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Mitogen-activated protein kinase-activated protein kinase-2 (MK2) and its role in cell survival, inflammatory signaling, and migration in promoting cancer

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Abstract

Cancer and the immune system share an intimate relationship. Chronic inflammation increases the risk of cancer occurrence and can also drive inflammatory mediators into the tumor microenvironment enhancing tumor growth and survival.

The p38 MAPK pathway is activated both acutely and chronically by stress, inflammatory chemokines, chronic inflammatory conditions, and cancer. These properties have led to extensive efforts to find effective drugs targeting p38, which have been unsuccessful. The immediate downstream serine/threonine kinase and substrate of p38 MAPK, mitogen-activated-protein-kinase-activated-protein-kinase-2 (MK2) protects cells against stressors by regulating the DNA damage response, transcription, protein and messenger RNA stability, and motility. The phosphorylation of downstream substrates by MK2 increases inflammatory cytokine production, drives an immune response, and contributes to wound healing.

By binding directly to p38 MAPK, MK2 is responsible for the export of p38 MAPK from the nucleus which gives MK2 properties that make it unique among the large number of p38 MAPK substrates. Many of the substrates of both p38 MAPK and MK2 are separated between the cytosol and nucleus and interfering with MK2 and altering this intracellular translocation has implications for the actions of both p38 MAPK and MK2.

The inhibition of MK2 has shown promise in combination with both chemotherapy and radiotherapy as a method for controlling cancer growth and metastasis in a variety of cancers.

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Whereas the current data are encouraging the field requires the development of selective and well tolerated drugs to target MK2 and a better understanding of its effects for effective clinical use.

Keywords

cancer; cell survival; inflammation; MAPKAPK2; metastasis; migration; MK2; p38 MAPK

1 | INTRODUCTION

There exists an intimate relationship between inflammation and tumorigenesis. The presence of inflammatory or autoimmune conditions increases the likelihood of developing cancer.[1,2] This chronic inflammation attracts fibroblasts, myeloid, and lymphoid cells to the tumor microenvironment (TME) which can then maintain the inflammatory phenotype and propagate tumorigenesis. Additionally, inflammatory signals secreted from the tumor itself, the inflammatory TME, and/or cancer therapies can also exacerbate inflammation and drive tumor progression.[1,2] Given the well-documented contribution of inflammation to tumor growth and tumor progression, ongoing research targeting the mechanisms of tumor inflammation is invaluable and may lead to therapies that can be applied to myriad cancer types.

The p38 MAPK-MAPKAPK2 (mitogen-activated-protein-kinase-activated-protein-kinase-2 [MK2]) signaling axis is activated by cellular or environmental stressors and stimulates the expression of downstream effector proteins that activate inflammatory cytokines, chemokines, and transcription factors.[3,4] MK2 also contributes to inflammatory processes via posttranscriptional regulation of various cytokines.[5] This pathway has been implicated in multiple inflammatory conditions from fibrosis[6–8] to arthritis[4,9,10] and given the relationship among stress, inflammation, and cancer, it is likely that MK2 plays a significant role in cancer development and/or cancer progression.

Preclinical studies utilizing p38 MAPK inhibitors in multiple cancer types have shown success, but unfortunately no p38 MAPK inhibitors have been approved for use due to severe toxicity and side effects.[3] As a downstream target of p38 MAPK activation, MK2 has been investigated for its role in tumorigenesis, cancer progression, and metastasis. Overall, results have been positive demonstrating that inhibition of MK2 can decrease tumor inflammation and epithelial-to-mesenchymal transition (EMT) in vitro, and tumor growth and progression in vivo in multiple cancer types.[11–16] The purpose of this review is to highlight the downstream effectors of MK2 and their roles in both normal physiological and pathological processes, and to discuss the relevance of investigations of MK2 signaling in cancer.

2 | p38 MAPK-MK2 MOLECULAR BIOLOGY

2.1 | p38 MAPK and the pathway leading to MK2

The p38 MAPK pathway is considered a stress-response MAPK pathway due to its phosphorylation in response to environmental or cellular stressors such as ultraviolet (UV) radiation, inflammatory cytokines, heat shock, starvation, and osmotic shock.[3,17] p38

MAPK is a MAPK that comes in several isoforms, p38α (MAPK14), P38β (MAPK11), p38γ (MAPK12), and p38δ (MAPK13). The different isoforms are characterized by their expression levels; p38α and P38β are ubiquitously expressed in all cells and tissues with higher expression of p38β in the lungs. p38γ is expressed in skeletal muscle and p38δ is expressed in lung and kidney.[18–21] The functions of p38α are the most robustly studied among the isoforms. p38β is generally expressed at lower levels than p38α and appears to be redundant to the functions of the cell if p38α is present[22] although it does seem to have a role in in vivo bone formation that is independent of p38α.[23] p38γ and p38δ are sometimes known as alternative p38 isoforms and their roles involve posttranscriptional modification of cytokine release, mucus secretion, modulating insulin release, and amyloid plaque formation in neuronal tissue.[24] Of the different isoforms, only p38α knockout results in a lethal embryonic phenotype,[25,26] and p38β is unable to compensate for the deletion fully even when expressed by the same promoter. This demonstrates that even with expression normalized there are differences between the isoforms controlling downstream functions.[27] It is assumed that the p38α (p38 MAPK) isoform is most relevant to this review as it is the isoform that controls the response to lipopolysaccharide (LPS) induced tumor necrosis factor α (TNFα) release and its interaction with MK2 is the most studied.[28–30] Whereas we cannot discount any MK2 interactions with the other isoforms, to date no evidence to support their interaction exists.

The p38 MAPK pathway is one of the three highly conserved mammalian MAPK pathways that include the extracellular response kinase (ERK-1) and c-jun N-terminal kinases (JNK) signal transduction pathways. The ERK pathway is generally activated by extracellular mitogens whereas the JNK and p38 MAPK pathways were traditionally known as stress-activated protein kinases (SAPK) that respond to environmental stressors such as osmotic shock, UV radiation, and ischemic injury.[31] The three signaling pathways are characterized by the canonical triple-tiered cascade of kinases beginning with the MAPK kinase kinase (MAP3K), followed by MAPK kinase (MAP2K), and finally MAPK. The MAP3Ks are relatively non-specific kinases that are classed as MAPK/ERK kinase (MEK) kinases, mixed lineage kinases (MLKs), and thousand and one kinases (TAOs).[32] These factors are regulated by small GTPases or phosphorylation events such as the activation of transforming growth factor-β-activated kinase 1 (TAK1) which forms a complex with transforming growth factor binding proteins (TAB1, TAK1-binding protein 2 [TAB2]) to phosphorylate downstream MAP2Ks.[33] The MAP3K responsible for upstream activation of the p38 MAPK signaling pathway are diverse and include MEKK1–4, ASK1, DLK1, TAK1, TAO 1/2, and ZAK1.[3,34]

Downstream from the MAP3K, the MAP2Ks that phosphorylate p38 MAPK specifically are MKK3 and MKK6. These two proteins share an 87% homology[35,36] and activate p38 MAPK by phosphorylating Thr180 and Tyr182 in its activation loop. Although these MAP2Ks can activate other MAPKs (i.e., JNK[37]), they are vital for the canonical receptor activation of the p38 MAPK pathway. However, they are not the only MAP2K molecules capable of activating the p38 MAPK pathway. UV light has also been shown to cause the phosphorylation of p38 MAPK through the activity of MKK4 in mouse fibroblasts[38] and there are other mechanisms of p38 MAPK signaling that appear to be separate from the MKK3/MKK6 signaling. G-protein coupled signaling has been implicated in the activation

of p38 MAPK through the actions of E3 ubiquitin ligase neural precursor cell expressed developmentally downregulated 4–2 (NEDD4–2). Receptor binding causes the recruitment of NEDD4–2 which then ubiquitinates the receptor, orchestrating the binding of ubiquitin-binding adaptor protein TAB2. In turn, TAB2 then recruits TAB1, which binds and induces autophosphorylation of p38 MAPK.[39,40] The generation of a TAB/p38 MAPK signaling complex by the actions of AMP-activated protein kinase (AMPK) in response to ischemia and hypoxia is another proposed noncanonical activation of p38 MAPK.[41] The direct interaction of TAB1 with p38α induces a conformational change moving the active loop into the catalytic domain and enhancing ATP-binding, thus enabling cis-autophosphorylation of the active loop at Thr180 and Tyr182.[40] Another method of MKK3/6 independent activation of p38 is through the actions of Src-family zeta-chain-associated protein kinase 70 (Zap70) in T cells. This activation is important for T-cell receptor-mediated activation of T cells. Zap70 causes phosphorylation of p38α and p38β at Tyr323. This results in dimerization of the p38 MAPK molecules and autophosphorylation at Thr180.[42]

