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REVIEW ARTICLE

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# RAS/MAPK signaling functions in oxidative stress, DNA damage response and cancer progression

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## Abstract

Mitogen-activated protein kinase (MAPK) signaling pathways organize a great constitution network that regulates several physiological processes, like cell growth, differentiation, and apoptotic cell death. Due to the crucial importance of this signaling pathway, dysregulation of the MAPK signaling cascades is involved in the pathogenesis of various human cancer types. Oxidative stress and DNA damage are two important factors which in common lead to carcinogenesis through dysregulation of this signaling pathway. Reactive oxygen species (ROS) are a common subproduct of oxidative energy metabolism and are considered to be a significant physiological modulator of several intracellular signaling pathways including the MAPK pathway. Studies demonstrated that the MAP kinases extracellular signal-regulated kinase (ERK) 1/2 and p38 were activated in response to oxidative stress. In addition, DNA damage is a partly common circumstance in cell life and may result in mutation, cancer, and even cell death. Recently, accumulating evidence illustrated that the MEK/ERK pathway is associated with the suitable performance of cellular DNA damage response (DDR), the main pathway of tumor suppression. During DDR, the MEK/ERK pathway is regularly activated, which contributes to the appropriate activation of DDR checkpoints to inhibit cell division. Therefore, the aim of this review is to comprehensively discuss the critical function of MAPK signaling in oxidative stress, DNA damage, and cancer progression.

**KEYWORDS**

DNA damage, DNA repair, ERK, MAPK, reactive oxygen species, cancer

## 1 | INTRODUCTION

Mitogen-activated protein kinase (MAPK) pathways organize a great constitution network that regulates several physiological processes such as cell growth, differentiation, and apoptotic cell death (Junttila, Li, & Westermarck, 2008). The mammalian MAPK family contains the extracellular signal-regulated kinase (ERK), p38, and c-jun NH2-terminal kinase (JNK; further termed stress-activated protein kinase [SAPK]; Santarpia, Lippman, & El-Naggar, 2012). Meanwhile, dysregulation of the RAS/RAF/MAPK/ERK kinase and the ERK1/2 is one of the major disturbances through various MAPK signaling cascades in human cancer (Majidinia, Sadeghpour, & Yousefi, 2018). Furthermore, activating mutations of the RAS/RAF/MAPK pathway are illustrated in almost one-third of all human cancers (Dow et al., 2008). Activation of this

  

pathway triggers a signal link to protein tyrosine kinase receptors such as the epidermal growth factor receptor (EGFR) and the platelet-derived growth factor receptor (PDGFR; Molina & Adjei, 2006). Moreover, several upstream receptors containing other receptor tyrosine kinase (RTK), integrin, serpentine receptors, heterotrimeric G-protein, and cytokine receptors are able to activate K-RAS (Molina & Adjei, 2006). In the RAS/RAF/MEK/ERKs cascade, activated RAS employs RAF to the plasma membrane, which results in phosphorylation of MEK, a dual feature kinase that phosphorylates the ERK on threonine or tyrosine residues (Chung & Kondo, 2011). As well as activation, ERK translocates to the nucleus and adjusts the activation of several transcription factors (Wang, Buchanan, Wang, Dey, & DuBois, 2005). In fact, the crucial role of RAS/RAF/MEK/ERK MAPK pathway in various cellular functions depends on the significance of the pathway in oncogenesis and the growth of transformed cells (Friday & Adjei, 2008). Oncogenic RAS genes (H-RAS, N-RAS, and K-RAS) are the mostly mutated oncogenes in human cancer cells (Molina & Adjei, 2006). Oxidative stress and DNA damage are two major factors which in common lead to carcinogenesis through dysregulation of this signaling pathway. Reactive oxygen species (ROS) are a common subproduct of oxidative energy metabolism and are considered to be a significant physiology modulators of several intracellular signaling pathways, which are regularly counterbalanced via antioxidants like glutathione, vitamins C and E, and also via enzymes like catalase, superoxide dismutase, and glutathione peroxidase that convert ROS to less harmful molecules (Karimaian, Majidinia, Bannazadeh Baghi, & Yousefi, 2017). Studies demonstrated that the MAP kinases ERK1/2 and p38 were activated in response to oxidative stress. It is suggested that induction of ROS production in rat vascular smooth muscle cells results in elevated disulfide bond constitution between glutathione and several Cys residues in RAS comprising Cys118 in GTP binding domain (Clempus & Griendling, 2006). In contrast, exogenous expression of a RAS mutant in which Cys118 is altered to Ser arrests ROS-related activation of p38 and protein kinase B (AKT), while does not inhibit ERK1/2 activation. This evidence proposes that ERK1/2 have been activated through further pathways than the RAS/MEK/ERK signaling pathways (Kimball, Abbas, & Jefferson, 2008). DNA damage is a partly common circumstance in cell life and may result in mutation, cancer, and even cell death (Majidinia & Yousefi, 2016). DNA repair and the cell cycle checkpoint are two substantial mechanisms by which genome integrity is controlled and both are strongly interlinked in their signaling pathways and share several signaling molecules (Majidinia & Yousefi, 2016). Recently, arising evidence demonstrated that the MEK/ERK pathway is associated with the suitable performance of cellular DNA damage response (DDR), which is the main pathway of tumor suppression. During DDR, the MEK/ERK pathway is regularly activated, which contributes to the appropriate activation of DDR checkpoints to inhibit cell division (Wei, Yan, & Tang, 2011). The focal role of the RAS/MAPK pathway in growth and survival regulation of cells in a wide range of tumor cells has been well-established. Therefore, it appears to be an attractive pathway for anticancer target therapies. The RAS/RAF/MAPK signaling pathway can be targeted in a variety of steps such as the following procedure: (1) suppressing RAS protein expression (antisense RAS DNA, adenovirus expressing K-RAS, and small interference RNA [siRNA]); (2) suppressing membrane position via posttranslational alteration or transmission (farnesyltransferase inhibitors [FTIs] and geranylgeranyltransferase inhibitors [GGTIs]); (3) inhibiting RAS interplay with GEF and elevating RAS/GAP interaction; (4) targeting oncogenic K-RAS (immunological treatment vs. mutant K-RAS and yeast expressing systems); (5) suppressing downstream targets of K-RAS like RAF and MEK (RAF kinase suppressor-BAY 43–9006 and MEK suppressors like CI-1040, PD0325901, and ARRY-142886; Molina & Adjei, 2006). Various anticancer drugs enforce their effects via induction of apoptosis in tumor cells through mitochondrial and death receptor pathways. Despite the great number of reports indicating the role of DNA damage in drug-associated chemotherapy, it seems that more undeviating research will be required to decipher the precise molecular mechanisms of apoptosis-inducing effect in detail.

## 2 | RAS/MAPK SIGNALING AND CANCER

Cancer can be interpreted as a disorder of communication between and within cells. In cancer cells, improper gene expression may be arising from alternations in the signaling pathways that regulate transcription factor activity or from mutation and expression modification of transcription factors themselves. Many of cancer-dependent MAPK signaling pathway mutations have been seen in RAS and RAF components, which both participate in the ERK signaling pathway (Kim & Choi, 2010). MAPK pathways are evolutionary kinase models, which used to connect extracellular signals to machinery that regulated cells' pivotal processes like growth, proliferation, differentiation, migration, and apoptosis. Cancerous mutations in MAPK pathways mostly work on RAS and RAF function in ERK pathway. Over the last three decades, many studies focus on the RAS oncogene family. Consequently, due to the importance of RAS/MAPK pathway disorder in carcinogenesis, we provide evidence that separately demonstrates the participation of this pathway in various prevalent cancers (Table 1).

