficient in G2/M checkpoints induced by gamma irradiation. The PI3K/Akt pathway is required for G2/M transition.	117
Human glioma cells	Temozolomide	–	G2 arrest	Chk1, Chk2, and p38	Cdc25C and Cdc2	Akt-mediated suppression of G2 arrest was associated not with alterations in Chk1 or p38 activation but rather with suppression of Chk2 activation and reduced recruitment of Chk2 to sites of damage in chromatin. Unlike bypass of the G2 checkpoint induced by pharmacologic inhibitors of Chk1 or p38, however, Akt-induced bypass of G2 arrest suppressed, rather than enhanced, temozolomide-induced senescence and mitotic catastrophe.	118

Abbreviations: 6-TG, 6-thioguanine; ATM, Ataxia-telangiectasia mutated; Chk1, checkpoint kinase 1; FOXO3a, forkhead box O 3; HR, homologous recombination; JAK3, janus kinase 3; MDQ, methyl 3,5-dicaffeoyl quinate; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NHEJ, nonhomologous end joining; PARP, poly (ADP-ribose) polymerase; PCNA, proliferating cell nuclear antigen; PDGF-BB, platelet-derived growth factor BB; PIK3R2, phosphoinositide-3-Kinase Regulatory Subunit 2; PI3K, phosphatidylinositide 3-kinase; PTEN, phosphatase and tensin homolog; ROS, reactive oxygen species; siRNA, small interfering RNA; STAT3, signal transducer and activator of transcription 3.

This study found that a functional interaction existed in-between PI3K signaling, DNA-PKcs, and XRCC1. Basal level regulation of XRCC1 was dependent on DNA-PKcs function, which was itself regulated by PI3K signaling. But the radiation-induced change in expression of XRCC1 was dependent on MAPK-ERK1/2 signaling cascade. The authors suggested that these interactions could be targeted in cell lines of lung cancer and glioblastoma, via using kinase inhibitors against DNA-PKcs and PI3K/Akt signaling.[126]

The interplay between two other important components of repair machinery, excision repair cross-complementary gene 1 (ERCC1) and BRCA1, and PI3K signaling was evaluated in NSCLC.[127] It was illustrated that downregulation of ERCC1 and BRCA1 decreased cell proliferation and PI3K and Akt activity while increasing caspase 3 activity. This relation was shown in a study where ERCC1 and BRCA1 were overexpressed in drug-resistant NSCLC cells. They contributed to the malignant phenotype occurrence and development by affecting the PI3K/Akt signaling pathway.[127] In addition to excision repair, HR is also regulated by the PI3K signaling pathway, as demonstrated by recent studies. For example, it was reported that the combined inhibition of PI3K and PARP effectively synergized to block the growth of ovarian cancer cell lines.[127] Double blockade of PARP and PI3K in these cell lines by Olaparib and BKM120 resulted in substantially weakened PI3K/Akt/mTOR signaling, defective DDR as well as deficient HR DNA repair, with significant downregulation of BRCA and reduced RAD51 foci formation.[127] In addition, McEllin et al, noticed that the loss of PTEN in astrocytes resulted in increased sensitivity to N-methyl-N′-nitro-N-nitrosoguanidine (MNNG), a temozolomide analog with similar functions. They showed that MNNG causes secondary DSBs that are not repaired properly in PTEN deficient cells due to compromised DNA repair, which might be because of reduced expression of Rad51 paralogs.[128] Another study reported that Astaxanthin, a red dietary carotenoid from terpenes, inactivated Akt, thus down-regulating RAD51, and enhancing mitomycin C-induced cytotoxicity in NSCLC.[129] Transfecting cells with si-Rad51 RNA leading to inhibited RAD51 expression or introduction of LY294002 to the cells further increased the cytotoxicity and cell proliferation inhibition of astaxanthin. In addition, a combination of mitomycin C and astaxanthin synergistically resulted in cell death and inhibition of proliferation and growth in NSCLC cells, which as expected, was caused by reduced Akt function and decreased the level of Rad51 expression. Furthermore, overexpression of Akt or Rad51 reversed the effects of astaxanthin and mitomycin C. In contrast, pretreatment with LY294002 increased the effectiveness of cotherapy by astaxanthin and mitomycin C.[129] PI3K/Akt /mTOR signaling was also involved in the promotion of the repair of DSB by modulating FANCD2,[130] and BRCA1-A complex, other key players of HR.[131] DNA-PKcs and Ku80,[132] Ku70,[133] and XRCC4-like factor (XLF),[134] which are involved in the NHEJ, are potential targets of the PI3K signaling pathway. Akt phosphorylates DNA-PKcs and Ku80 which results in radiosensitization of DNA-PKcs and Ku80 expression.[132] Akt 1 interacts with and phosphorylates UBE2S, a novel substrate of Akt1, enhancing its stability by inhibiting proteasomal degradation. Accumulated UBE2S is associated with Ku70, as well as regulating DNA repair.[133] Akt exerts a regulatory function on XLF by phosphorylating it, which causes XLF to dissociate from the DNA ligase IV/XRCC4 complex. Furthermore, phosphorylation of XLF leads to an increased interaction between 14-3-3b and XLF, causing XLFs retention in the cytoplasm, where cytosolic XLF is then degraded in a CKI-dependent manner by SCFb-TRCP. Therefore, upon DNA damage, XLF-T181E expressing cells display increased cell death because of impaired NHEJ.[134]