p38 MAPK acts on many downstream targets that are involved in the stress response including embryonic development, immune response, cell cycle, cell differentiation, metabolism, senescence, and survival. The number of downstream targets currently exceeds more than 100 and that number will likely increase as a complete phospho-proteome on p38 MAPK targets has not been completed.[3,43–45] The wide-reaching impact of p38 MAPK has made it an attractive target for treatment of immune disorders and cancer for the past two decades. However, the search for drugs that act on p38 MAPK has been hampered by a wide range of side effects including hepatic toxicity, cardiac toxicity, and central nervous system disorders, or a lack of efficacy.[46–48] The lack of effective drugs may be due to the pleiotropic effects of p38 MAPK downstream signaling or off-target effects of the drugs. As a result, except for the weak and nonselective p38 MAPK inhibitor pir-fenidone, no approved drug that targets p38 MAPK inhibitors have passed Phase III clinical trials.[48–50] Efforts continue as Ralimetinib (LY2228820) is in multistage Phase I and II testing and shows promise when combined with chemotherapy in female cancers and glioblastoma.[3] A significant amount of effort was placed into finding drugs targeting p38, negatively impacting efforts to examine other kinases for suitable inhibitors. Although, in recent years the understanding of related signaling cascades has improved and efforts to look for targets that have fewer toxicities but comparable efficacy have advanced. MK2, a molecule that is directly downstream to p38 MAPK, is one such target that controls a significant portion of the inflammatory signaling post p38 MAPK phosphorylation. The inhibition of MK2 is not predicted to be as harmful as p38 MAPK inhibition because MK2 KO mice were viable and fertile, grew to normal size, and did not exhibit obvious behavioral defects whereas p38 MAPK knockout mice are embryonically lethal.[26,28,51,52] Assuming the issues of p38 MAPK inhibition arise from its pleiotropic nature then MK2 may be a more attractive target for inhibition of inflammation and other cellular responses driven by the activation of the p38 MAPK-MK2 pathway.

2.2 | MK2 structure and interaction with p38

MK2 is serine/threonine kinase that was identified in 1992 by Stokoe et al.[53] who were looking for kinases that could phosphorylate glycogen synthase. MK2 was found to be expressed in several tissues including kidney, skeletal muscle, liver, testis, lung, and

spleen.[53] A recent large-scale proteome showed very little protein expression in muscle tissue but high expression in gastrointestinal tissue and immune organs like lymph nodes and bone marrow.[54]

Gene data show that there are two main transcripts to MK2; Isoform 1 (**NM_004759.5**, $MK2_s$) is a 370 amino acid protein isolated by Zu et al.,[55] whereas Isoform 2 (**NM_032960.4**, MK2) is a 400 amino acid in length similar to the protein isolated initially by Stokoe and colleagues.[53] The latter variant uses an alternate splice junction at the 5′ end of the last exon compared to variant 1 and as a result, has a longer C-terminus (Figure 1). The full-length transcript (transcript 2, MK2) has a proline-rich N terminal domain (10–40) followed by XI catalytic subdomains (64–325) and a regulatory C-terminus domain (338–400). The c-terminal regulatory domain has an auto-inhibitory domain (339–353, a nuclear export sequence [NES; 356–365]), and a bipartite nuclear localization sequence [NLS; 371–374, 385–389]) that governs the activity and cellular location of the enzyme.[56] For the enzyme to display kinase activity, two of three major phosphorylation sites (Thr222, Ser272, Thr334) must be phosphorylated with maximal activity if all three are phosphorylated.[57] Two of these sites reside in the catalytic domain (Thr222 and Ser272), one of which is located between the catalytic domain and the auto-inhibitory domain (Thr334).

The proline-rich N terminal domain was originally thought of as a potential binding site for SH3 binding domains[58] and has been shown to be important to the motility of cells.[59] Stokoe et al.,[53] found that the catalytic subdomains require a minimum amino acid sequence of HYD–X–R–X–X–Ser–X–X, where HYD is a hydrophobic residue, for efficient phosphorylation of target kinases. A more precise optimal sequence based on several known substrates of MK2 was generated later ([Leu/Phe/Ile]–[X]–[Arg]–[Gln/Ser/Thr]–[Leu]–[Ser/Thr]–[Hydrophobic]).[60]

The catalytic subdomain contains two of the three phosphorylation sites required for kinase activity. Thr222 is of particular relevance because it sits in the activation loop (207–233) between catalytic subdomains VII and VIII and is thought to cause a conformational change in the catalytic domain to activate the kinase.[61,62] The homology of the kinase domain makes it most similar to various calcium-activated kinases and myosin kinases.[53,58] The C-terminal domain regulates the kinase activity of the cell, its cellular location, and its binding to its activating enzyme p38 MAPK. MK2 contains an inhibitory peptide that obscures both the catalytic domain and the ATP-binding site preventing activity.[56] The phosphorylation of Thr334 weakens the binding of the autoinhibitory domain to the catalytic site, increasing kinase activity, and is also critical to the cellular localization of MK2 as it exposes the NES sequence that is otherwise hidden during its resting state.[58,62,63]

MK2 is a direct substrate of the p38 MAPK protein and has a unique relationship with the enzyme because of the physical partnership the two molecules display. While we have a strong understanding of the pairing of the two molecules, we do not fully understand its implications. There appears to be a mutual stabilization of the p38 MAPK and MK2 molecules as genetic deletion of either results in reduced expression of the other[59,64] although how this stabilization occurs is not clear. In resting cells, p38 is located mainly in the cytoplasm and MK2 is located primarily in the nucleus[63,65] upon phosphorylation

of p38 it is translocated to the nucleus via importins.[66] Unphosphorylated MK2 has a high affinity for p38 MAPK (K_d 2.5 nM) implying that upon p38 entering the nucleus these two molecules form a tight bond.[67,68] The bond is formed by five connection points on the MK2 molecule; Gly73 and ILe74 form a stable backbone, Tyr288-Tyr240 binds to the catalytic site and may move on activation, Tyr264–284 is where regulatory phosphorylation domains from both molecules interact, Asp345-Val365 binding limits access to the MK2 substrate binding site and Asp366-Ala390 binds to p38 via extensive H-bonds, salt bridges, and a favorable docking groove on p38 MAPK (glutamate-aspartate, ED, and common docking, CD, regions common to MAP kinases).[29,30] This latter interaction provides a significant contribution to the binding between these two molecules as demonstrated by inhibition of MK2 phosphorylation by a peptide mimic of the MK2 C-terminal sequence at a concentration of 60 nM.[68] The binding of the two molecules come together in face to face fashion, where the ATP binding sites of both kinases are at the heterodimer interface. The C-terminus of MK2 wraps around p38 MAPK, inserts in the p38 MAPK docking groove and becomes sandwiched between the two molecules kinase domains.[29,30] By binding in the docking groove, MK2 also binds to the same place as many other substrates of p38 MAPK. The implication is that other substrates may be able to disrupt p38 MAPK-MK2 interaction generating a fluid on/off pattern to the binding of the two molecules. It is worth mentioning that MK2 fits in the “reverse” configuration compared to other p38 MAPK docking substrates and thus may not be removed as easily as implied by the communal docking regions.

Upon MK2 phosphorylation by p38 MAPK, the affinity between the two proteins decreases slightly as MK2 changes conformation. This conformational change also exposes the NES, which overrides the NLS, and exports the complex to the cytoplasm.[57,62,69] This conformational change occurs after the phosphorylation of Thr334 and opens the NES sequence for binding to exportin-1 that transports both MK2 and p38 to the cytoplasm.[62] The transport of the complex out of the nucleus exposes the two kinases to different substrates, the nuclear substrates are more likely to be transcription factors whereas cytoplasmic targets include the small heat shock proteins (sHSP) (HSP25/27) and tristetraprolin (TTP). It is therefore an interesting facet of the kinase that Thr334 is phosphorylated at half the rate of Thr222 and Ser272[68] possibly giving the complex an opportunity to activate nuclear substrates before moving to the cytoplasm for alternative functions.