## 3 | RAS/MAPK SIGNALING AND DNA DAMAGE

DNA is the genetic matter that comprises the instruction that not only contributes to life continuance but also manages the progression, metabolism, and living organisms function. DNA damage maybe due to several exogenous (environmental) genotoxic factors and common metabolic processes within cells. Even in natural growth and metabolic status, DNA damage happens at a rate of about 10,000 lesions per cell per hour in mammalian cells. DNA damage that is improperly and quickly repaired can result in genomic instability; elevates the probability of gene mutation or even death of the cell. Thus, cells cannot function properly if DNA damage destructs the integrity and access of pivotal information in the genome, which in turns has a detrimental impact on health, like carcinogenesis, tissue degradation or functional failure, and accelerating aging (Majidinia et al., 2017). In

**TABLE 1** RAS/MAPK signaling in various types of cancer

| Type | Related molecules | Target | Effects | Ref |
|---|---|---|---|---|
| Breast cancer | ERK1/2 | ER | ↑Phosphorylation of ER<br>↑Transcription of ER<br>↑Proliferation | Santen et al. (2002) |
| | Estradiol progesterone estrogen | Production of growth factor (IGF-1, EGF, insulin prolactin) | ↑Growth factor<br>↑Activation of MAPK<br>↑Proliferation | Santen et al. (2002) |
| | PTEN | Mitogen-activated protein kinase kinase (MEK)/ERK | Phosphorylation of MEK/ERK↓<br>Phosphorylation of IRS-1↓<br>Formation of IRS-1/Grb2/SOS↓ complex<br>Inhibition of cell progression | Weng et al. (2001) |
| | PAK1 | MEK-1, RAF-1 | ↑Activation of MEK1, RAF-1<br>↑Activation of RAS/MAPK signaling, promote oncogenic transformation | Shrestha et al. (2012) |
| | TRPM7 | src, p38, ERK, JNK | ↑Activation of MAPK<br>↑Cell migration<br>↑Invasion and metastasis | Meng et al. (2013) |
| | MEK | p27 $^{Kip1}$ | P27↓<br>Cdk2 inhibitory activity↓, contributes to antiestrogen resistance, cell cycle growth | Donovan, Milic, and Slingerland (2001) |
| Prostate cancer | TGF-β1 | Smad2, NF-κB, JNK, RAS | ↑RAS/MAPK<br>↑Induction of IL-6, tumor aggressiveness | Park et al. (2003) |
| | integrin | ECM, FAK | ↑Activation of src, PI3K, Rac<br>↑Phosphorylation of PAK<br>↑Activation of c-RAF and MEK1, promote cell growth | Slack-Davis and Parsons (2004) |
| | cAMP | EGF and IL-6 | ↑Activation of MAPK in Lncap cells Progression of prostate cancer | Chen, Cho, Stork, and Weber (1999) |
| | Antibody treatment | C-terminal domain of GRP78 | Suppressing RAS-dependent signaling<br>Suppressing PI3K signaling<br>Antiapoptotic Bcl2↓<br>↑Proapoptotic BAD, BAK, BAX | Misra and Pizzo (2010) |
| Colorectal cancer | MAPK inhibitor | MAPK | Proliferation, block cell-cell↓ contact and motility required for invasion<br>Growth and metastasis↓ | Sebolt-Leopold et al. (1999) |
| | Mutant K-RAS | catenin β | ↑Nuclear β-catenin accumulation<br>↑WNT target genes, whereas blocking EGFR, WNT activity with limited tumorigenic effects | Horst et al. (2012) |
| | MiR-31 | RASA1 | ↑Activating RAS signaling Inhibition of RASA1 translocation<br>↑Cell growth and proliferation<br>↑tumorigenesis | Sun et al. (2013) |
| | RASSF1–10 | RAS | Stimulate growth arrest and proapoptotic signal | Zenonos and Kyprianou (2013) |
| | Cannabinoid | CB1 and CB2 receptor | Induces apoptosis, inhibition of RAS/MPK signaling<br>Inhibition of PI3K/AKT signaling | Greenhough, Patsos, Williams, and Paraskeva (2007) |
| | FRA1 | RAS/ERK and TGF-β | Mediating cross talk between oncogenic RAS/ERK and TGF-β, mediating migration and invasion in tumor cell | Diesch et al. (2014) |
| Lung cancer | RAS | AP1 and miR21 | Inhibition of negative regulators of RAS/MAPK pathway, over expression of miR-21<br>↑Tumorigenesis, inhibition apoptosis | Hatley et al. (2010) |
| | GATA2 | k-RAS mutant | GATA2 is essential for the survival and tumorigenesis of RAS mutant NSCLC | Kumar et al. (2012) |

(Continues)

**TABLE 1** (Continued)

| Type | Related molecules | Target | Effects | Ref |
|---|---|---|---|---|
| Gastric cancer | BMP2 | AKT and ERK | ↑Phosphorylation of AKT and ERK<br>↑Metastasis<br>↑Induction of NF-κB and MMP-9<br>↑Migration and invasion activity | Kang et al. (2011) |
| | PKGII | EGF-induced | Inhibited Phosphorylation of ERK and MEK1/2<br>Inhibited Phosphorylation/activation of RAF-1 and RAS<br>Inhibited EGFR proliferation↓ | Wu, Chen, Qu, Lan, and Sang (2012) |
| | NAIF1 | MMP2 and MMP9 | Expression MMP2 and MMP9↓<br>Activation FAK↓<br>Expression of ERK at mRNA↓ level<br>Cell proliferation↓<br>Migration | Yang et al. (2015) |
| | CCDC134 | ERK1/2<br>JNK/SAPK | Activation of ERK↓<br>Activation of JNK/SAPK↓<br>Cell migration↓ | Zhong et al. (2013) |
| | IL-22 | ERK, STAT3 | ↑ERK and STAT3<br>↑Cancer cell invasion | Fukui et al. (2014) |

*Note*. AKT: protein kinase B; CCDC134: coiled coil domain containing 134; ECM: extracellular matrix; EGF: epidermal growth factor; ER: estrogen receptor; ERK: estrogen receptor kinase; FAK: focal adhesion kinase; IGF-1: insulin-like growth factor 1; IL: interleukin; JNK: c-Jun NH2-terminal kinase; MAPK: mitogen-activated protein kinase; MMP: matrix metallopeptidase; NAIF1: nuclear apoptosis-inducing factor 1; NF-κB: nuclear factor κB; PI3K: phosphoinositide 3-kinases; SAK: stress-activated protein kinases; STAT3: signal transducer and activator of transcription 3; TGF-β: transforming growth factor β.

reply to DNA damage, the cell activates checkpoint pathway, which allows the DNA repair system to correct the damage (Majidinia et al., 2017). Checkpoint kinase (i.e., Chk1 and Chk2) shows the key ingredients of the DNA damage checkpoint system, which monitors DNA breaks as a result of endogenous/metabolic or environmental genotoxic insults or from replication stress (Majidinia et al., 2017). Furthermore, they enable natural cells with a critical surveillance system designed to enhance genomic integrity and survival. Instead, checkpoint impairment contributes to tumorigenesis via allowing cell proliferation in confronting with genomic instability. Chk1 plays a pivotal role in the retention of genomic integrity via regulating DNA damage-related checkpoint responses, and an engrossing therapeutic target (Tse, Carvajal, & Schwartz, 2007).