4 | PI3K/Akt SIGNALING PATHWAY AND MODULATION OF OXIDATIVE STRESS

ROS interfere in multiple signaling pathways essential for cellular hemostasis. Cells have adopted various strategies to neutralize the negative effects of ROS through upregulation of antioxidant enzymes such as manganese superoxide dismutase, catalase and sestrin 3, to name a few.[135] This response is dependent on the activation and function of FOXO, a group of transcription factors that regulate the survival of the cell by regulating quiescence and cell cycle arrest in response to cellular stress caused by oxidative stress. Oxidative stress resulted from overproduction of ROS activates the expression of FoxO in affected cells.[19] The activity of the PI3K/Akt signaling pathway causes direct phosphorylation FoxO family transcription factors and prevents their entry into the cell nucleus. At the same time, the PI3K/Akt signaling pathway activity increases ROS levels intracellularly by enhancing oxygen consumption and oxidative metabolism in mitochondrial. PTEN is a tumor-suppressor phosphatase and is important in the regulation of oxidative stress. PTEN modulates PI3K/Akt signaling pathway activity negatively through conversion of PIP3 to PIP2.[136-138] Production of ROS (H_2O_2 is prototypical of ROS) endogenously suppresses PTEN during oxidative stress and, as a result, activates Akt signaling pathway and produces more ROS.[139] Studies have shown that

tumor suppressor p53 which is also a key effector of DDR, and peroxisome proliferator-activated receptor γ can increase PTEN expression.[137] PI3K/Akt signaling pathway increases nuclear factor erythroid 2-related factor 2 (Nrf2) important for eliminating xenobiotics and ROS. Nrf2 modulates genes encoding antioxidant proteins under various stress conditions through interacting with the antioxidant-responsive element and increases a group of enzymes, called phase II antioxidant enzymes such as glutathione peroxidases, quinone oxidoreductase 1, NAD(P)H, glutathione S-transferases, glutamate-cysteine ligase, and heme oxygenase-1.[140-142] From this perspective, the signaling PI3K/Akt pathway acts like a double-edged knife, as it increases phase II antioxidant enzymes by activating Nrf2 and therefore knocks down ROS production. On the other hand, it decreases phase I antioxidant enzymes, thus enhancing the production of ROS through phosphorylation and inhibition of FoxO. Because Akt increases cell metabolism and proliferation, it consequently produces ROS. FoxO can eliminate ROS but paradoxically is inhibited by Akt. Alternatively, Akt uses another strategy, the activation of Nrf2, to counteract the production of ROS in this pathway. Regulation of balance between these pathways by PI3K/Akt signaling pathway helps to preserve the integrity and hemostasis of the cells.

5 | CONCLUSIONS

This review aimed at exploring the factors causing the DNA damage, which endangers cell viability vs those working to maintain the integrity and hemostasis of the cell. The Akt/PKB kinase maintains an important role in signaling pathway controlling numerous cellular processes which eventually cause the cell life to continue or culminate in the cell death. A cumulative body of evidence implicates the hyperactivation of PI3K/Akt in multiple types of human cancer. The evidence amply shows that the PI3K/Akt signaling pathway is also activated in cells upon DNA damage, which in turn stimulates some important signaling networks involved in the maintenance, as well as restoration of cellular homeostasis. In this review, we discussed the involvement of the PI3K/Akt signaling pathway in the regulation of DDR by interaction and crosstalk with three important part of DDR including sensors, transducers, and effectors.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interests.

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REFERENCES

1. Yousefi B, Samadi N, Ahmadi Y. Akt and p53R2, partners that dictate the progression and invasiveness of cancer. *DNA Repair*. 2014;22:24-29.
2. Majidinia M, Sadeghpour A, Yousefi B. The roles of signaling pathways in bone repair and regeneration. *J Cell Physiol*. 2018;233(4):2937-2948.
3. Asati V, Mahapatra DK, Bharti SK. PI3K/Akt/mTOR and Ras/Raf/MEK/ERK signaling pathways inhibitors as anticancer agents: structural and pharmacological perspectives. *Eur J Med Chem*. 2016;109:314-341.
4. Vara JÁF, Casado E, de Castro J, Cejas P, Belda-Iniesta C, González-Barón M. PI3K/Akt signalling pathway and cancer. *Cancer Treat Rev*. 2004;30(2):193-204.
5. Yuan TL, Cantley LC. PI3K pathway alterations in cancer: variations on a theme. *Oncogene*. 2008;27(41):5497-5510.
6. Martini M, De Santis MC, Braccini L, Gulluni F, Hirsch E. PI3K/AKT signaling pathway and cancer: an updated review. *Ann Med*. 2014;46(6):372-383.
7. Wick MJ, Dong LQ, Riojas RA, Ramos FJ, Liu F. Mechanism of phosphorylation of protein kinase B/Akt by a constitutively active 3-phosphoinositide-dependent protein kinase-1. *J Biol Chem*. 2000;275(51):40400-40406.
8. Yousefi B, Azimi A, Majidinia M, et al. Balaglitazone reverses P-glycoprotein-mediated multidrug resistance via upregulation of PTEN in a PPARγ-dependent manner in leukemia cells. *Tumor Biol*. 2017;39(10):1010428317716501.
9. Yousefi B, Zarghami N, Samadi N, Majidinia M. Peroxisome proliferator-activated receptors and their ligands in cancer drug-resistance: opportunity or challenge. *Anti-Cancer Agents in Med Chem*. 2016;16(12):1541-1548.
10. Yousefi B, Samadi N, Baradaran B, et al. Differential effects of peroxisome proliferator-activated receptor agonists on doxorubicin-resistant human myelogenous leukemia (K562/DOX) cells. *Cell Mol Biol (Noisy-le-Grand, France)*. 2015;61(8):118-122.
11. Sansal I, Sellers WR. The biology and clinical relevance of the PTEN tumor suppressor pathway. *J Clin Oncol*. 2004;22(14):2954-2963.
12. Hay N, Sonenberg N. Upstream and downstream of mTOR. *Genes Dev*. 2004;18(16):1926-1945.
13. Hay N. The Akt-mTOR tango and its relevance to cancer. *Cancer Cell*. 2005;8(3):179-183.
14. Altomare DA, Testa JR. Perturbations of the AKT signaling pathway in human cancer. *Oncogene*. 2005;24(50):7455-7464.
15. Mirza-Aghazadeh-Attari M, Darband SG, Kaviani M, et al. DNA damage response and repair in colorectal cancer: defects, regulation and therapeutic implications. *DNA Repair*. 2018;69:34-52.
16. Majidinia M, Sadeghpour A, Mehrzadi S, Reiter RJ, Khatami N, Yousefi B. Melatonin: a pleiotropic molecule that modulates