The smaller Isoform 1, at 370 amino acids, does not include the NLS, the NES, and a significant portion of amino acids in the c-terminus that allows MK2 to bind tightly to p38. The kinase activity is 2 orders of magnitude weaker than the longer form and its binding to p38 is also much weaker. The significance of the shorter form is not well understood and macrophages expressing the shorter form exclusively show a reduced release of TNFα compared to macrophages expressing the full-length transcript.[59] It is possible that the $MK2_s$ isoform is a nuclear resident isoform that is only concerned with the activity of nuclear-based transcription factors and that the main function of the longer MK2 isoform is to confer MK2/P38 MAPK signaling to the cytosol. As the loss of full-length MK2 is all that is required to reduce TNFα release we can conclude that the migration of MK2 to the cytosol is critical for its effects on TNFα release.

2.3 | MK2 inhibitors and their mechanism of action

Although it was mentioned in a previous section that significant efforts to target p38 has left drug design studies on MK2 lacking, there have been several attempts at targeting MK2 or the p38-MK2 interaction through rational drug design approaches.

The majority of MK2 inhibitors designed have focused on molecular interactions of the ATP binding site between p38 and MK2.[47,70] The ATP-binding site is formed by a flexible glycine rich group that connects the small N-terminus with a large α-helical domain and the catalytic group and this sits in the heterodimer interface of the p38-MK2 heterodimer.[30] The difficulty in designing drugs for this site is increased because of the similarity of the ATP binding site to other similar kinases such as MK3, MK5, PKA, and CDK2 which affects the selectivity of the drugs for its preferred target. Furthermore, although many of these competitive inhibitors have high affinity for the ATP binding site, the affinity of ATP for the site (K_m 2 μM) and its high cellular concentration in the cell (~2–5 mM) results in a discrepancy between the binding affinity and its cellular effectiveness (the ratio of a drugs binding affinity to its cellular activity is known as the biochemical efficiency or BE).[71,72] Many of the current ATP competitive inhibitors show functional responses 10–100-fold greater than their affinity to the kinase (resulting in BE values of 0.1–0.01). This aspect of ATP competitive inhibitors and the issues with their solubility and cellular permeability have eroded enthusiasm of these drugs.[47] Nevertheless, there are several available research grade drugs that can be used to probe the functions of MK2 while acknowledging the deficiencies in their selectivity and BE. PF3644022 is an ATP-competitive benzothiophene inhibitor of MK2 developed by Pfizer with kinase IC_{50} of 5.2 nM for the enzyme and IC_{50} of 160 nM for inhibition of TNFα from LPS stimulated whole blood.[73] This is a widely used drug in preclinical settings but suffers from the low BE issues mentioned previously and has poor solubility in aqueous solutions (~5 μM). Other ATP-competitive MK2 inhibitors commonly available include PHA 767491 (IC_{50} 171 nM) which also inhibits cyclin-dependent kinase (CDK1–5) at similar concentrations.[74] CAS 1186648-22-5 (aka MK2 inhibitor III) is also available as an ATP-competitive inhibitor of MK2 with an IC_{50} of 8.5 nM for MK2 and an EC_{50} of TNFα release of 4.4 μM. However, it also inhibits MK3 and MK5 with IC_{50}s of 81 and 210 nM, respectively, illustrating the difficulties of targeting a molecular location with similarities to other kinases.[74] So far, no ATP-competitive inhibitors have made it to clinical trials.

Noncompetitive inhibitors for MK2 were available as early as 2004 with CMPD-1 functioning as an inhibitor of p38 preventing the phosphorylation of MK2 without inhibiting the phosphorylation of other p38 substrates such as ATF-2 and MBP. The binding of CMPD-1 to p38 appeared to alter the active site region of p38 causing the suboptimal positioning of substrates and selectively inhibiting p38 phosphorylation of MK2.[75] With a IC_{50} of 330 nM the drug appears not as effective as some of the ATP-competitive inhibitors and has off target effects that cause cytotoxicity by inhibiting tubulin formation.[76] The MK2 inhibitor, MK-25 (also known as MK2 inhibitor IV), is a noncompetitive inhibitor of MK2 with an IC_{50} of 110 nM and and EC_{50} of 4 μM for TNFα release from LPS treated THP-1 cells.[72]

The peptide inhibitor of MK2, MMI-0100, has been studied in a number of different systems.[77–80] This peptide drug targets the substrate-binding site of MK2, is carried into cells via cell-permeant domains and is rapidly taken up by macropinocytosis and targeted to endosomal compartments.[8] The sequence of the peptide was designed from the consensus sequence of phosphorylation of HSP-27 and inhibits the phosphorylation of the protein as a result. It showed efficacy in reducing pulmonary and cardiac fibrosis and inflammation in animal models at micromolar concentrations and had entered clinical trials in 2014 but has not appeared to progress since.

A recently developed MK2 inhibitor, ATI-450 (also known as CDD-450) selectively blocks p38α activation of MK2 while sparing the inhibition of other effectors of p38α. The inhibitor was designed to interact with the binding surfaces interface near the p38α ATP site and a natural cleft in MK2. The presence of ATI-450 prevents phosphorylation of MK2 by p38 due to this in a manner 700-fold greater than its ability to inhibit phosphorylation of ATF-2 and PRAK.[10] The drug has shown efficacy in preclinical trials, inhibiting interleukins (IL)-1β and TNFα at 1–10 μM concentrations. The drug was demonstrated to be safe and well tolerated following completion of a Phase 1 clinical trial.[81] Current Phase 2a trials for rheumatoid arthritis (NCT04247815) and COVID-19 (NCT04481685) have both recently completed patient accrual and safety and efficacy results from both of these trials are forthcoming.

3 | DOWNSTREAM TARGETS AND CELLULAR FUNCTION OF MK2

With the activation of p38 MAPK, MK2 becomes activated via phosphorylation and in turn phosphorylates downstream substrates that mediate migration, cell growth, differentiation, inflammation, and apoptosis in downstream pathways (Figure 2). Whereas some of the downstream targets have well-known functions, there are other targets that we can only speculate about their cellular effects based on the understanding we have of the physiological response to the phosphorylation and activation of the relevant protein species. Typically, examining the consequences of signaling cascades results in protein blots and kinetic experiments that capture early events in what are often processes that occur over days, weeks, or months in vivo. Hence, we are left trying to extrapolate from intracellular signaling into whole-body physiology that may leave many of the details up to interpretation.

We list the known substrates for MK2 based on experiments that have shown direct MK2 phosphorylation (Table 1), and attempt to delineate what this might mean for the fate of cells responding to MK2 activation below. When considering the different types of substrates phosphorylated by MK2 a pattern of activity is seen. Under stress conditions, MK2 action slows the cell cycle to enable repair, stabilizing necessary protein structures and eliminating potential hazardous proteins, increasing transcription of immediate early genes for rapid cellular reaction, stabilizing messenger RNA (mRNA) for rapid translation, regulating cellular motility and initiating immune signals for leukocyte influx and tissue repair. Many of these mechanisms have been explored in detail and are covered below.

3.1 | Cell cycle and the DNA damage response

The DNA damage response results in a series of steps that are designed to halt the cell cycle to facilitate repair of DNA before cell division occurs. Damage to the DNA results in the activation of the proteins ATM and ATR and subsequent phosphorylation of a range of proteins including p38, MK2, p53, MDM2, ChK1, and ChK2.[117,118]

The tumor suppressor, p53, is typically regarded as one of the main effector molecules of the DNA damage response by transcribing the protein p21 that inhibits CDK2-cyclin and CDK1-cyclin activities leading to an arrest of the cell cycle in either the G1/S or G2/M phases, respectively.[119] In the absence of an effective p53 response, the cell short circuits and begins to rely on MK2 for cell cycle arrest[117] because several its substrates are involved in the regulation of the cell cycle during the DNA damage response.

The cell cycle phosphatases M-phase inducer phosphatase 2 and 3 (CDC25B, CDC25C) play an important role in determining the transitions between the different phases of the cell cycle. Various CDK/cyclin complexes are activated in rhythmic patterns as the cell cycle progresses. The CDC25 proteins dephosphorylate CDK proteins and activate them, progressing the cell cycle forward. CDC25B and CDC25C are both involved in regulating the G2/M transition by activating CDK1-cyclinB causing the cycle to advance.[120] MK2 phosphorylates CDC25B and CDC25C in response to UV radiation[112] increasing the binding to 14-3-3 proteins, altering the cellular location of CDC25, marking the CDC25 molecules for degradation, and arresting the cell cycle in the G2/M phase[60,117,121] (see Figures 3 and 4). Further, MK2 phosphorylates 14-3-3ζ as determined by computer modeling and mutagenesis.[110] These proteins are ubiquitously expressed in nature and serve as scaffold proteins that form complexes with themselves and other molecules to regulate processes in the cell such as the cell cycle and RNA stability.[122] The phosphorylation of 14-3-3 alters their ability to dimerize and bind other substrate proteins where they act as chaperones and stabilization proteins.[123] There are 7 known 14-3-3 isoforms and, although we know 14-3-3ζ is the molecule targeted by MK2 isoforms, 14-3-3β, 14-3-3ε, and 14-3-3γ contain a serine in a MK2 consensus phosphorylation site at a location similar to that of 14-3-3ζ. Thus, MK2 may regulate the function of several 14-3-3 isoforms and a wide range of cellular processes including cell cycle, apoptosis and autophagy.[110,124] In this case, the phosphorylation of 14-3-3 proteins by MK2 enhances the arrest of the cell cycle by targeting CDC25C/B. It is through this mechanism that MK2 can act as a checkpoint molecule allowing the cell to halt division before adequate DNA repair has taken place.