## 3.1 | RAS/RAF/MEK/ERK Signaling

UCN-01, a first descendant Chk1 inhibitor, is capable of blocking Chk1 performance at low, submicromolar concentration, which can develop DNA damage by itself or along with DNA damage factors (Senderowicz, 2003). Moreover, UCN-01 triggers rectify activation of the prosurvival RAS/MEK/ERK cascade in several tumor cell types. Previous reports indicated that UCN-01, as Chk1 inhibitor, not only increases genotoxic agent-associated DNA damage but also induces DNA breaks by themselves (Dai et al., 2008). Therefore, induction of DNA damage via Chk1 inhibitors may help to their anticancer activity. Recently, it is proposed that RAS/MEK/ERK pathway activation displays cytoprotective reply of transformed cells to Chk1 inhibitor like UCN-01. The mechanism (s) responsible for the capacity of Chk1 inhibitor mortality by RAS/MEK/ERK pathway interruption may reflect several mutual events. For instance, ERK1/2 activation applies cytoprotective function through posttranslational modification of various ingredients of the apoptotic pathway or proapoptotic Bcl-2 family members. Interestingly, disruption of RAS/ERK pathway via pharmacologic or genetic approaches (i.e., cells expressing S17N RAS) elevated Chk1 inhibitor-interceded CDC-2 activation, an event related to apoptosis (Allan et al., 2003). Together, activation of RAS/RAF/MEK/ERK signaling displays a self-protective reply restricting DNA damage in Chk1 inhibitor-treated cells (Inaba, Kuboniwa, Sugita, Lamont, & Amano, 2012). Furthermore, the RAF/MEK/ERK pathway has been connected to DNA repair through an ATM-associated procedure. In contrast, the intervention with RAS/RAF/MEK/ERK signaling cascade interrupts DNA repair processes, consequently potentiating DNA damage caused by Chk1 inhibitors (Dai et al., 2008). Records proposed that chromosomal instability caused by a flaw in the recognition and/or processing of DNA damage is stimulated by RAS. Significantly, RAS stimulates a checkpoint response, determined by the induction of γH2A.X and activation of ataxia telangiectasia mutated (ATM) and Rad3-related protein kinase (ATR). ATR is a fundamental gene, in which its products play a vital role in the normal cell cycle progression and in the cellular response to disturbances in DNA replication and/or repair (Brown & Baltimore, 2000). Although cells that survive RAS exposure display checkpoint activation, they continue to cycle and are declined in reply to DNA damage. Consequently, these cells indicate significant chromosomal instability, and are resistant to apoptosis and get transformation features (Abulaiti, Fikaris, Tsygankova, & Meinkoth, 2006). Normal cells generally respond to preserved mitogenic signals with growth prevention and/or apoptosis, a substantial safeguard that is protective against unlimited proliferation. ATR is activated through normal semistandpat replication and in reply to single- and double-strand

breaks (DSB) under the circumstance of replication stress (Fernandez-Capetillo, Lee, Nussenzweig, & Nussenzweig, 2004). Considering the effects on ATR activity, RAS induced the constitution of γH2A.X, as a feature of DNA damage. γH2A.X functions in the modification of chromatin structure and central assembly of proteins implicated in the determination and repair of DNA damage. Therefore, RAS induces replication stress in spite of activation of a cell cycle checkpoint (Abulaiti et al., 2006).

## 3.2 | EGFR signaling

Many tumor existences are providing overexpression of EGFR, which contrary impacts prognosis and outcome of treatment due to EGFR-related therapy resistance (Rowinsky, 2004). Various reports consider the feasibility that blockage of the EGFR pathway generally leads to decreased cell survival by upregulation of apoptosis and downregulation of survival mechanisms, like DNA repair after being exposed to DNA damage ingredients (Friedmann et al., 2004; Shintani et al., 2003). Furthermore, inhibition of each ingredient of the EGFR/phosphoinositide 3-kinases (PI3K)/AKT pathway in K-RAS-mutated human tumor cells increased radiosensitivity significantly (Toulany, Dittmann, Krüger, Baumann, & Rodemann, 2005). DNA DSB are the main DNA lesions that result in cell death after being exposed to ionizing radiation. Consequently, the significant role of EGFR/PI3K/AKT signaling in the initiation of DSB repair is to be the functional endpoint of the radiation response of K-RAS-mutated human tumor cell. Eventually, targeting the EGFR-associated PI3K/AKT pathway in K-RAS-mutated A549 cells considerably modify post-radiation survival by affecting the activation of DNA-PKcs, leading to decreased DSB repair capacity (Toulany et al., 2006). The EGFR is a focal player in the modulation of various signaling pathways controlling the fate of a variety of normal cell types and tumor cells (Lindsey & Langhans, 2015). Elevated expression of wild-type and mutant EGFR is a prevalent feature in many cancers. Many potential mechanisms comprising suppression of DNA damage repair, promoted apoptosis, modulation of cell cycle kinetics, and tumor angiogenesis has been suggested to be implicated in radiosensitization following EGFR targeting (Sebastian et al., 2006). The evidence demonstrated that the activation of erbB receptors and their downstream pathways promote the repair of radiation-induced DNA damage and thereupon radioresistance. Recently, different reports have provided evidence that radioresistance of RAS-mutated cells is most probably the consequence of effectively activated autocrine loop of EGFR-ligand production and receptor stimulation. It is illustrated that fundamental activity of mutated RAS, particularly K-RAS, lead to increased production of EGFR-ligands, such as TGFα and amphiregulin. These ligands bind to EGFR in an autocrine mode and stimulate this receptor and its downstream signaling cascade. Yet leave many sights of the role of membrane receptors signaling in the cellular radiation reaction unclear. However, the recent knowledge of EGFR-modulated pathways and their stimulation via ionizing radiation provides evidence that EGFR signaling plays an essential role in the regulation of cell survival after exposure to ionizing radiation. Furthermore, downstream signaling pathways of erbB receptors, such as PI3K/AKT and RAS/MAPK pathways cross with DNA repair mechanisms to regulate postirradiation survival of cells (Toulany & Rodemann, 2010). The acquired results not only may enhance our knowledge of basic mechanisms of radiation sensitivity/resistance but also will improve the translational procedure to test new strategies for clinically appropriate molecular targeting.

## 3.3 | Crosstalk with other signaling pathways

The two essential downstream signal transduction pathways of EGFR, RAS/MAPK, and phosphatidylinositol 3-kinase/AKT are both involved in the radiation response (Reardon et al., 1999). A focal hypothesis is that EGFR signaling regulates the DDR pathway, however, how, when, and which EGFR downstream signaling pathway is associated with the DDR is still unknown. One view is that EGFR signaling affects the DNA damage checkpoint, according to the relation between radiation-induced EGFR signaling and the interval of the G2 checkpoint. Others suggested that EGFR signaling postirradiation exactly affects DNA repair pursuant to the following record: DNA damage repair genes are upmodulated after EGFR/RAS/MAPK signaling, and EGFR signaling leads to activation of the nonhomologous DNA repair gene complex, DNA-related protein kinase, after translocation to the nucleus postirradiation (Weidhaas, Eisenmann, Holub, & Nallur, 2006). The report which had utilized a tissue model of radiation-induced reproductive cell death in *C. elegans* (Radelegans) to investigate the role of the EGFR signaling pathway in the radiation response demonstrated that the EGFR downstream signal conduction pathway RAS/MAPK is pivotal for protection from radiation-induced reproductive cell death. Moreover, it is stated that radiosensitizing mutation in the RAS/MAPK signaling pathway protein MEK is epistatic to a radioresistant mutation in the cycle checkpoint protein CDC25, which proves that these pathways are linear (Dittmann et al., 2005; Friedmann et al., 2006; Lin et al., 2001). Furthermore, the RAS/MAPK signaling works in the downstream of DNA damage checkpoint in the radio response, incorporating this condition pathway straightly in DNA repair postirradiation (Weidhaas et al., 2006). Variety of reports have demonstrated that various survival-associated or death-related signaling pathways, play essential roles in the modulation of DNA-damage-induced apoptosis, the complete molecular mechanisms responsible for doxorubicin-induced apoptosis have yet to be explained in detail (Lee et al., 2006). The evidence proposing that antitumor agents modify the activation of various MAPK subgroups in a host of cancer cell lines. The pharmacological or molecular regulation of MAPK signaling has been illustrated to influence apoptotic responses to the anticancer drugs (Munshi & Ramesh, 2013). However, the role played by MAPK highly affiliated with context and was deeply affected by the type of cell, drug concentration, and exposure time as well as with the type of test used to monitor apoptosis or cell survival (Fan & Chambers, 2001). It is noted that the p38 MAPK and PI3K/AKT pathways apparently apply a modulatory effect considering the induction of cell death and the stable activation of ERK1/2 that seem to be positively associated with apoptosis. Moreover, studies have demonstrated that AKT activation due to the overexpression of Myr-AKT