DNA damage response and repair pathways. *J Pineal Res*. 2017;63:e12416.
17. Majidinia M, Yousefi B. DNA damage response regulation by microRNAs as a therapeutic target in cancer. *DNA Repair*. 2016;47:1-11.
18. Majidinia M, Yousefi B. DNA repair and damage pathways in breast cancer development and therapy. *DNA Repair*. 2017;54: 22-29.
19. Karimaian A, Majidinia M, Bannazadeh baghi H, Yousefi B. The crosstalk between Wnt/β-catenin signaling pathway with DNA damage response and oxidative stress: implications in cancer therapy. *DNA Repair*. 2017;51:14-19.
20. Ribezzo F, Shiloh Y, Schumacher B, (eds.) *Systemic DNA damage responses in aging and diseases. Seminars in cancer biology*. Elsevier; 2016.
21. Li Z, Pearlman AH, Hsieh P. DNA mismatch repair and the DNA damage response. *DNA Repair*. 2016;38:94-101.
22. Liu Y, Li Y, Lu X. Regulators in the DNA damage response. *Arch Biochem Biophys*. 2016;594:18-25.
23. Chen Y-C, Chiang H-Y, Yang M-H, et al. Activation of phosphoinositide 3-kinase by the NBS1 DNA repair protein through a novel activation motif. *J Mol Med*. 2008;86(4):401-412.
24. Yang M-H, Chiang W-C, Chou T-Y, et al. Increased NBS1 expression is a marker of aggressive head and neck cancer and overexpression of NBS1 contributes to transformation. *Clin Cancer Res*. 2006;12(2):507-515.
25. Sagan D, Mörtl S, Müller I, Eckardt-Schupp F, Eichholtz-Wirth H. Enhanced CD95-mediated apoptosis contributes to radiation hypersensitivity of NBS lymphoblasts. *Apoptosis*. 2007;12(4):753-767.
26. Uziel T, Lerenthal Y, Moyal L, Andegeko Y, Mittelman L, Shiloh Y. Requirement of the MRN complex for ATM activation by DNA damage. *EMBO J*. 2003;22(20):5612-5621.
27. Lee J-H, Paull TT. ATM activation by DNA double-strand breaks through the Mre11-Rad50-Nbs1 complex. *Science*. 2005;308(5721):551-554.
28. Lee JH, Goodarzi AA, Jeggo PA, Paull TT. 53BP1 promotes ATM activity through direct interactions with the MRN complex. *EMBO J*. 2010;29(3):574-585.
29. Zou L, Elledge SJ. Sensing DNA damage through ATRIP recognition of RPA-ssDNA complexes. *Science*. 2003;300(5625): 1542-1548.
30. O'Connor MJ. Targeting the DNA damage response in cancer. *Mol Cell*. 2015;60(4):547-560.
31. Smits VAJ, Gillespie DA. DNA damage control: regulation and functions of checkpoint kinase 1. *FEBS J*. 2015;282(19): 3681-3692.
32. Choi SH, Yoo HY. Mdc1 modulates the interaction between TopBP1 and the MRN complex during DNA damage checkpoint responses. *Biochem Biophys Res Commun*. 2016;479(1):5-11.
33. Liu K, Paik JC, Wang B, Lin FT, Lin WC. Regulation of TopBP1 oligomerization by Akt/PKB for cell survival. *EMBO J*. 2006;25(20):4795-4807.
34. Zhou Y, Lee J-H, Jiang W, Crowe JL, Zha S, Paull TT. Regulation of the DNA damage response by DNA-PKcs inhibitory phosphorylation of ATM. *Mol Cell*. 2017;65(1):91-104.
35. Mukherjee B, Tomimatsu N, Amancherla K, Camacho CV, Pichamoorthy N, Burma S. The dual PI3K/mTOR inhibitor NVP-BEZ235 is a potent inhibitor of ATM-and DNA-PKCs-mediated DNA damage responses. *Neoplasia*. 2012;14(1):34IN5-43IN8.
36. Gil del alcazar CR, Hardebeck MC, Mukherjee B, et al. Inhibition of DNA double-strand break repair by the dual PI3K/mTOR inhibitor NVP-BEZ235 as a strategy for radiosensitization of glioblastoma. *Clin Cancer Res*. 2014;20(5): 1235-1248.
37. Toulany M, Kasten-Pisula U, Brammer I, et al. Blockage of epidermal growth factor receptor-phosphatidylinositol 3-kinase-AKT signaling increases radiosensitivity of K-RAS mutated human tumor cells in vitro by affecting DNA repair. *Clin Cancer Res*. 2006;12(13):4119-4126.
38. Burrows N, Williams J, Telfer BA, et al. Phosphatidylinositide 3-kinase (PI3K) and PI3K-related kinase (PIKK) activity contributes to radioresistance in thyroid carcinomas. *Oncotarget*. 2016;7(39):63106.
39. Chen J-H, Zhang P, Chen W-D, et al. ATM-mediated PTEN phosphorylation promotes PTEN nuclear translocation and autophagy in response to DNA-damaging agents in cancer cells. *Autophagy*. 2015;11(2):239-252.
40. Biechonski S, Gourevich D, Rall M, et al. Quercetin alters the DNA damage response in human hematopoietic stem and progenitor cells via TopoII-and PI3K-dependent mechanisms synergizing in leukemogenic rearrangements. *Int J Cancer*. 2017;140:864-876.
41. Viniegra JG, Martínez N, Modirassari P, et al. Full activation of PKB/Akt in response to insulin or ionizing radiation is mediated through ATM. *J Biol Chem*. 2005;280(6):4029-4036.
42. Caporali S, Levati L, Starace G, et al. AKT is activated in an ataxia-telangiectasia and Rad3-related-dependent manner in response to temozolomide and confers protection against drug-induced cell growth inhibition. *Mol Pharmacol*. 2008;74(1):173-183.
43. Bozulic L, Surucu B, Hynx D, Hemmings BA. PKBα/Akt1 acts downstream of DNA-PK in the DNA double-strand break response and promotes survival. *Mol Cell*. 2008;30(2):203-213.
44. Tehrani SS, Karimian A, Parsian H, Majidinia M, Yousefi B. Multiple functions of long non-coding RNAs in oxidative stress, DNA damage response and cancer progression. *J Cell Biochem*. 2018;119(1):223-236.
45. Harper JW, Elledge SJ. The DNA damage response: ten years after. *Mol Cell*. 2007;28(5):739-745.
46. Stucki M, Jackson SP. γH2AX and MDC1: anchoring the DNA-damage-response machinery to broken chromosomes. *DNA Repair*. 2006;5(5):534-543.
47. Liu W-L, Gao M, Tzen K-Y, et al. Targeting phosphatidylinositide 3-kinase/Akt pathway by BKM120 for radiosensitization in hepatocellular carcinoma. *Oncotarget*. 2014;5(11):3662-3672.
48. Gwak H-S, Kim TH, Jo GH, et al. Silencing of microRNA-21 confers radio-sensitivity through inhibition of the PI3K/AKT pathway and enhancing autophagy in malignant glioma cell lines. *PLoS One*. 2012;7(10):e47449.
49. Kao GD, Jiang Z, Fernandes AM, Gupta AK, Maity A. Inhibition of phosphatidylinositol-3-OH kinase/Akt signaling impairs DNA repair in glioblastoma cells following ionizing radiation. *J Biol Chem*. 2007;282(29):21206-21212.
50. Pappas G, Zumstein LA, Munshi A, Hobbs M, Meyn RE. Adenoviral-mediated PTEN expression radiosensitizes non-small cell lung cancer cells by suppressing DNA repair capacity. *Cancer Gene Ther*. 2007;14(6):543-549.