The phosphorylation of poly(A)-specific ribonuclease (PARN) by MK2 is another mechanism by which MK2 regulates the cell cycle. The protein is an 3′-exoribonuclease that deadenylates mRNA, reducing their stability and facilitating their degradation. The protein favors binding to poly(A) tails of mRNA and exonucleolytic degradation of the tail is often the first step in the decay of eukaryotic mRNAs. The protein is found in nucleoli, cajal bodies and the endoplasmic reticulum (ER) where it regulates the fate of ER associated mRNA. A significant number of the ER associated mRNA were found to code for proteins involved in the cell cycle and DNA damage response.[111] MK2 phosphorylates PARN resulting in the stabilization of mRNA, such as GADD45α which also inhibits the Chk1-cyclin checkpoint responsible for G2/M progression in the face of cellular stress.[121]

Without this phosphorylation, cells were able to initiate but not maintain cell cycle arrest due to DNA damage by doxorubicin.[121] This MK2-dependent mechanism of action required MK2 to translocate to the cytoplasm, as the stabilization of GADD45α also required the phosphorylation of the RNA binding protein hnRNP A0 (Figure 4).

A loss or inhibition of MK2 in p53 deficient cells that were damaged by cytotoxic DNA stress resulted in death due to mitotic catastrophe,[121] whereas cytotoxic damage to wild type p53 cells resulted in no increased cell death. This revealed an avenue for the generation of synthetic lethality (SL) mutants in cancer cells with p53 mutations.[117,121,126–130] KRAS and BRAF cancers commonly express p53 mutations or CDKN2A mutations that destabilize cell cycle checkpoints through p53 and instead become reliant on MK2 and CHK1 for cell cycle stability. Inhibition of CHK1 and MK2 led to apoptosis in KRAS and BRAF mutant cancers, showing the importance of MK2 in cell cycle regulation under these conditions.[129] Later studies described a concept of augmented SL in tumors with defective p53 by targeting MK2 and the DNA repair protein XPA with small interfering RNA (siRNA) peptides. The tumors from these mice exhibited an enhanced cisplatin response and in turn the mice lived longer, particularly when these tumors were treated with both MK2 and XPA compared to MK2 inhibition alone.[130] It remains to be discovered if there are other lethal combinations between MK2 and other molecules that may target mutant p53 cells while causing little effects to p53 positive cells.

P53 plays a large role in the DNA damage response by activating repair proteins, arresting the cell cycle in G1/M and causing apoptosis if the damage is too severe.[131] Under resting conditions, the activity of p53 is kept low by its interaction with the protein HDM2 which signals the p53 for degradation through its E3 ubiquitin ligase activity. Phosphorylation of p53 causes a dissociation with HDM2 enabling the accumulation of cellular p53 through enhanced protein stability. MK2 was found to phosphorylate HDM2 at locations that increased HDM2 affinity for p53 thereby enhancing its degradation in what could be described as a blunting of p53 function. In contrast, loss of MK2 in murine embryonic fibroblasts (MEFs) led to reduced MDM2 (HDM2 in humans) and increased p53 levels following UV irradiation. This apparently paradoxical role MK2 is possibly a form of negative feedback of cell cycle arrest and DNA damage sensing.[51]

An additional mechanism of cell cycle control by MK2 is through TRIM29/ATDC which is a member of the tripartite motif (TRIM) protein family that consists of 70 members. The TRIM family of proteins has been implicated in a variety of physiologic processes, such as development, oncogenesis, apoptosis, and antiviral defense. TRIM is highly expressed in pancreatic cancer cells, promoting pancreatic tumor growth via stimulation of the β-catenin pathway. MK2 was shown to phosphorylate TRIM29 which correlated with an increased resistance of pancreatic tumor cells to radiation.[113] The mechanism of this action is unclear but TRIM has been shown to act as a regulator of the assembly of DNA-damage proteins and so phosphorylation may alter the conformation of the assembly to promote repair.[132]

3.2 | Transcription

Several transcription factors are known to be phosphorylated by MK2 activating genes that code for immediate early genes, heat shock proteins and inflammatory mediators.[89,91,93,94]

Serum response factor (SRF) is a protein that belongs to the MADS superfamily of transcription factors that binds to the serum response element of promoters of immediate early genes.[133] Immediate early genes are a collection of genes such as c-fos, c-jun, and c-myc that need to be activated for later responses to occur. Many of these genes are transcription factors themselves and they activate genes involved in changes to the cell cycle, cell growth, cell differentiation, apoptosis, and the immune response.[134,135] Heidenreich et al., (1999)[88] showed the MK2 phosphorylated SRF in both in vitro and in vivo conditions. Whereas the role of phosphorylation is currently unknown, the study demonstrated an increase in the affinity and rate of SRF to the binding to serum response element suggesting activation of gene transcription.

Myocardin-related transcription factor A (MRTFA) is a known actin-regulated transcriptional coactivator of SRF. Actin polymerization activates MRTF-A by releasing it from G-actin and thus allowing it to bind to and activate SRF. MRTF-A is phosphorylated by MK2 at in a stress but not mitogen dependent manner. However, the phosphorylation led to no increase in dimerization, no change in subcellular localization and translocation or interaction with actin or SRF. Therefore, the physiological role of this phosphorylation is unknown.[90]

Heat shock transcription factor-1 (HSF-1) is a highly evolutionary conserved transcription factor responsible for initiating the transcription of heat shock proteins during times of cellular stress. HSF-1 upregulates the transcription of several heat shock proteins such as HSP27, HSP40, HSP70, and HSP90. As with HSP27, these proteins refold misfolded proteins and confer resistance against cellular stress. Under normal conditions, HSF-1 is inactive and found in monomeric form in cellular complexes with HSP proteins. Activation of HSF-1 involves binding of misfolded proteins with the complex and relieving the binding and inhibition of HSF-1. It then undergoes homo-trimerization and activates transcription by binding to heat shock elements (HSE) on the DNA.[136] HSP-1 also plays a role in inhibiting the transcription of proinflammatory genes such as IL-1β, IL-6, and TNFα.[137,138] Wang et al.,[136] showed that MK2 can phosphorylate HSF-1 reducing the ability to bind to HSE and increasing its affinity to HSP90 thus inhibiting HSP1 function. Therefore, MK2 influences transcription by inhibiting repressors of inflammatory signaling.

Steroid receptor coactivator 3 (SRC-3) is a transcriptional cofactor from the p160 family that binds to steroid hormone receptors in a ligand-dependent manner serving as a coactivator of transcription.[139] It is a cofactor to steroid nuclear receptors and as a number of transcription factors including E2F transcription factor 1 (E2F1), polyomavirus enhancer activator 3 (PEA3), activator protein-1 (AP-1), and nuclear factor-κB (NF-κB). Its activity has been implicated in cell proliferation, development, survival, metabolism and is linked to the severity of both hormone-dependent and independent cancers. The function of this gene is heavily regulated by phosphorylation which alters the transcription of hormone receptors and NF-κB. One of its primary phosphorylation sites was shown to be phosphorylated by MK2 implicating a role for the p38/MK2 pathway in modulating the transcriptional activation of NF-κB and releasing IL-6 in A549 cells.[89]

The transcriptional changes stimulated by MK2 are not well characterized but likely enhance the role of MK2 in directing cells toward a path of survival and resilience in the face of cell stress. Although MK2 activates several transcription factors directly, there is also evidence that its signaling affects other transcription elements, particularly NF-κB, in endothelial cells.[125] Part of the effects of MK2 on NF-κB signaling is governed by the trafficking of p38 from the nucleus to the cytosol. When NF-κB is activated, its activity is checked by IκBα activity that mediates nuclear export of p65, a component of the NF-κB family.[140] The export of p65 results in reduced expression of NF-κB genes and a blunted inflammatory response. Phosphorylation of p65, increased expression of IκBα and extracellular transport of p65 is initiated by p38 MAPK phosphorylation of nuclear MSK1. The activation of MK2 results in the trafficking of p38 out of the nucleus causing a reduced phosphorylation of MSK1 and a more sustained activation of NF-κB genes.[125] Thus, MK2 can alter transcription of genes by altering the location of p38 MAPK and altering cellular function as a result (Figure 5).