apparently repressed the phosphorylation of ERK1/2 and ERK inactivation, whereas via overexpression of ERK-DN had a negative influence on apoptosis (Lee et al., 2006). Furthermore, the positive correlation between constant ERK1/2 activation and DNA damage anticancer drug-induced apoptosis, which was considered to be in association with the etoposide-induced apoptosis. These findings demonstrate that the AKT signaling pathway negatively modulates the activation of ERK and the constant ERK activation is positively implicated in the apoptosis. Consequently, the interaction between the AKT signaling pathway and the activation of ERK play a pivotal role in the apoptosis induced by DNA damaging drugs, comprising doxorubicin and etoposide (Lee et al., 2006). Arising evidence indicates that radiation resistance is related to the abnormal expression of activated oncogenes, comprising RAS and c-Myc. The RAS/RAF/MEK/ERKs pathway induces c-Myc sustainability, whereas GSK-3β decreases its sustainability, which leads to RAS/MEK/ERK activation and PI3K/AKT-mediated GSK-3β inactivation thereupon the agglomeration of c-Myc. In addition, the radiation-resistant phenotype of cells converted by mutated RAS is enhanced via the c-Myc oncogene. DNA DSB is important in DNA damages induced by radiation. In mammalian cells, the repair of these damages takes place by nonhomologous end attaching employing Ku70/Ku86 and DNA-PKcs, which phosphorylates and regulates proteins implicated in the ligation process. DNA PKcs also functions in cell cycle checkpoint revision, cell death, and protein consolidation like p53 and c-Myc. DNA PKcs is essential for genomic sustainability while abnormal levels in cancer cells may help to cell proliferation, radioprotection, and modification in c-Myc levels, finally helping to oncogenic phenotype (Marampon et al., 2011). The RAS/MAPK pathway has a focal role in transmitting the extracellular signals to cellular target proteins implicated in cell growth and proliferation. Moreover, activated ERK1/2 phosphorylate various ingredients containing members of the p90 ribosomal S6 kinase (RSK) family of protein kinases. Suppression of RSK activity in cell culture systems decreases cancer cell proliferation and, therefore, RSK1 and RSK2 are overexpressed or hyperactivated in various cancers. It is demonstrated that RSK1 and RSK2 are the main protein kinases that phosphorylate Chk1 on ser280 in response to mitogens and growth factors (Ray-David et al., 2013). Generally, RSK suppresses Chk1 activation in response to DNA damage thus RSK enhances G2 DNA damage checkpoint recovery. Furthermore, evidence exhibits that the suppression of MEK1/2 and RSK does not enhance G2 arrest in the lack of DNA damage, whereas treatment of cells with MEK1/2 and RSK suppressors augments the G2 DNA damage checkpoint triggered by doxorubicin. These records involve the RAS/MAPK pathway in G2 DNA damage checkpoint recovery and propose that RSK plays an essential role in this process (Ray-David et al., 2013). The RAS signaling pathway adjusts normal cellular functions comprising growth, differentiation, and cell morphology. Furthermore, RAS signaling pathways not only intercede the responses to stress conditions like hypoxia but also contribute to the induction of apoptosis in hematopoietic cells in reply to FAS or TNF (Gulbins et al., 1995). Mutation within cellular RAS genes effectively activate RAS and its signal transmission pathway and lead to potentially harmful cellular exposure comprising a cellular mutation, uncontrolled growth rate, and genomic instability. Available evidence also indicates which of the RAS-related pathway most effectively enhances genomic instability. The evidence that mitotic instability induced by oncogenic RAS generates the MAPK pathway may explain the mechanism(s) that create this instability in mammalian cells. Microinjection of fibroblasts with antibodies versus c-Src blocks login to mitosis, proposing a link between upstream ingredients of signal conduction pathways and mitosis. Activated MAPK is localized to the kinetochores through mitosis and phosphorylates proteins like CENP-E, a motor protein related to chromosome movement. Moreover, MAPK phosphorylates proteins including 3F3/2 phosphoantigen, which is implicated in the mammalian mitotic checkpoint. One of the proteins sharing the 3F3/2 antigens is topoisomerase πα, which has been assumed to be the enzyme that may be implicated in the chromosomal breaks and recombination induced and adjusted by the RAS oncogene and activated by the MAPK pathway (Saavedra, Fukasawa, Conn, & Stambrook, 1999). One of the early genetic disturbances involved in tumor progression may dispose of cells to a "mutator" phenotype and, therefore, potency to the accumulation of additional abnormalities. In fact, germline mutation in genes such as p53, ATM (ataxia telangiectasia mutated), and BRCA1/2 that are implicated in DNA damage repair and adjustment of the cell cycle checkpoint is specified in cancer susceptibility syndromes. Although proteins encoded by p53, ATM, and BRCA1/2 have multiple functions, development to the malignant condition in these cancer syndromes is probably to be at least partly due to genomic instability. However, oncoproteins like RAS have also been suggested to enhance tumor progression by induction of genomic instability. For instance, it is indicated that substitution of a normal H-RAS gene with an activated mutant H-RAS via homologous recombination in rat1 fibroblasts is not adequate and leads to change but more implicate secondary modifies such as amplification events, comprising an increase of mutant RAS allele. Some studies demonstrate that the expression of the human H-RAS oncogene in p53-null cells contributes to the early entrance of cells into the S phase, the elevated irregularity for gene amplification, and the production of improper chromosomes within the single cell cycle, all of which prove the capability of the activated RAS to enhance chromosomal instability (Knauf et al., 2006). Moreover, the enhanced expression of the activated H-RAS by pass of G2 DNA damage checkpoint in p53 mutant cells proposes that the oncogenic RAS-induced genomic instability is possibly caused by a relaxation of this checkpoint (Agapova et al., 1999). In addition, the activation of the RAS downstream effectors MEK1/2 and ERK are essential for regression from DNA damage-induced G2 cell cycle intercept and the transmission from G2 into M phase, respectively. Activated ERK is considered to be involved in the spindle microtubule motor CENP-E through mitosis and is able to modulate microtubule dynamics through mitosis, which highly support a role for MEK and ERK in regulating the promotion of cells during G2 and mitosis and propose that in oncogenic RAS expressing cells the improper activation of RAS

effectors could susceptibility interrupt their regular transmission through the latter cell cycle stages that are pivotal for sustaining genomic integrity (Knauf et al., 2006). Various members of the MAPK family have been related to the DDR and ATM-associated signaling incidents. For instance, low level of DNA damage initiates prosurvival signals associated with ERK1/2 phosphorylation; p38γ MAPK commences G2-M arrest in reply to IR in an ATM-related circumstance and JNK activation has been illustrated to enhance base excision repair of the cisplatin DNA damages. Reports demonstrate that all three main MAPK pathways include ERK, JNK, and the p38 MAPK pathways modulate homologous recombination repair (HRR) in human cancer cells. Considerably, ERK1/2 signaling is a constructive and ATM-related regulator of HRR. The phosphorylated (S1981) ATM foci formation in response to IR is potentially related to MAPK/MEK/ERK signaling pathway. Indeed, suppression of MEK/ERK signaling did not result in IR-induced phosphorylation of p53 and H2AX, which are both exact ATM phosphorylation targets. This is likely the result of excess phosphorylation of (S15) p53 and (S139) H2AX via other PIKKs like DNA-PK and ATR. How ERK affects ATM activation is unclear. However, ATM and ERK signaling could be controlled by a regulatory feedback loop (Golding et al., 2007; Figure 1).