51. Azimi A, Majidinia M, Shafiei-Irannejad V, et al. Suppression of p53R2 gene expression with specific siRNA sensitizes HepG2 cells to doxorubicin. *Gene*. 2018;642:249-255.
52. Kolas NK, Chapman JR, Nakada S, et al. Orchestration of the DNA-damage response by the RNF8 ubiquitin ligase. *Science*. 2007;318(5856):1637-1640.
53. Huen MSY, Grant R, Manke I, et al. RNF8 transduces the DNA-damage signal via histone ubiquitylation and checkpoint protein assembly. *Cell*. 2007;131(5):901-914.
54. Mailand N, Bekker-Jensen S, Faustrup H, et al. RNF8 ubiquitylates histones at DNA double-strand breaks and promotes assembly of repair proteins. *Cell*. 2007;131(5):887-900.
55. Bekker-Jensen S, Lukas C, Kitagawa R, et al. Spatial organization of the mammalian genome surveillance machinery in response to DNA strand breaks. *J Cell Biol*. 2006;173(2):195-206.
56. Ibrahim YH, García-García C, Serra V, et al. PI3K inhibition impairs BRCA1/2 expression and sensitizes BRCA-proficient triple-negative breast cancer to PARP inhibition. *Cancer Discov*. 2012;2(11):1036-1047.
57. Xiang T, Ohashi A, Huang Y, et al. Negative regulation of AKT activation by BRCA1. *Cancer Res*. 2008;68(24):10040-10044.
58. Hinton CV, Fitzgerald LD, Thompson ME. Phosphatidylinositol 3-kinase/Akt signaling enhances nuclear localization and transcriptional activity of BRCA1. *Exp Cell Res*. 2007;313(9):1735-1744.
59. Altiok S, Batt D, Altiok N, et al. Heregulin induces phosphorylation of BRCA1 through phosphatidylinositol 3-Kinase/AKT in breast cancer cells. *J Biol Chem*. 1999;274(45):32274-32278.
60. Stechow L, Olsen JV. Proteomics insights into DNA damage response and translating this knowledge to clinical strategies. *Proteomics*. 2016;17:3-4.
61. Kozlov SV, Waardenberg AJ, Engholm-Keller K, Arthur JW, Graham ME, Lavin M. ROS-activated ATM-dependent phosphorylation of cytoplasmic substrates identified by large scale phosphoproteomics screen. *Mol Cell Proteomics*. 2015;15:1032-1047.
62. Branzei D, Foiani M. Regulation of DNA repair throughout the cell cycle. *Nat Rev Mol Cell Biol*. 2008;9(4):297-308.
63. Jeyamohan S, Moorthy RK, Kannan MK, Arockiam AJV. Parthenolide induces apoptosis and autophagy through the suppression of PI3K/Akt signaling pathway in cervical cancer. *Biotechnol Lett*. 2016;38(8):1251-1260.
64. Bai C, Yang X, Zou K, et al. Anti-proliferative effect of RCE-4 from Reineckia carnea on human cervical cancer HeLa cells by inhibiting the PI3K/Akt/mTOR signaling pathway and NF-κB activation. *Naunyn-Schmiedeberg's Arch Pharmacol*. 2016;389(6):573-584.
65. Lee E-R, Kim J-Y, Kang Y-J, et al. Interplay between PI3K/Akt and MAPK signaling pathways in DNA-damaging drug-induced apoptosis. *Biochim Biophys Acta Mol Cell Res*. 2006;1763(9):958-968.
66. Hao W, Yuan X, Yu L, et al. Licochalcone A-induced human gastric cancer BGC-823 cells apoptosis by regulating ROS-mediated MAPKs and PI3K/AKT signaling pathways. *Sci Rep*. 2015;5:10336.
67. Demel H-R, Feuerecker B, Piontek G, et al. Effects of topoisomerase inhibitors that induce DNA damage response on glucose metabolism and PI3K/Akt/mTOR signaling in multiple myeloma cells. *Am J Cancer Res*. 2015;5(5):1649-1664.