MK2 also supports the activity of NF-κB through the activation of SRC-3 by phosphorylation.[89] The phosphorylation site was dependent onTNFα activation of MK2 as it was blocked by the inhibitor PF3644022 that blocks MK2 kinase activity. Phosphorylation caused the translocation of SRC-3 into the nucleus, creation of the NF-κB-SRC-3 complex and transcription of inflammatory genes such as IL-6. The indirect action of MK2 on NF-κB demonstrates the role of MK2 in stimulating the expression inflammatory gene transcription in addition to the direct activation of genes due to the phosphorylation of direct targets such as SRF, HSF1, and CREB.[73]

The transcription factor cyclic adenosine monophosphate (cAMP) response element-binding protein (CREB) is a nuclear transcription factor that binds to CRE elements on the genome to promote transcription of genes such as somatostatin, c-fos and genes regulating the circadian clock. It was shown to be phosphorylated by MK2 after stimulation of cells by fibroblast growth factor in vitro suggesting a role for MK2 in CREB activation[91,92] that was contradicted later with the knowledge that CREB activation was far more likely to be dependent on mitogen and stress activated kinase (MSK1) due to the much lower K_m MSK1 had for CREB.[141] However, a subsequent study concluded that when cells are exposed to mitogens, p38 MAPK is activated, but the response is transient and not able to activate CREB, but with cell stress (i.e., anisomycin) the activation of p38 MAPK is sustained resulting in MK2 and subsequent CREB phosphorylation.[93]

3.3 | Role in RNA-binding-protein function

MK2 has a central role in the regulation of mRNA binding proteins by stabilizing transcripts for inflammatory cytokines, growth factors and cell cycle checkpoint stabilizers.[5] Through its action of stabilizing transcripts, the translation response to MK2 activation is accelerated compared to stimulating transcription of genes. Therefore, it appears the p38/MK2 axis is evolved for rapid response to stress by stabilizing inflammatory mRNA and initiating an appropriate response from the cell.

Several RBPs are known to be direct phosphorylation targets of MK2.[5,103–109] These mRNA binding proteins are structured to bind to adenylate and uridylate-rich elements (ARE) found

on the 3′-untranslated regions of mRNAs. The binding of mRNA to RBPs results in either the degradation or stabilization of these mRNAs depending on the RBP species and ARE binding competition. This facet of control over the fate of mRNA by binding to different RBPs results in posttranscriptional gene regulation to control the translation and expression of effector genes. A census of RBPs shows that there are over 1500 of these molecules in the human genome with different abilities to regulate the binding of RNA to effector proteins that govern the fate of the transcript.[142] Many of these RNA binding proteins compete for the same targets and confer opposite fates to the bound mRNAs. Therefore, MK2's ability to phosphorylate certain RBP will allow for transcriptional-translational modulation.[143]

TTP is one RBP that is directly phosphorylated by MK2.[103,144] Phosphorylation of TTP increases its binding to 14-3-3 proteins that prevent the recruitment of deadenylases by TTP thereby prolonging the half-life of cytokine mRNA such as TNFα (Figure 4).[145,146] The mRNA that would be bound to TTP then binds to other RBPs like Human antigen R (HuR or ELAVL1) or hnRNP A0 and these transcripts are stabilized and go forward to translation.[147,148] The end result of mRNA stabilization by the sequestration of TTP results in increased production of many inflammatory mRNAs such asTNFα, IL-2, GC-MSF, COX2, and Nitric oxide synthase.[149–152] The effect of downregulation of TTP was shown in studies examining $TTP^{-/-}$ mice that demonstrated an overexpression of TNFα by macrophages causing severe arthritis and cachexia.[149,153,154] Inhibition of MK2 in LPS treated macrophages caused a reduction in TNFα production but no change in TNFα transcript concentration, giving further evidence for the critical role of MK2 in posttranscriptional control of inflammatory cytokines.[28,155] Thus, MK2 effects on RBPs is a potent way of regulating inflammation in response to stress. The activation of MK2 also results in feedback mechanisms as TTP expression is enhanced by MK2 signaling demonstrating tight control of this cellular mechanism.[147,156]

The subcellular location of HuR changes with stress and cytoplasmic accumulation of HuR occurs in cells that are subjected to oxidative stress, or cells that transiently overexpressed constitutively active MK2.[148,157,158] Although HuR and TTP are highly interconnected, there does not appear to be a sequence within HuR that MK2 phosphorylates.[159] It has been reported that p38 phosphorylates HuR, but the shuttling of HuR from the nucleus to the cytoplasm, required for mRNA stability of IL-6, TNFα etc., is MK2 dependent. However, the specific interactions that allow this mechanism to function are not clear.[160–162] Although it is not known how MK2 is involved in the translocation of HuR, the cycling of molecules out of the nucleus appears to be a mechanism that MK2 regulates in several cell systems. Its role in cytoplasmic translocation of p38 MAPK can alter NF-κB signaling and the MK2 functions that occur in the cytoplasm such as the phosphorylation of hnRNP A0 for the stabilization of GADD45α in the DNA damage response[121] suggest that much of MK2 signaling relies on its cycling out of the nucleus (Figures 4 and 5). This is exemplified by the reduction in TNFα release in murine macrophages that only express the shorter form of MK2 without the NES sequence preventing cytosolic MK2 accumulation.[59]

Bollig et al.,[108] demonstrated that MK2 can phosphorylate the RBP polyadenylate-binding protein 1 which is also involved in the regulation of RNA stability by TTP as part of a complex that must dissociate in order for HuR to bind and stabilize mRNAs. The RBP

HNRNP A0 binds to mRNA sequences for TNFα, COX2, GADD25α and macrophage inhibitory protein-2 when phosphorylated by MK2.[105,121] This resulted in the stabilization of these mRNA moieties and subsequent translation of their target proteins.

The nuclear exosome targeting complex is required for degradation of nuclear noncoding RNAs endowed with 3′–5′ exo- and endoribonuclease lytic activities. In the nucleoplasm, this complex is composed of hMTR4, ZCCHC8, and RBM7. RBM7 is phosphorylated by MK2 leading to a reduction in affinity of this complex and a stabilization of promoter upstream transcripts (PROMPTS) that normally undergo rapid nucleolysis.[107]

MK2 has been shown to phosphorylate the negative elongation factor complex (NELF) subunit E (NELFE), the RBP part of the complex, at serine positions 51, 115, and 251. This phosphorylation enhances the binding of NELF to 14-3-3 proteins. The binding of 14-3-3 proteins to NELFE causes its dissociation from the complex allowing gene transcription by RNA polymerase II. The function of these genes includes telomere maintenance, RNA metabolism, cell cycle, and DNA repair.[106] In addition to this direct measure of MK2 on NELFE, the study demonstrated the phosphorylation of 122 proteins by the p38 MAPK-MK2 axis suggesting a large list of unknown targets for MK2 phosphorylation.

3.4 | Cytoskeletal activity, motility, and migration

Genetic depletion of MK2 has profound effects on motility as seen in MK2 KO mouse embryonic fibroblasts and smooth muscle cells that displayed reduced migration,[59] whereas MK2 KO neutrophils showed a loss of directionality but higher migration rate.[51,163] This implies a complicated regulatory role for MK2 in motility and migration. Further, the wide array of targets affecting actin polymerization and other structural proteins suggests a role in regulating intracellular trafficking in addition to motility.