### 3.4 | Crosstalk with oxidative stress-induced DDR

The mechanisms for monitoring DNA damage are essential for keeping genome integrity and cell survival. Studies proposed that MAPK signaling is substantial for cell survival after exposure to oxidative stress, containing $H_2O_2$. Moreover, MAPK activation via DNA damage factors, comprising $H_2O_2$, is directly related to the levels of DNA damage (Upadhyay, Bundesmann, Panduri, Correa-Meyer, & Kamp, 2004). Some studies illustrated that mutagenic DNA damage, 8-oxodG and 8-nitroguanine were found in adenocarcinoma initiated by K-RASval12 in mice (Ohnishi et al., 2011). It is demonstrated that oncogenic K-RASval12 activation interceded inducible nitric oxide synthase (iNOS)-dependent DNA damage in mice, which is considered to be implicated in carcinogenesis. Moreover, it is confirmed that iNOS was colocalized with nuclear factor-κB (NF-κB), IKK, phospho-MAPK, phosphor-MEK in adenocarcinomas initiated by K-RASval12. Aforementioned findings propose that the oncogenic K-RASval12 activation enhances the MEK/MAPK/IKK cascade, NF-κB activation, and iNOS induction, resulting in the production of 8-nitroguanine and 8-oxodG by reactive oxygen species/reactive nitrogen species over a generation. Recently, in vitro studies illustrated that ROS production and oxidative DNA damage can intercede via mutant K-RAS. In the status of carcinogenesis initiated by RAS mutation, iNOS is likely to be induced by inflammation among abnormal cell proliferation due to the RAS stable activation (Ohnishi et al., 2011). DDR is induced by activated RAS oncogene via triggering ROS generation and this is essential for oncogene-induced senescence. Practically, DNA damage signaling associates to oncogenic-induced senescence. The mechanism whereby deregulated oncogenes induce DNA damage is not specified yet (Figure 2). One feasibility is that the DDR is triggered via extreme replication from a preserved oncogenic signal. Other probable mechanisms include elevated cellular levels of ROS that leads to DNA damage, like guanine oxidation, single-strand breaks and DSB. This is pursuant to the fact that RAS-expressing cells cultured in low oxygen level or treated with a hydrogen peroxide scavenging agent, for example, *N*-acetyl cysteine, inhibited RAS-induced senescence. Furthermore, studies indicate that oncogenic H-RAS enhances the NADH (the reduced form of nicotinamide adenine dinucleotide) oxidase NOX4 (NADPH Oxidase 4) and its functional associate p22phox, which generates ROS and thereupon induces DNA damage and consequently brings about senescence. In addition, the evidence demonstrated that RAS expression is associated with the potency of the senescence response. Therefore, great levels of activated H-RAS are capable of commencing senescence in mammary epithelial cells in an in vivo environment proposing that second incidence that leads to the enhanced mutated levels of RAS is necessary to prevent aging. Eventually, various mechanisms have been suggested to intercede DDR under oncogenic stimulation: DDR may be initiated by replication stress arisen from a sustained oncogenic signal or probably from an oncogenic-driven accumulation of ROS (Weyemi et al., 2012). Thus oncogenic-induced senescence has been suggested to be initiated through an agglomeration of ROS.

## 4 | RAS/MAPK SIGNALING AND OXIDATIVE STRESS

The term "oxidative stress" refers to the state of a cell specified by excessive production of ROS or comprehensively, identified as a disturbance in the balance between free radicals, ROS, and endogenous antioxidant defense mechanisms (Dayem, Choi, Kim, & Cho, 2010). It has been illustrated that oxidative stress is implicated in multiple physiological and pathological processes, comprising DNA damage, cell proliferation, cell adhesion, and cell survival. Free radicals like superoxide radicals ($O_2^{\cdot-}$) and nonradical ROS like hydrogen peroxide $H_2O_2$ are two subgroups of ROS, which can be originated from the pollutants, tobacco smoke, iron salt, and radiation or can be produced inside cells, mostly in mitochondria, and by membrane electron transport chain (Dayem et al., 2010). ROS have been regularly considered as substances with carcinogenic potential and have been related to tumor progression. Some tumor cells generate ROS; however, the origin of these products and their association with the transformed phenotype is unknown. The intracellular pathways are best marked in phagocytic cells due to the production of ROS. In these specialized cells, the superoxide's free radical ($O_2^{\cdot-}$) is produced via the multimolecular β-nicotinamide adenine dinucleotide phosphate (NADPH)-oxidase complex, which contains Rac, a member of the RAS family of small GTP-binding proteins. In addition, the evidence demonstrated that oncogenic RAS-transformed fibroblasts generate the superoxide's free radical ($O_2^{\cdot-}$) by a mechanism analogous to that of the NADPH-oxidase complex in phagocytes, which is related to Rac1. Despite temporary increment in intracellular ROS that occurs in response to extracellular stimuli in plant and animal cells, it is found

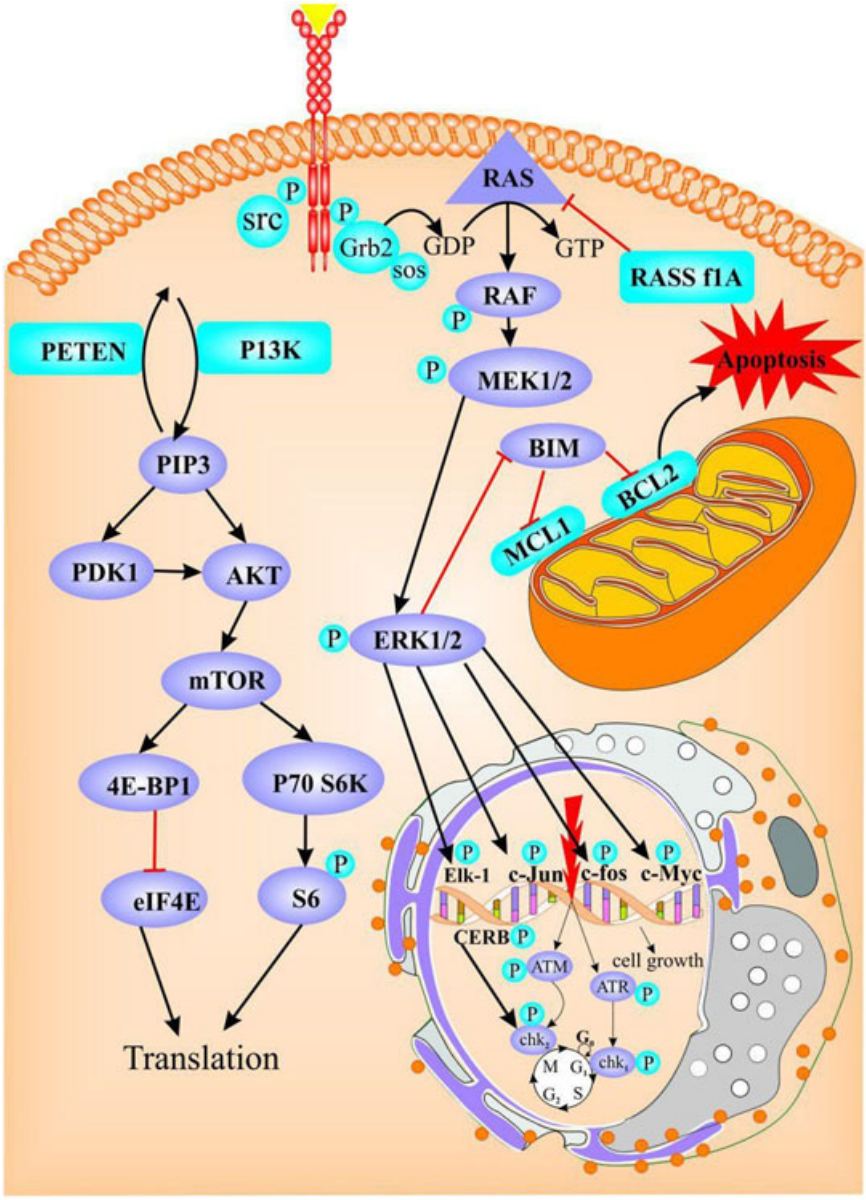


**FIGURE 1** The RAS/MAPK signaling associated with different cell processes and DNA damage. RAS proteins acts as pivotal mediators between RTKs and downstream serine/threonine kinase include RAF-1, MEKs, and ERKs. The affiliation of Grb2/SOS with activated RTKs is reversible processes which are regulated via growth factor stimulation. In normal cells, constant activation of ERK1/2 is essential for G1 to the S phase transition and is associated with cell cycle control via targeting the transcription factors which are involved in cell proliferation, differentiation, and oncogenic transformation, and DDR pathway that acts downstream of cell cycle checkpoint. AKT: protein kinase B; DDR: DNA damage response; ERK: extracellular signal-regulated kinase; GDP: guanosine diphosphate; GTP: guanosine triphosphate; MAPK: mitogen-activated protein kinase; mTOR: mechanistic target of rapamycin; PDK1: pyruvate dehydrogenase kinase 1; PI3K: phosphoinositide 3-kinases; RTK: receptor tyrosine kinase [Color figure can be viewed at wileyonlinelibrary.com]