68. Yousefi B, Rahmati M, Ahmadi Y. The roles of p53R2 in cancer progression based on the new function of mutant p53 and cytoplasmic p21. *Life Sci*. 2014;99(1):14-17.
69. Levine AJ, Hu W, Feng Z. The P53 pathway: what questions remain to be explored? *Cell Death Differ*. 2006;13(6):1027-1036.
70. Lindsey-Boltz L, Kemp M, Reardon J, et al. Coupling of human DNA excision repair and the ATR-mediated DNA damage checkpoint. *FASEB J*. 2015;29(1 Suppl):490.1.
71. Fang J, Xia C, Cao Z, Zheng JZ, Reed E, Jiang B-H. Apigenin inhibits VEGF and HIF-1 expression via PI3K/AKT/p70S6K1 and HDM2/p53 pathways. *FASEB J*. 2005;19(3):342-353.
72. Fang L, Li G, Liu G, Lee SW, Aaronson SA. p53 induction of heparin-binding EGF-like growth factor counteracts p53 growth suppression through activation of MAPK and PI3K/Akt signaling cascades. *EMBO J*. 2001;20(8):1931-1939.
73. Yin D, Woodruff M, Zhang Y, et al. Morphine promotes Jurkat cell apoptosis through pro-apoptotic FADD/P53 and anti-apoptotic PI3K/Akt/NF-κB pathways. *J Neuroimmunol*. 2006;174(1-2):101-107.
74. Li Y, Qu X, Qu J, et al. Arsenic trioxide induces apoptosis and G2/M phase arrest by inducing Cbl to inhibit PI3K/Akt signaling and thereby regulate p53 activation. *Cancer Lett*. 2009;284(2):208-215.
75. Qiu W, Leibowitz B, Zhang L, Yu J. Growth factors protect intestinal stem cells from radiation-induced apoptosis by suppressing PUMA through the PI3K/AKT/p53 axis. *Oncogene*. 2010;29(11):1622-1632.
76. Guo C, Gasparian AV, Zhuang Z, et al. 9-Aminoacridine-based anticancer drugs target the PI3K/AKT/mTOR, NF-κB and p53 pathways. *Oncogene*. 2009;28(8):1151-1161.
77. Niwa K, Inanami O, Yamamori T, Ohta T, Hamasu T, Kuwabara M. Redox regulation of PI3K/Akt and p53 in bovine aortic endothelial cells exposed to hydrogen peroxide. *Antioxid Redox Signal*. 2003;5(6):713-722.
78. Mayo LD, Dixon JE, Durden DL, Tonks NK, Donner DB. PTEN protects p53 from Mdm2 and sensitizes cancer cells to chemotherapy. *J Biol Chem*. 2002;277(7):5484-5489.
79. Fraser M, Leung BM, Yan X, Dan HC, Cheng JQ, Tsang BK. p53 is a determinant of X-linked inhibitor of apoptosis protein/Akt-mediated chemoresistance in human ovarian cancer cells. *Cancer Res*. 2003;63(21):7081-7088.
80. Yang X, Fraser M, Moll UM, Basak A, Tsang BK. Akt-mediated cisplatin resistance in ovarian cancer: modulation of p53 action on caspase-dependent mitochondrial death pathway. *Cancer Res*. 2006;66(6):3126-3136.
81. Skladanowski A, Bozko P, Sabisz M, Larsen AK. Dual inhibition of PI3K/Akt signaling and the DNA damage checkpoint in p53-deficient cells with strong survival signaling: implications for cancer therapy. *Cell Cycle*. 2007;6(18):2268-2275.
82. Bastian L, Hof J, Pfau M, et al. Synergistic activity of bortezomib and HDACi in preclinical models of B-cell precursor acute lymphoblastic leukemia via modulation of p53, PI3K/AKT, and NF-κB. *Clin Cancer Res*. 2013;19:1445-1457.
83. Rasul A, Ding C, Li X, et al. Dracorhodin perchlorate inhibits PI3K/Akt and NF-κB activation, up-regulates the expression