HSP27/25 was one of the earliest found substrates of MK2 and its function in cell motility is widely researched. In unstressed cells, it provides cytoskeletal stability by capping actin filaments and this activity is altered by phosphorylation during times of stress. Although the precise mechanisms of HSP27 on motility is unknown, the capping of actin filaments by HSP27 likely alters the polymerization of actin filaments and HSP27 phosphorylation changes what kinds of actin filaments are capped. When HSP27 was knocked down genetically, the result was reduced motility in a monolayer wound healing assay. HSP27 has also been immunoprecipitated with actin after heat shock demonstrating its colocalization with actin fibers.[164]

Heat shock proteins are divided into five families identified by size; HSP100, HSP90, HSP70, HSP60, and sHSP and the members phosphorylated by MK2 are the sHSPs (HSP27 and HSP25).[58,82,165] These are highly evolutionarily conserved proteins that are part of the alpha-crystallin family, which share a conserved 80–100 amino acid sequence.[166,167] These proteins have conserved β-sheet regions in their secondary structure that allows these sHSPs to form large oligomers in cells.[168,169] In addition to interacting with actin, the oligomers stabilize peptides and act as molecular chaperones that modulate protein degradation in an ATP-independent manner (induced by thermal, radiation, dehydration, redox, or other forms of stress).[170]

HSP27 exists in both the cytosol and nucleus and is found as monomers, dimers, and large oligomers. Nonphosphorylated HSPs have been shown to exist as monomers in vitro. However, the nonphosphorylated HSPs combine to form large oligomeric structures (~24mer) that bind to proteins, preventing excessive protein aggregation and refolding of denatured proteins.[171–173] When the cell is exposed to heat or other stressors the cell responds by phosphorylating the sHSPs causing a reduction in the oligomer size.[174] The phosphorylation alters the ability of the sHSPs to function as molecular chaperones and facilitate protein folding. Under these conditions, the sHSPs dissociate to form dimers that comprise the building blocks of the oligomers. In addition to the reduction in size, the location of the HSPs change when phosphorylated. Non-phosphorylated HSP27 is found predominantly in the cytosol, but migrates to the nucleus upon stress and phosphorylation.[175] There is evidence that these oligomers can form multimers with other sHSPs, altering their ability to chaperone.[176] In resting cells, the expression of sHSP is maintained in oligomers of different sizes at a certain ratio (38% <150 kDa, 14% 150–400 KDa, 52% 400 KDa). These ratios have been shown to fluctuate with different cellular states such as starvation, serum feeding, apoptosis, oxidative stress, and heat shock. With increased cellular stress, HSP27 forms more of the smaller complexes to increase the number of substrates it binds to and stabilizes. Alternatively, the smaller complexes may bind to different types of substrates in the nucleus. Another mechanism that HSP27 uses to facilitate cell survival is through its antioxidant properties. HSP27 can stimulate glucose-6-phosphate dehydrogenase by the small and highly phosphorylated HSP27 oligomers. It also maintains reduced glutathione and displays an iron-chelating activity helping to maintain a reduced oxidative state in the cell.[177]

As well as serving as regulators of motility, protein stability and aggregation the sHSP also have functions in normal development, cell signaling, and apoptosis.[178,179] HSPs interact with actin, in both their large oligomeric and smaller phosphorylated forms, altering the motility of the cell after cellular stimulation by factors' such as VEGF.[180] HSP27 has antiapoptotic functions through binding of its non-phosphorylated or phosphorylated oligomeric form to the apoptotic factors' cytochrome-C and DAXX. Although named as small molecules that respond to heat stresses, their functions have been implicated in motility, differentiation, apoptosis, heat tolerance, chaperoning, stress, and the immune response, and are a major effector molecule of MK2 signaling.[181]

LIMK1 is a serine/threonine kinase that regulates actin polymerization via phosphorylation and inactivation of the actin binding factor cofilin. This protein is involved in the VEGF stimulated actin remodeling by depolymerizing and severing actin filaments. The downstream effects lead to migration of endothelial cells and angiogenesis.[182] Kobayashi et al.,[83] showed that MK2 phosphorylated LIMK1 causing activation of the kinase, which resulted in stress fiber formation, cell migration and tube formation. This is an additional mechanism of MK2 to regulate cell motility and possibly angiogenesis.

In conjunction with HSP27, LIMK1 is phosphorylated by MK2 and activates various GTPases that function at the leading edge assembly of actin and cell migration.[83,183] LLIMK1 was shown to act in parallel with HSP27 to cause actin rearrangements, by affecting the actin depolymerizing protein cofilin to increase cell motility after stimulation

by bone morphogenic proteins.[184] MK2 knockdown in endothelial cells reduced VEGF induced migration, actin formation and tubule formation.[83]

The lymphocyte specific protein 1 (LSP1) gene encodes an intracellular F-actin binding protein and is expressed in lymphocytes, neutrophils, macrophages, and endothelium.[185] The function of the molecule is believed to regulate migration and chemotaxis by polarizing F-actin.[186] MK2 phosphorylates LSP1, resulting in the colocalization of LSP1 with polarized F-actin at the leading edge of polarized neutrophils, contributing to the directionality and polarization of migrating cells.[84]

Capping protein (CP) binds to the barbed head of fast-growing actin regulating its assembly by preventing addition or removal of actin subunits as the dynamic actin remodels cellular structure.[187] CapZ-interacting protein (CAPZIP) is a binding protein that is localized at the membrane of cells where it can bind to CP and regulate its function. CAPZIP itself has several phosphorylation sites that regulate its function and were found to be phosphorylated by MK2 after osmotic shock. While the specific role of CAPZIP is still unknown, phosphorylation of CAPZIP caused dissociation from the CP complex. Therefore, the stress-induced phosphorylation of CAPZIP may regulate the ability of F-actin-CP to remodel actin filament assembly.[87]

Reticulon 4 (Isoform B) or Neurite outgrowth inhibitor protein B (NOGO-B), is a protein from the reticulon family of proteins that were originally found to inhibit axonal regeneration in the CNS. Since they have been found to function in endothelial cells, vascular smooth muscle cells and cells of the immune system. It has been shown to be a modulator of vascular remodeling, promoting the migration and lipid synthesis of endothelial cells but inhibits the migration of vascular smooth muscle cells. NOGO-B promotes macrophage homing and functions as a cytokine in angiogenesis, arteriogenesis and tissue repair.[188] It also mediates ICAM1 induced transendothelial migration of leukocytes such as monocytes and neutrophils in acute inflammation.[189] The protein of NOGO-B was found to be phosphorylated by MK2, although how it modulates cellular function by this mechanism is not understood.[85]

Ribosomal Protein S6 Kinase (RSK) acts as a downstream kinase of the MAPK ERK (MAPK1/ERK2 and MAPK3/ERK1) and mediates mitogenic and stress-induced activation of several transcription factors through phosphorylation. The enzyme also regulates translation, and mediates cellular proliferation, survival, and differentiation by modulating mTOR signaling.[190] However, in LPS-stimulated dendritic cells RSK proteins were phosphorylated by TLR dependent mechanisms. Absence of MK2 prevented this phosphorylation and reduced dendritic cell macropinocytosis.[100] Therefore, in dendritic cells, MK2 can regulate TLR responses through crosstalk with kinases usually phosphorylated by pathways other than p38 MAPK.

Intermediate filaments (IF) are found preferentially expressed in epithelial cells that provide structural support for epithelial cells and respond to external stresses and transduce signals into the cells. The filaments' basic structure are coiled-coils of two different proteins formed from different types of keratins and other proteins that combine to produce six different

types of filaments (Types I–VI).[191,192] The filaments assemble into lateral tetramers with N and C termini that are non-helical, have vimentin caps, and can bind DNA. There are a wide range of IF molecules (~70) but they all show the same polymer characteristics to serve as building blocks for the filaments. MK2 was found to phosphorylate the IF proteins Keratin 18 and 20. Vimentin was also phosphorylated, but the phosphorylation site is unknown.[86,193] The IF proteins function as stress induced proteins where they are upregulated and phosphorylated in times of cellular stress. While the implications of phosphorylation are still unknown, it is suggested that MK2 contributes to the stress and cell cycle dependent reorganization of the keratin cytoskeleton, possibly altering the stiffness and mobility of the cells.

There are indications that the potential of MK2 to regulate motility is affected by its protein structure. Kotlyarov et al.,[59] demonstrated that MK2 KO reduced the formation of filopodia in macrophages, and reduced migration of fibroblasts and smooth muscle cells. The restoration of this required not only a functional kinase, but also the proline rich N terminus. It is not well understood what role the N-terminus plays in facilitating migration, but it is interesting to note that the splice variant, with a longer N-terminus that includes an additional phosphorylation, site was not able to phosphorylate HSP27 or support migration.[194] Another nonkinase activity altering the ability of MK2 to affect cell migration concerns SUMOylation, a unique posttranslational modification akin to ubiquitination that conjugates small ubiquitin-like proteins called SUMO (Small Ubiquitin-like MOdifier) to proteins, which was shown to affect the motility regulated by MK2. A SUMOlation site on MK2 was found (Lys339) to reduce the phosphorylation of HSP27 and its effects on actin polymerization.[195]

These findings along with the ability of MK2 to phosphorylate many molecules that are involved in cytoskeletal and actin stability demonstrate a significant role for MK2 in regulating motility. As the activation of p38 MAPK-MK2 pathway can occur via proteases like matrix metalloproteinase 2 (MMP2), that have a well-defined role in migration. It suggests that MK2 may be a key player in regulating migration and possibly metastasis.[196]

3.5 | Other cell responses

Outside of the more established role of MK2 in cellular functions (DNA damage response, transcription activation, inflammatory mediator production and migration), there are several emerging processes that the signaling of MK2 may control.