that fundamental generation of ROS in cell lines transformed via overexpression of oncogenic RAS. The ROS generated effectively via A6 cells seem to function distinctly from the burst of ROS produced by growth factors activating the RAS pathway. The reduced activation of MAPK pathway in A6 cells is in contrast to the evidence obtained by growth factor-induced ROS generation or temporary expression of oncogenic RAS in nontransformed cells (Irani et al., 1997). This evidence proposes that regulation of the redox state of a cell may provide one mechanism to illustrate the observation that some antioxidants seem to play a protective effect against human cancers. Moreover, production of ROS via RAS oncogene-induced NADPH-oxidase (Nox) 1 is needed for RAS transformation phenotypes comprising anchorage-independent growth, morphological transformation, and tumorigenicity. It has been demonstrated that Nox1-induced ROS generation is an essential step for the signaling cascade adjusting modification of stress fibers and focal adhesion related to RAS transformation. This process contributes to oxidative inactivation of LMW-PTP by Nox1-produced ROS and consequently, to the activation of p190RhoGAP that leads to downregulation of Rho resulting in the dysregulation of actin stress fibers and central adhesion. This redox signaling is imposed by RAS oncogene-induced upregulation of Nox1 through the MEK/MAPK pathway, which is confirmed by the verity that inhibition of MAPK signaling via PD98059 restored the Rho activity in KNRK cells. It has been proposed that reactive oxygen radicals associate with the actin cytoskeleton reorganization and are essential for cell migration and cell adhesion of endothelial cells (Shinohara et al., 2007). Furthermore, it has been suggested that Rho is uncoupled to both ROCK and stress fiber formation in RAS-transformed Swiss3T3 and that retained the activation of MAPK and its repressing effects on ROCK cells, which results in stress fibers' disassembly. This is based on the evidence that stress fibers were lost in spite of an elevated active Rho levels in RAS-transformed Swiss3T3 cells and were restored via MAPK suppression (Sahai et al., 2001). It is feasible to articulate that the activation of ERK/MAPK is closely

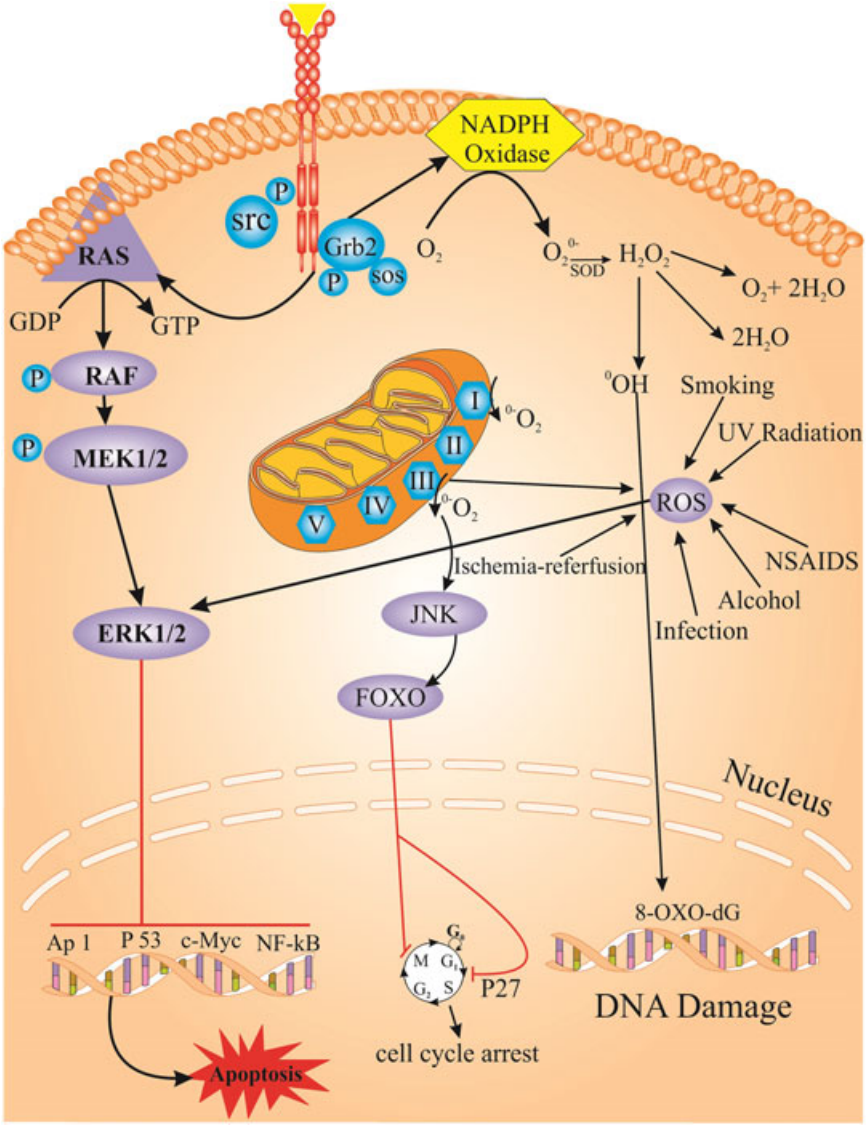


**FIGURE 2** The relationship between RAS/MAPK signaling and ROS. There is various endogenous and exogenous mechanism by which cell exposed to ROS. The oxidative stress implicated in both activation and also inhibition of MAPK signaling. The oxidant can stimulate several signaling pathways, comprising the phosphorylation of MAPKs cascade, which results in phosphorylation of transcription factors that involve in apoptosis, cell proliferation, transformation, differentiation and other changes. DNA damage which induced by the exceeded amount of ROS is one of the main cause of cancer. ERK: estrogen receptor kinase; FOXO: Forkhead box proteins; GDP: guanosine diphosphate; GTP: guanosine triphosphate; JNK: c-Jun NH2-terminal kinase; NADPH: Nicotinamide adenine dinucleotide phosphate; NF-κB: nuclear factor κB; ROS: reactive oxygen species; UV: ultra violet [Color figure can be viewed at wileyonlinelibrary.com]

associated with the loss of stress fibers only by stimulating the Nox1-redox signaling and not by ROCK downregulation. Altogether, Nox1 is a pivotal modulator of cellular redox state related to RAS oncogene-induced actin cytoskeleton rearrangement through Rho signaling (Shinohara et al., 2007). Redox alteration of amino acid residue Csy118 of the RAS protein was determined to be pivotal for its activation. Activation-induced conformational alters the result in its interaction with several signaling proteins, nominated effectors. PI3K, an effector of GTP-bound RAS is involved in the modulation of several biological responses; comprising cell survival, mitogenesis, differentiation, the oxidative burst, membrane ruffling, and glucose uptake (Deora, Win, Vanhaesebroeck, & Lander, 1998). Furthermore, oxidative and nitrosative factors are found to adjust the functions of proteins via altering cysteine residues that are practically located in catalytic or allosteric sites. Several proteins whose functions are modulated via alteration of cysteine residue are RAS, calcium-dependent potassium channels, N-methyl-D-aspartate receptor, caspases, the mammalian transcription factors, NF-κB, activator protein1, and the bacterial transcription factors OxyR and SoxR (Lander, 1997). However, RAS, major redox-sensitive proteins are not implicated in producing various cellular outcomes. The evidence proposes that one of the effectors used by redox-activated RAS is PI3K. SNP and advanced glycation product (AGE)-induced an elevation in levels of RAS and p85α in the immunoprecipitated complex of anti-p85α anti-body and RAS antibody, respectively, proposing a redox-induced interplay of RAS and PI3K. Amplification of this interplay was discovered when cells were pretreated with L-buthionine-(S,R)-sulfoximine, emphasizing the redox nature of the signal. The SNP-induced elevation in lipid kinase activity of PI3K proposed that the physical interaction between RAS and PI3K was biologically considerable. Similarly, the elevated lipid kinase activity in immunoprecipitates of both anti-p85α and anti-RAS antibodies, illustrates that the stimulation in the kinase activity was because of a redox-activated RAS and PI3K interaction. Furthermore, evidence proposes that PI3K is merely responsible for the signal between RAS and AKT kinase and slightly responsible for the signal between RAS and ERK1/2. In addition, other effector pathways like RAF kinase is probably associated with signaling between RAS and ERK1/2 (Deora et al., 1998). Ligand-related dimerization of growth