of p53, and enhances apoptosis. *Apoptosis*. 2012;17(10): 1104-1119.
84. Paul A, Bishayee K, Ghosh S, et al. Chelidonine isolated from ethanolic extract of *Chelidonium majus* promotes apoptosis in HeLa cells through p38-p53 and PI3K/AKT signalling pathways. *Zhong Xi Yi Jie He Xue Bao=J Chin Integr Med*. 2012;10(9):1025-1038.
85. Dung TD, Day CH, Binh TV, et al. PP2A mediates diosmin p53 activation to block HA22T cell proliferation and tumor growth in xenografted nude mice through PI3K–Akt–MDM2 signaling suppression. *Food Chem Toxicol*. 2012;50(5):1802-1810.
86. Park K-R, Nam D, Yun H-M, et al. β-Caryophyllene oxide inhibits growth and induces apoptosis through the suppression of PI3K/AKT/mTOR/S6K1 pathways and ROS-mediated MAPKs activation. *Cancer Lett*. 2011;312(2):178-188.
87. Kang S, Dong SM, Kim B-R, et al. Thioridazine induces apoptosis by targeting the PI3K/Akt/mTOR pathway in cervical and endometrial cancer cells. *Apoptosis*. 2012;17(9):989-997.
88. Chen J, Jin X, Chen J, Liu C. Glycyrrhiza polysaccharide induces apoptosis and inhibits proliferation of human hepatocellular carcinoma cells by blocking PI3K/AKT signal pathway. *Tumor Biol*. 2013;34(3):1381-1389.
89. Harashima N, Inao T, Imamura R, Okano S, Suda T, Harada M. Roles of the PI3K/Akt pathway and autophagy in TLR3 signaling-induced apoptosis and growth arrest of human prostate cancer cells. *Cancer Immunol Immunother*. 2012;61(5):667-676.
90. Yuan L, Wei S, Wang J, Liu X. Isoorientin induces apoptosis and autophagy simultaneously by reactive oxygen species (ROS)-related p53, PI3K/Akt, JNK, and p38 signaling pathways in HepG2 cancer cells. *J Agricult Food Chem*. 2014;62(23):5390-5400.
91. Seo BR, Min K, Cho IJ, Kim SC, Kwon TK. Curcumin significantly enhances dual PI3K/Akt and mTOR inhibitor NVP-BEZ235-induced apoptosis in human renal carcinoma Caki cells through down-regulation of p53-dependent Bcl-2 expression and inhibition of Mcl-1 protein stability. *PLoS One*. 2014;9(4):e95588.
92. Maurya AK, Vinayak M. Quercetin regresses Dalton's lymphoma growth via suppression of PI3K/AKT signaling leading to upregulation of p53 and decrease in energy metabolism. *Nutr Cancer*. 2015;67(2):354-363.
93. Zhou B-BS, Elledge SJ. The DNA damage response: putting checkpoints in perspective. *Nature*. 2000;408(6811):433-439.
94. Jackson SP, Bartek J. The DNA-damage response in human biology and disease. *Nature*. 2009;461(7267):1071-1078.
95. Hirao A, Kong Y-Y, Matsuoka S, et al. DNA damage-induced activation of p53 by the checkpoint kinase Chk2. *Science*. 2000;287(5459):1824-1827.
96. Dai Y, Grant S. New insights into checkpoint kinase 1 in the DNA damage response signaling network. *Clin Cancer Res*. 2010;16(2):376-383.
97. Eo S-H, Kim J-H, Kim S-J. Induction of G2/M arrest by berberine via activation of PI3K/Akt and p38 in human chondrosarcoma cell line. *Oncol Res*. 2015;22(3):147-157.
98. Nie Z-C, Weng W-H, Shang Y-S, et al. MicroRNA-126 is down-regulated in human esophageal squamous cell carcinoma and inhibits the proliferation and migration in EC109 cell via PI3K/AKT signaling pathway. *Int J Clin Exp Pathol*. 2015;8(5):4745.
99. Li A, Wang J, Wu M, Zhang X, Zhang H. The inhibition of activated hepatic stellate cells proliferation by arctigenin through G0/G1 phase cell cycle arrest: persistent p27Kip1 induction by interfering with PI3K/Akt/FOXO3a signaling pathway. *Eur J Pharmacol*. 2015;747:71-87.