TNFα signaling can result in inflammation, proliferation, differentiation, survival, and cell death and activates the p38 MAPK-MK2 pathway.[197] The binding of TNFα to its receptor (TNFR1) forms a complex composed of TRADD, TRAF, RIPK1, and cIAP1/2, which is involved in the activation of NF-κB (Complex I) and activation of an immune response. Once the immune response is initiated many of the proteins in Complex I will reorganize to stimulate cell death. The second complex (Complex II) forms from RIPK1, RIPK3, TRADD, FADD, TRAF2, Caspase 8, and cIAP1/2, and stimulates apoptosis via caspase 8 or stimulating RIPK3, which leads to necroptosis.[198–200] The formation of Complex II depends on cytosolic RIPK1 and partially from the dissociation of RIPK1 from complex I and binding to FADD and caspase 8. MK2 phosphorylates RIPK1, reducing its affinity to bind to

FADD and inhibiting TNFα induced cell death.[102,201] Hence, MK2 controls inflammation by increasing cytokine expression and inhibiting RIPK1-dependent cytotoxicity.

Experiments in Drosophila have shown an antiapoptotic effect of p38 MAPK-MK2 by downregulating JNK mediated apoptosis in gut epithelium.[202] However, a proapoptosis effect of MK2 was seen in human lung microvascular endothelial cells stimulated with LPS, causing nuclear translocation of cleaved caspase 3 and apoptosis, which were both prevented by MK2 silencing.[203] The discrepancy in the pro/antiapoptotic activity of MK2 possibly relies on the strength of the stimuli and the cells and tissue of origin.

The ability of MK2 to affect cell motility may also contribute to a growing body of evidence that the kinase has some control over angiogenesis as implied by the LMK1 data referred to in the motility section above. IL-1β is a known angiogenic cytokine that stimulates inflammation and angiogenesis in vascular pathophysiological processes such as atherosclerosis and tumor neo-angiogenesis.[204] IL-1 stimulation assembles a proangiogenic signaling module consisting of caveolin-1, TRAF6, p38 MAPK, and MK2 in endothelial cells.[205] MK2 KO mice were used to examine the effect of MK2 on angiogenesis in mouse retina and the study revealed MK2 had no effect on physiological retinal angiogenesis but lowered arterial area and altered smooth muscle cell genetic profiles.[206] The authors concluded a cell specific mechanism of MK2 regulation of angiogenesis.

Two recent studies by the Yaffe group implicated MK2 in the role of angiogenesis stimulation by tumor resident macrophages. Using MK2 KO mice, Suarez-Lopez et al.,[207] showed that MK2 supported tumor associated macrophage polarization and transformation into proangiogenic M2-like macrophages. This ability was reversed by chemical inhibition of MK2. A follow-up study concluded that these effects occurred through MK2 regulation of the angiogenic factor CXCL-12/SDF-1 secreted by tumor associated-macrophages, in addition to MK2-dependent regulation of Serpin-E1/PAI-1 by several cell types within the TME.[208]

5-lipoxygenase (5LO) catalyzes the 1st step in the synthesis of leukotrienes, which are mediators of inflammation. They are released from activated leukocytes and exhibit several biological effects such as contraction of bronchial smooth muscles, stimulation of vascular permeability, and attraction and activation of leukocytes. Although necessary for a complete immune response, the pathophysiological role of leukotrienes has been realized by therapies that inhibit leukotriene function seen in patients suffering from asthma, allergies and chronic obstructive pulmonary disease.[209] The activity of 5LO depends on the concentration of it in the nucleus, the greater the concentration of 5LO in the nucleus, the greater the concentration of leukotriene released. The activity and the cellular location of the enzyme is modulated by phosphorylation. MK2 has been shown to phosphorylate the protein which alters the cellular location of 5LO by inhibiting its export from the nucleus.[95,96] This suggests a role of MK2 in potentiating leukotriene release by keeping the enzyme in its most active location and consistent with the role of MK2 potentiating the inflammatory response.

The mechanisms of MK2 on cell function can be broadly considered to be an adaptation to cell stress that activates immune cell function for clean up and repair and supports cell

survival through DNA checkpoint regulation and migration. Under conditions of stress, the regulation of autophagy would appear to be in line with the cellular programming of the MK2 pathway, as it is a method of fuel generation and protein recycling suitable for a damaged cell attempting to repair and survive. Autophagy is a cellular process where cellular proteins are broken down and recycled to provide energy and new substrates for growth. It is both a method of cellular recycling and clean up where damaged and dysfunctional proteins and organelles are removed, as well as a means for cells to survive and maintain energy when external nutrient sources are scarce.[210] Beclin-1 is an essential protein for autophagy and its complexing with Bcl-2/Bcl-xL stabilizes homodimerization of beclin-1 and prevents its interaction with PI3KC3 complexes inhibiting autophagy. Activation of beclin-1, and thus autophagy, involves its phosphorylation which disrupts its binding to Bcl-2. Starvation caused phosphorylation of Beclin-1 by MK2, disruption of its binding to Bcl-2, and initiation of autophagy.[116] Thus, MK2 may regulate the initiation of autophagy under certain conditions.

Phosphodiesterase 4A (PDE4) is part of the cyclic nucleotide phosphodiesterase (PDE) family and the PDE4 subfamily is encoded by 4 genes making 20 different isoforms. Long forms of PDE4 are regulated by phosphorylation that fine tunes their activity. PDE hydrolyzes the second messenger, cAMP, which is a regulator and mediator of many cellular functions including inflammatory signaling.[211] Therefore, the regulation of the cellular concentration of cAMP plays a key role in many important physiological processes. MK2 phosphorylates PDE4 with the resulting effect of attenuating the activity of PKA activation of PDE4. The attenuation of PKA activity on PDE4 causes cAMP levels to be maintained and fine tunes the ability of PKA to activate PDE4. Further, the phosphorylation of PDE4 by MK2 enhances its binding to p75NTR (p75 neurotrophin receptor) reducing the breakdown of fibrin.[97–99]

Ubiquitination is a method for cells to mark proteins for degradation, alter their cellular location, affect their activity, or for protein-protein interactions. UBE2j1 (ubiquitin-conjugating enzyme) is a noncanonical ubiquitin-conjugating E2 family of proteins. It is an ER-bound protein that has been shown to affect the proteosomal degradation of TCRα (T cell receptor), mutant CFTR (cystic fibrosis transmembrane conductance factor), TRAF2 (TNF associated factor 2), and MHC I. MK2 was shown to phosphorylate UBE2J1, and genetic silencing of the UBE2J1 reduced the release of TNFα from immortalized macrophages.[114] This implies the involvement of UBE2J1 in the activation of TNFα and MHC1 translation in LPS stimulated macrophages.

Centrosomal satellites (CS) are small granular clusters of proteins that cluster around centrosomes and traffic along microtubules. While their role is poorly defined, it is suggested that they act as mobile packages that facilitate cell processes. UV stress causes abrupt placement of CS constituents in the cytoplasm, one of which is the protein CEP131. Once CEP131 is released into the cytoplasm, MK2 phosphorylates the protein catalyzing the binding of CEP131 to 14-3-3 proteins leading to a rapid clearance of the protein and other moieties in the CS.[115] The implications of this effect are not well understood, but the actions of MK2 on protein released from CSs suggests a form of cytosolic clean up.

The TAB proteins are protein binding subunits that are involved in the signaling activation of Toll-like receptors, IL-1 and TNFα receptors. Upon receptor binding, molecules, such as TRAF6 promote the formation of the TAB-TAK complex resulting in autophosphorylation and activation of TAK1 that stimulates the activation of NF-κB and AP1 transcription factors.[212] TheTAB binding proteins are extensively phosphorylated in this process and MK2 phosphorylates TAB3 (transforming growth factor [TGF]-beta activated kinase 3 [MAP3K7]) possibly contributing to the activation and binding of TAB3 to the TAB/TAK process.[101] However, the mechanistic effect of this phosphorylation event is currently unknown.