factor receptors stimulates primary tyrosine kinase activities, which results in autophosphorylation of receptor tyrosine residues such as docking sites for the employment of downstream signaling intermediary that is essential for activation of membrane-localized RAS. RAS activates RAF, so that marks the beginning of the ordinal phosphorylation cascade in which RAF phosphorylates and activates MEK and consequently phosphorylates and activate ERK. In addition, the expression of inactive forms of various growth factor receptors decreases the activation of ERK via oxidative stress. Conversely, overexpression of normal growth factor receptors leads to enhanced activation of ERK via hydrogen peroxide. Various studies have demonstrated that generally pharmacologic factors (containing inhibitors of EGFR receptor phosphorylation) along with molecular changes contribute to decreased ERK activation and consequently sensitization of cells' hydrogen peroxide, whereas molecular strategies lead to increased ERK activation as well as cell survival promotion with the oxidant (Holbrook & Ikeyama, 2002). It has been reported that oxidative stress in some type of cells activates ERKs. Further evidence demonstrated that hydrogen peroxide-derived free radicals activated MAPKs, ERKs, and p38 MAPK pathways, in cultured cardiac myocytes of neonatal rats (Aikawa et al., 1997). It is postulated that tyrosine kinases containing Src family tyrosine kinases, RAS, and RAF-1 are significant for $H_2O_2$-induced activation of ERKs. Signal transmission pathways resulting in activation of ERKs are strongly varied between cell types. Furthermore, RAS has been illustrated to be essential for ERK activation via $H_2O_2$ in HeLa, Rat1, NIH3T3, PC12, and smooth muscle cells. Lately, studies have demonstrated that activation of ERKs enhances cell survival, while activation of JNK and p38 MAPK induces apoptosis. These reports propose that ERKs take a protecting function against cellular stresses, whereas activation of p38 MAPK/JNK results in the induction of apoptotic death (Aikawa et al., 1997). Generally, the potency of ROS to induce an elevation in the ERK signaling pathway is pleiotropic and is triggered via various reactive oxygen intermediaries and in different cell types. Reactive oxygen imposes effects on receptors through which induces the ERK signaling pathway. Indeed, oxygen radicals activate the ERK signaling pathway not only by a mechanism which EGF and/or PDGF receptor but also by a mechanism which results in activation of certain Src kinases (Aikawa et al., 1997). Src kinases are illustrated to have a role in RAS activation and they have the potency to intercede oxidative stress-induced ERK activation by this activity. Nitric oxide induces the nitrosylation of a reactive cysteine residue in RAS and causes an elevation of RAS activity, and is a potential mechanism through which nitric oxide causes ERK activation. Therefore, reactive oxygen intermediaries are not necessary to act by growth factor receptor stimulation but also seem to intercede the activation of RAS independently from reactive oxygen intermediary-induced receptor activation. It is proposed that the hydroxyl radical can induce ERK activation in the absence of growth factor receptors. In addition, elevation in intracellular calcium induced by inositol triphosphate, originated from superoxide treatment, can intercede activation of several signaling pathways including the ERK activation by the CaM-kinases or pyk2. Therefore, the reactive oxygen mediators are signaling molecules that can activate several of receptors and signaling pathways through kinase activity (McCubrey, LaHair, & Franklin, 2006). Although cyclic AMP and calcium are a classical second messenger, evidence has illustrated a role for ROS as second messengers and decisive regulators of protein phosphorylation and gene transcription (Torres & Forman, 2003). It has been demonstrated that human fibroblasts arrest in the G1 phase of the cell cycle as soon as arriving the senescent state; this process is irreversible and cells do not reply to another mitogenic signaling. In addition to prolonged passaging or disposal to oxidant stress, senescence-like growth arrest may also be induced in normal human fibroblasts via the activation of some cellular proto-oncogenes. For instance, it has been determined that the expression of an activated oncogene causes growth arrest with various facilities of senescence in diploid human fibroblasts. Furthermore, there is close relevancy between oxidative stress and RAS-interceded signaling: NIH3T3 fibroblasts containing transformed and effectively active RAS oncogene (v-H-RAS or EJ-RAS), generate abundant ROS superoxide, and RAS-induced cell proliferation is suppressed via treatment with chemical antioxidant, proposing a feasible mechanism for the influences of antioxidants against RAS-induced cellular variation. These reports propose that RAS proteins modulate oxidant generation and that enhancement in intracellular $H_2O_2$ demonstrates an essential signal interceding replicative senescence; while some other evidence suggests that RAS-dependent signaling is not effectively activated in senescent human fibroblasts (Hütter, Unterluggauer, Überall, Schramek, & Jansen-Dürr, 2002). Evidence from an examination of a genetically certain human ovarian cancer cell model demonstrated a significant cellular pathway that is potentially implicated in RAS-related oncogenic transformation (Mei, Young, Liu, & Cheng, 2006). This study proposes that activation of RAS signaling pathways elevates the threshold of ROS tolerance via upregulating the entire antioxidant pathways in cells, particularly in the mitochondria. This advanced antioxidant capacity protects the transformed cells from great levels of ROS related to the uncontrolled growth potential of tumor cells. It is possible that an increased antioxidant potency will organize a common mechanism for tumor cells to elude apoptosis induced by oxidative stress at great ROS loads. Apparently, inhibitors of mitochondrial antioxidant enzymes as cancer therapeutic factor may be effective through distinguished aggregation of ROS in malignant cells that predominantly generate great levels of ROS and are under intrinsic oxidative stress (Young et al., 2004).

## 5 | TARGETING RAS/MAPK SIGNALING AS A POSSIBLE CANCER TREATMENT STRATEGY

Up to the early 1980s, drug exploration for cancer was regularly concentrated on DNA synthesis and cell division, resulting in (1) antimetabolites, which involve intervention with metabolism of proliferation; (2) alkylating/cross-linking agents, which are associated with cellular DNA, DNA damage, and result in the death of growing cells; (3) mitosis inhibitors, which target microtubules and related proteins involved in cell division. These drugs exhibit efficiency and