100. Roy SK, Srivastava RK, Shankar S. Inhibition of PI3K/AKT and MAPK/ERK pathways causes activation of FOXO transcription factor, leading to cell cycle arrest and apoptosis in pancreatic cancer. *J Mol Signal*. 2010;5(1):10.
101. Xu X, Zhang Y, Qu D, Jiang T, Li S. Osthole induces G2/M arrest and apoptosis in lung cancer A549 cells by modulating PI3K/Akt pathway. *J Exp Clin Cancer Res*. 2011;30(1):33.
102. Park H-S, Park K-I, Lee D-H, et al. Polyphenolic extract isolated from Korean *Lonicera japonica* Thunb. induce G2/M cell cycle arrest and apoptosis in HepG2 cells: involvements of PI3K/Akt and MAPKs. *Food Chem Toxicol*. 2012;50(7):2407-2416.
103. Chai Y-S, Hu J, Lei F, et al. Effect of berberine on cell cycle arrest and cell survival during cerebral ischemia and reperfusion and correlations with p53/cyclin D1 and PI3K/Akt. *Eur J Pharmacol*. 2013;708(1-3):44-55.
104. Hu W, Shen T, Wang M-H. Cell cycle arrest and apoptosis induced by methyl 3,5-dicaffeoyl quinate in human colon cancer cells: involvement of the PI3K/Akt and MAP kinase pathways. *Chem Biol Interact*. 2011;194(1):48-57.
105. Chang L, Graham PH, Hao J, et al. PI3K/Akt/mTOR pathway inhibitors enhance radiosensitivity in radioresistant prostate cancer cells through inducing apoptosis, reducing autophagy, suppressing NHEJ and HR repair pathways. *Cell Death Dis*. 2014;5(10):e1437.
106. Zanotto-Filho A, Braganhol E, Battastini AMO, Moreira JCF. Proteasome inhibitor MG132 induces selective apoptosis in glioblastoma cells through inhibition of PI3K/Akt and NFkappaB pathways, mitochondrial dysfunction, and activation of p38-JNK1/2 signaling. *Invest New Drugs*. 2012;30(6):2252-2262.
107. Van Duijn PW, Ziel-van der Made AC, van der Korput JA, Trapman J. PTEN-mediated G1 cell-cycle arrest in LNCaP prostate cancer cells is associated with altered expression of cell-cycle regulators. *Prostate*. 2010;70(2):135-146.
108. Li J-P, Yang Y-X, Liu Q-L, et al. The investigational Aurora kinase A inhibitor alisertib (MLN8237) induces cell cycle G2/M arrest, apoptosis, and autophagy via p38 MAPK and Akt/mTOR signaling pathways in human breast cancer cells. *DDDT*. 2015;9:1627-1652.
109. Wang F, Wang Q, Zhou Z-W, et al. Plumbagin induces cell cycle arrest and autophagy and suppresses epithelial to mesenchymal transition involving PI3K/Akt/mTOR-mediated pathway in human pancreatic cancer cells. *DDDT*. 2015;9:537-560.
110. Pan S-T, Qin Y, Zhou Z-W, et al. Plumbagin induces G2/M arrest, apoptosis, and autophagy via p38 MAPK-and PI3K/Akt/mTOR-mediated pathways in human tongue squamous cell carcinoma cells. *DDDT*. 2015;9:1601.
111. Wanzel M, Kleine-Kohlbrecher D, Herold S, et al. Akt and 14-3-3η regulate Miz1 to control cell-cycle arrest after DNA damage. *Nat Cell Biol*. 2005;7(1):30-41.
112. Raja Singh P, Sugantha Priya E, Balakrishnan S, et al. Inhibition of cell survival and proliferation by nimbolide in human androgen-independent prostate cancer (PC-3) cells: involvement of the PI3K/Akt pathway. *Mol Cell Biochem*. 2017;427(1-2):69-79.
113. Jing X, Cheng W, Wang S, Li P, He L. Resveratrol induces cell cycle arrest in human gastric cancer MGC803 cells via the

PTEN-regulated PI3K/Akt signaling pathway. *Oncol Rep*. 2016;35(1):472-478.
114. Zhang R, Zhu L, Zhang L, et al. PTEN enhances G2/M arrest in etoposide-treated MCF-7 cells through activation of the ATM pathway. *Oncol Rep*. 2016;35(5):2707-2714.
115. Djuzenova CS, Fiedler V, Katzer A, et al. Dual PI3K-and mTOR-inhibitor PI-103 can either enhance or reduce the radiosensitizing effect of the Hsp90 inhibitor NVP-AUY922 in tumor cells: the role of drug-irradiation schedule. *Oncotarget*. 2016;7(25):38191.
116. Wang F-Z, Chang Z-Y, Fei H-R, Yang M-F, Yang X-Y, Sun B-L. CCT128930 induces cell cycle arrest, DNA damage, and autophagy independent of Akt inhibition. *Biochimie*. 2014;103:118-125.
117. Kandel ES, Skeen J, Majewski N, et al. Activation of Akt/protein kinase B overcomes a G2/M cell cycle checkpoint induced by DNA damage. *Mol Cell Biol*. 2002;22(22):7831-7841.
118. Hirose Y, Katayama M, Mirzoeva OK, Berger MS, Pieper RO. Akt activation suppresses Chk2-mediated, methylating agent–induced G2 arrest and protects from temozolomide-induced mitotic catastrophe and cellular senescence. *Cancer Res*. 2005;65(11):4861-4869.
119. Tessitore A, Cicciarelli G, Del Vecchio F, et al. MicroRNAs in the DNA damage/repair network and cancer. *Int J Genomics*. 2014;2014:1-10.
120. Jiricny J. The multifaceted mismatch-repair system. *Nat Rev Mol Cell Biol*. 2006;7(5):335-346.
121. Hoeijmakers JHJ. DNA damage, aging, and cancer. *N Engl J Med*. 2009;361(15):1475-1485.
122. Caldecott KW. Single-strand break repair and genetic disease. *Nat Rev Genet*. 2008;9(8):619-631.
123. San Filippo J, Sung P, Klein H. Mechanism of eukaryotic homologous recombination. *Annu Rev Biochem*. 2008;77:229-257.
124. Harkavyi A, Whitton PS. Glucagon-like peptide 1 receptor stimulation as a means of neuroprotection. *Br J Pharmacol*. 2010;159(3):495-501.
125. Yang J-L, Chen W-Y, Chen Y-P, Kuo C-Y, Chen S-D. Activation of GLP-1 receptor enhances neuronal base excision repair via PI3K-AKT-induced expression of apurinic/apyrimidinic endonuclease 1. *Theranostics*. 2016;6(12):2015-2027.
126. Toulany M, Dittmann K, Fehrenbacher B, Schaller M, Baumann M, Rodemann H. PI3K-Akt signaling regulates basal, but MAP-kinase signaling regulates radiation-induced XRCC1 expression in human tumor cells in vitro. *DNA Repair*. 2008;7(10):1746-1756.
127. Wang D, Li C, Zhang Y, et al. Combined inhibition of PI3K and PARP is effective in the treatment of ovarian cancer cells with wild-type PIK3CA genes. *Gynecol Oncol*. 2016;142(3):548-556.
128. McEllin B, Camacho CV, Mukherjee B, et al. PTEN loss compromises homologous recombination repair in astrocytes: implications for glioblastoma therapy with temozolomide or poly (ADP-ribose) polymerase inhibitors. *Cancer Res*. 2010;70(13):5457-5464.
129. Ko J-C, Chen J-C, Wang T-J, et al. Astaxanthin down-regulates Rad51 expression via inactivation of AKT kinase to enhance mitomycin C-induced cytotoxicity in human non-small cell lung cancer cells. *Biochem Pharmacol*. 2016;105:91-100.
130. Shen C, Oswald D, Phelps D, et al. Regulation of FANCD2 by the mTOR pathway contributes to the resistance of cancer cells to DNA double-strand breaks. *Cancer Res*. 2013;73(11):3393-3401.
131. Brown KK, Montaser-Kouhsari L, Beck AH, Toker A. MERIT40 is an Akt substrate that promotes resolution of DNA damage induced by chemotherapy. *Cell Rep*. 2015;11(9):1358-1366.
132. Toulany M, Lee K-J, Fattah KR, et al. Akt promotes post-irradiation survival of human tumor cells through initiation, progression, and termination of DNA-PKcs–dependent DNA double-strand break repair. *Mol Cancer Res*. 2012;10(7):945-957.
133. Hu L, Li X, Liu Q, et al. UBE2S, a novel substrate of Akt1, associates with Ku70 and regulates DNA repair and glioblastoma multiforme resistance to chemotherapy. *Oncogene*. 2016;36:1145-1156.
134. Liu P, Gan W, Guo C, et al. Akt-mediated phosphorylation of XLF impairs non-homologous end-joining DNA repair. *Mol Cell*. 2015;57(4):648-661.
135. Nogueira V, Park Y, Chen C-C, et al. Akt determines replicative senescence and oxidative or oncogenic premature senescence and sensitizes cells to oxidative apoptosis. *Cancer Cell*. 2008;14(6):458-470.
136. Howes AL, Arthur JF, Zhang T, et al. Akt-mediated cardiomyocyte survival pathways are compromised by Gαq-induced phosphoinositide 4, 5-bisphosphate depletion. *J Biol Chem*. 2003;278(41):40343-40351.
137. Teresi RE, Shaiu CW, Chen CS, Chatterjee VK, Waite KA, Eng C. Increased PTEN expression due to transcriptional activation of PPARγ by Lovastatin and Rosiglitazone. *Int J Cancer*. 2006;118(10):2390-2398.
138. Kitagishi Y, Matsuda S. Redox regulation of tumor suppressor PTEN in cancer and aging (Review). *Int J Mol Med*. 2013;31(3):511-515.
139. Covey TM, Edes K, Coombs GS, Virshup DM, Fitzpatrick FA. Alkylation of the tumor suppressor PTEN activates Akt and β-catenin signaling: a mechanism linking inflammation and oxidative stress with cancer. *PLoS One*. 2010;5(10):e13545.
140. Wang L, Chen Y, Sternberg P, Cai J. Essential roles of the PI3 kinase/Akt pathway in regulating Nrf2-dependent antioxidant functions in the RPE. *Invest ophthalmol Vis Sci*. 2008;49(4):1671-1678.
141. Salazar M, Rojo AI, Velasco D, de Sagarra RM, Cuadrado A. Glycogen synthase kinase-3β inhibits the xenobiotic and antioxidant cell response by direct phosphorylation and nuclear exclusion of the transcription factor Nrf2. *J Biol Chem*. 2006;281(21):14841-14851.
142. Chen H-H, Chen Y-T, Huang Y-W, Tsai H-J, Kuo C-C. 4-Ketopinoresinol, a novel naturally occurring ARE activator, induces the Nrf2/HO-1 axis and protects against oxidative stress-induced cell injury via activation of PI3K/AKT signaling. *Free Radic Biol Med*. 2012;52(6):1054-1066.

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