still are being utilized extensively, however, due to the low selectivity for tumor cells over normal cells lead to high toxicity with intense side effects (Arslan, Kutuk, & Basaga, 2006). Previously, oncology drug improvements had concentrated on manifesting the maximum-tolerated dose, safety profile, and efficacy of an agent, while mechanistic studies were rarely done (Roberts & Der, 2007). RTKs have been the major target for cancer treatment for over 20 years. A group of adaptors transmits the signal from activated RTKs to effector molecules like the PI3K and RAS, which commence the signaling pathways, PI3K/AKT/mTOR (mechanistic target of rapamycin), and RAS/RAF-1/MEK/ERK, respectively, which lie in cells' deep homeostasis (Arslan et al., 2006). In contrast, several processes implicated in tumor growth and metastasis intercede via signaling pathways triggered by activated RTK. RAS works downstream of many RTKs and activation of RAS signaling pathways is a pivotal mechanism in the development of human cancer. In addition, RAS adjusts various pathways that synergistically trigger the cellular transformation, containing the well-identified RAF/MEK/ERK cascade. Studies propose that BAY 43–9006 is a novel biaryl inhibitor of RAF kinase and vascular endothelial growth factor receptor (VEGFR), targeting both RAF/MEK/ERK and RTKs pathways (Wilhelm et al., 2004). RTKs promotes tumor angiogenesis, as a strong suppressor of RAF kinase, BAY 43–9006 suppressed ERK1/2 phosphorylation and is considered to be representative of MAPK pathway blockade in several tumor cell lines, whereas having no impact on the repression of the protien kinase B pathway. The evidence demonstrated that BAY 43–9006 inhibited autophosphorylation of VEGFR-2, VEGFR-3, PDGFR-β, Flt-3, and c-KIT. Moreover, studies have shown that in human umbilical vein endothelial cells, BAY 43–9006 blocked both VEGFR-2 autophosphorylation and ERK1/2 phosphorylation. Generally, since VEGF triggers angiogenesis, it involves RAS activation, BAY 43–9006 suppression of VEGF signaling can befall both at the level of the VEFGR-2 receptor and later through suppression of the RAF/MEK/ERK signaling pathway (Wilhelm et al., 2004). The SB 203580 and PD 98059 are two other suppressors of the MAPK signaling pathway, which has been strongly helpful for understanding some of the physiological roles of the cell signaling pathway that they suppress. The pyridinyl imidazole SB 203580 suppresses the MAPK family member so-called stress-activated protein kinase 2a (SAPK 2a further known as P38), which is the pathway that is highly activated through cellular stresses, proinflammatory cytokines, and bacterial lipopolysaccharide. While PD 98059 inhibits the activation of MEK1, a member of the classical MAPK cascade, which is induced mostly via growth factors and tumor-progressing phorbol esters (Davies, Reddy, Caivano, & Cohen, 2000). Moreover, several RTKs are able to commence MAPK signaling and contain receptors critical in cancer biology, like the human EGFR, platelet-derived growth factor receptors, VEGFRs, and c-KIT. The EGFR pathway avails as a relevant model for investigating the activation and targets of MAPK signaling. The important role of the MAPK in cancer biology has been well identified (Friday & Adjei, 2008). Since the high percentage of human tumors presenting oncogenic RAS mutants, intercept the RAS-signaling pathway, which has been the main concentration of new-drug-improvement attempts. The main attention is as follows: (1) the suppression of RAS expression via ribozymes, antisense oligonucleotides, or RNA; (2) the interruption of membrane situation of RAS; and (3) the suppression of downstream effectors of RAS signaling. The antisense function contains targeting special RNA sequences to prevent translating the RNA message to the protein. Oligonucleotides, which are supplementary to messenger RNA transcripts of activated RAS oncogene, have been used to reduce RAS protein expression. Mammalian farnesyl protein transferase (FTase) is a heterodimer zinc metalloenzyme and its known substrates comprise the RAS proteins, the nuclear lamin protein lamin-B and prelamin A6 cyclic guanosine monophosphate phosphodiesterase α, rhodopsin kinase, a peroxisomal protein PxF with unknown function, and the γ-subunit of the retinal protein transduction. Primary procedure for FTase suppression included the use of common inhibitors of isoprenylation to block the synthesis of farnesyl group via the HMG CoA reductase inhibitors, the nonspecific agents, such as lovastatin, and the mevalonate pyrophosphate carboxylase inhibitor phenylacetate. Although the FTase inhibitors only partly target RAS, these agents seem to have clinical activity in leukemia and in some solid tumors (Adjei, 2001). It has been suggested that the activity of oncogenic RAS could be blocked via FTase inhibitors because farnesylation is the main required post-translational modification for RAS membrane localization and cell-transforming activity. Treatment of RAS-transformed cells by FTase suppressor leads to selective repression of RAS-dependent oncogenic signaling. This contains the suppression of RAS processing, which leads to a reduction in the relative amount of completely processed RAS; the progression, dose-dependent cytoplasmatic repletion of no processing RAS and inactive RAS–RAF complex; suppression of RAS-induced fundamental activation of MAPK and reduced transcriptional activity of both c-jun and Elk-1. Since K-RAS mutations are most common in human cancers, an important purpose is the extension of suppressors that block the growth of human tumors that harbor K-RAS. The resistance of K-RAS to FTase inhibitors, the inability of FTase versus K-RAS-transformed cells, and the evidence that K-RAS is geranylgeranylated in the presence of FTase inhibitors result in the advancement of geranylgeranyltransferase inhibitors (GGTIs). Both FTase suppressors and GGT suppressors have been demonstrated to keep RAS-transformed cells in the G0/G1 phase of the cell cycle and to trigger apoptosis (Reuter, Morgan, & Bergmann, 2000). However, it has been indicated that GGTIs can influence the vital cellular process. These contain suppression of platelet-derived growth factor RTK phosphorylation and growth prevention of human neoplastic cells in G1, likely by repression of RhoA geranylation. Whereas FTase inhibitors suppress malignant growth in various human tumor cell lines, they apparently have a low effect on normal proliferation, survival, or differentiation. This selectivity proposes that these agents show a unique characteristic of neoplastic cell signaling (Adjei, 2001). FTIs have triggered tumor growth suppression rather than reversion when applied as monotherapies. It is suggested that the cross-prenylation of K-RAS and N-RAS is the major reason for poor efficacy of FTI monotherapy in clinical trials. Furthermore, FTIs probably have more efficacy in combination with cytotoxic, STI-571, or hormonal factors.

The other issue hindering the development of FTIs is a deficiency of valid genetic markers of response. FTI activity does not associate with K-RAS or N-RAS mutational expression. In contrast, FTIs have further targets than RAS proteins. For instance, the suppression of RhoB farnesylation appears to be more crucial for FTI antitumor activity (Gysin, Salt, Young, & McCormick, 2011). Suppression of posttranslational alteration of signaling proteins proposes a different approach to anticancer therapy. The enzyme catalyzing the three sequential biochemical reactions on CAAX motif proteins, where C is a cysteine residue, A is an aliphatic residue, and X can be a variety of residue, are possible targets for drug treatment. Lately, several studies have focused on small-molecule suppressors of the protein farnesyltransferase that catalyzes the binding of a C-15 isoprenyl group to the cysteine side chain of various CAAX motif-comprising proteins (Clarke & Tamanoi, 2004). Taken together EGFR overexpression has been determined in various epithelial malignancies, including breast, lung, bladder, ovary, prostate, head, and neck cancers. Furthermore, different pathways have been identified in the downstream of EGFR stimulation, comprising MAPK, PLC$\gamma$, PI3K, and signal transducer and activator of transcription (STAT). Activation of these pathways results in proliferation, survival, invasion, and angiogenesis in the cancer cell (Grandis & Sok, 2004). Recently, the oncogenic function of the EGFR has been more precisely determined to reach to the developed comprehension of the mechanisms of receptor activation, the detection of somatic mutations of the receptor as well as ingredients of mutations in signaling pathway of the receptor and finally to reach to clinical success of anti-EGFR therapies. Furthermore, arising evidence demonstrates that the EGFR family of +receptors has the potency to translocate to the nucleus where it may apply a variety of biological functions. The therapeutic involvements of these receptors localizing in the nucleus are that they can lead to resistance to the growth-suppressory effect of monoclonal antibodies (Scaltriti & Baselga, 2006). Finally, further endeavor must continue to better understand complication biology, genetic, and cross-talking signals of the cancer cells and to establish further methods to the improvement of successful small molecule inhibitors, which are less sensitive to the enhancement of resistance and display stronger potency against disease-associated signaling molecules (Majidinia, Alizadeh, Yousefi, Akbarzadeh, & Zarghami, 2016).

## 6 | CONCLUSION

Our review highlights the current knowledge of the alterations that occur in oxidative stress, DDR, and cancer progression involving MAPK pathways. Frequently, the topics included in the article that MAPK signaling pathways play a key role in the regulation of cancer metastatic processes such as proliferation, differentiation, and migration in the prevalence of cancers. Due to, the ERK/MAPK pathway is one of the most substantial pathways for cell proliferation, and several key growth factors and proto-oncogenes induce the signals that progress growth and differentiation in this cascade. Therefore, it appears to be an attractive pathway for anticancer target therapies. In contrast, MAPK signaling pathways have been implicated in the pathogenesis of the oxidative stress conditions and regularly cells are exposed to ROS; often all MAPKs are activated and send conflicting signals to determine cell fate as well as this requires strict regulation to guarantee that unsuitable responses are avoided and what determines the cell response is the availability of MAPK substrates to control oxidative injuries. Moreover, in reply to DNA damage, cell activates checkpoint pathway, which allows the DNA repair system to correct the damage, in this way, the activation of RAS/RAF/MEK/ERK signaling displays a self-protective reply restricting DDR in cells. Eventually, various mechanisms have been suggested to intercede DDR under oncogenic stimulation: DDR may be initiated by replication stress raised from a sustained oncogenic signal or probably from an oncogenic-driven accumulation of ROS. Thus oncogenic-induced senescence has been suggested to be initiated through an agglomeration of ROS.

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## CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

## AUTHOR CONTRIBUTIONS

S. R. contributed for writing and draft preparation, A. K. wrote the original draft, V. R., M. M. and A. S. performed data collection, H. P. and M. Y. reviewed and edited the manuscript, T. A. K. prepared the figures, A. B. performed final review and proof correction, and M. M. and B. Y. supervised this project.

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