4 | PHYSIOLOGICAL ROLES OF MK2

4.1 | Immune modulation

One of the main functions of the p38 MAPK-MK2 pathway is to regulate the immune response through the activation of transcription, and stabilization of mRNA, which increases the release of inflammatory mediators. Activation of the p38 MAPK-MK2 pathway can also be maintained by inflammatory cytokine signaling. For example, MK2 activation has been shown to increase TNFα levels,[197] and conversely TNFα can activate p38 MAPK and subsequently MK2.[89,102] This suggests that cytokine release can serve as a positive feedback signal for continued p38 MAPK-MK2 activation and could be one of several mechanisms for the maintenance of an inflammatory phenotype in a variety of biological or medical conditions.

The inflammatory function of MK2 was shown in experiments of $MK2^{-/-}$ mice where the splenic cells from these mice showed reduced release of the cytokines TNFα, IL-1β, IL-6, IL-10, and inter-feron gámma (IFNγ) compared to WT and these mice were resistant to LPS induced endotoxic shock, showing a 90% reduction in serum TNFα levels.[52,59] LPS-induced IFN-β and IL-10 gene expression is downregulated in MK2-deficient macrophages.[213] Later studies showed that in the absence of MK2, MK3 negatively regulates IFN-γ and delayed the nuclear translocation of NF-κB by delaying the ubiquitination and subsequent degradation of Iκ-Bβ.[214]

MK2 contributes to airway inflammation by signaling a Th2 response, as MK2 knockout mice are unable to mount localized Th2-type inflammation and development of experimental asthma. These effects were partially due to reduced endothelial permeability caused by a reduction in NF-κB mediated cytokines and mediators due to aberrant MK2 signaling. These animals displayed significant reduction in airway inflammation, mucus production and extracellular matrix (ECM) deposition. The reduced inflammation was associated with significantly decreased levels of many cytokines, (such as IL-5, IL-9, IL-13, and IL-25) in lung mRNA.[125]

The increased activation of MK2 is responsible for the elevated and post transcriptionally regulated TNFα protein expression in psoriatic skin (as described by the effect of MK2 on human kerati-nocytes).[215] When MK2 knockout mice were used to look at oxalone-induced lesional psoriasis it was found that skin inflammation was reduced and IL-1β, TNFα, and IFNγ expression were decreased in MK2 knockout mice compared with wild-type mice.[216]

However, later studies concluded that only certain chemically induced skin inflammation involves MK2.[217]

Examining MK2 KO mice in a model of experimental colitis indicated that the MK2 deletion in mice reduces colitis by dextran sodium sulfate (DSS).[218] Another study of colitis showed a reduction of IL-6, TNFα and reactive oxygen species (ROS) in DSS lesions from MK2 KO mice compared to control. The neutrophils from these mice had reduced capacity to produce ROS in response to stimulation, suggesting a role of MK2 in NADPH oxidase activity.[219] A role for MK2 in neutrophil ROS production was further supported by experiments examining liver reperfusion injury. The number of infiltrating neutrophils were reduced in MK2 KO mice compared to control, and NADPH oxidase phosphorylation was reduced in C5a stimulated mice from MK2 KO neutrophils.[220]

Microglia from MK2 KO mice showed reduced release of TNFα and macrophage inflammatory protein 1 after stimulation with LPS or amyloid peptides compared with wild-type microglia. Cortical neurons cocultured with these same factors and microglia were protected from microglial-mediated neuronal cell toxicity.[221]

The effects of MK2 on the inflammatory response is seen across an array of conditions including skin, colon, airway, and neuroinflammation. Due its pivotal role in stress induced cytokine release, it will likely be found to play a role in other inflammatory conditions as research continues.

4.2 | Wound healing and fibrosis

Wound healing is an integral part of self-repair following injury for complex organisms and can be characterized into four major phases: (1) hemostasis, (2) inflammation and innate and adaptive immune response, (3) epithelial and mesenchymal proliferation, (4) tissue remodeling. Immediately following hemostasis, growth factors and cytokines are released from damaged epithelial tissue and platelets, which lead to recruitment of diverse innate myeloid and adaptive immune response.[222,23,223] This immune component (i.e., macrophages, neutrophils, leukocytes) is necessary to limit pathogenic infection while further recruiting cells to initiate localized tissue fibrosis.[224–226] As the localized infection resolves, additional proangiogenic factors and growth cytokines are released, leading to epithelial and mesenchymal cell proliferation as inflammation begins to resolve in the wound.[227,228] Finally, the stromal component, consisting of endothelial cells, fibroblast and myofibroblasts, secrete new ECM proteins providing a new scaffold for a new epithelial layer to be generated.[226,228]

While wound healing is critical for normal tissue repair, this process can go awry following aberrant stimulation (i.e., infection, chronic inflammation). This can lead to myofibroblast over-stimulation, excessive ECM deposition and increased collagen production (as opposed to turnover) thereby resulting in the formation of fibrotic scarring.[229] Given that MK2 pathway regulates many of the same inflammatory factors that are triggered during chronic inflammation, its role in dysregulated tissue fibrosis and remodeling are currently being explored. However, conflicting results between different MEFs, murine animal models and human cell lines regarding the role of MK2 and myofibroblast activation have been

reported. One group had demonstrated that MK2 knockout MEFs upon TGFβ1 stimulation had reduced alpha-smooth muscle actin expression compared to wild-type MEFs.[230] This same group went on to demonstrate that MK2 disruption exacerbated fibrosis rather than ameliorate it. When mice lacking MK2 were exposed to bleomycin, increased collagen deposition, an exacerbated fibroblast response and reduced myofibroblast presence, was observed compared to wild-type mice. Their findings suggest that MK2 is necessary for myofibroblast development and for regulating tissue fibrosis.[231] The impact of genetic loss of MK2 in these murine models did not affect macrophage or neutrophil intravasation into wounds but did lead to substantially reduced inflammatory cytokine production and impaired wound healing. The impaired wound healing could be rescued by introducing MK2 wild-type macrophages highlighting the importance of intact MK2 in macrophages and its role in cutaneous wound healing.[232] Using a novel peptide-mimetic oligomer of HSP27 capable of selectively inhibiting MK2, Vittal and colleagues demonstrated that their pharmacologic agent could inhibit TGFβ1-mediated myofibroblast development similar to what Sousa and Liu had shown. However, using a similar lung-directed bleomycin fibrosis model, this group using their novel MK2 inhibitor could block the excessive collagen and fibronectin deposition in the lungs as well as reduce SMAD3, serpine1, IL-1β expression, and plasma IL-6 levels. This is a direct contrast to Liu's findings which demonstrated genetic loss of MK2 led to an exacerbation of the fibrotic response. Similarly, Wang et al.,[10] demonstrated using a novel reversible MK2 inhibitor (CDD-450) that it could selectively inhibit MK2, leading to a reduction in inflammatory cytokine activation from rheumatoid arthritis synovial fibroblasts. Furthermore, treatment with this drug could substantially reduce rat joint destruction in an inflammatory arthritis model. The observed discrepancy between the genetic and the pharmacologic models may suggest potential off-target interactions (pharmacologic), leading to reduced myofibroblast development and ECM deposition versus embryonic-physiologic compensation leading to an altered wound healing-fibrotic response in vivo (genetic). Additional work in this area is needed to improve our understanding of the temporal and cell compartmental contribution of MK2 inhibition on wound healing and fibrosis.

Investigations into the role of MK2 in remodeling and re-endothelialization after arterial injury in genetically modified mice in vivo showed MK2-deficiency nearly completely prevented hypertrophy and lumen loss after injury which was accompanied by reduced proliferation and migration of MK2-deficient smooth muscle cells. In addition, MK2-deficiency severely reduced monocyte adhesion to the arterial wall because of reduced expression of the chemokine ligands CCL2 and CCL5. MK2 KO also significantly reduced the infiltration of monocytes, neutrophils, and lymphocytes in the arterial wall. The authors concluded that deficiency of MK2 prevents adverse remodeling and promotes endothelial healing of the arterial wall after injury.[233] While the exact role for MK2 in wound healing is evasive its cellular functions suggest a regulatory influence on tissue repair and together with its effects on cell survival and the immune response, it is well suited to help aberrant cells survive hypoxia, acidosis and other stressors created in the microenvironment.

5 | MK2 IN CANCER

MK2 and its downstream cytokine, and transcription factor targets (i.e., EMT) have been associated with disease progression, metastasis, and poor survival outcomes in a variety of cancers including gastrointestinal, bladder, breast, lung and head and neck. Though the precise mechanisms by which MK2 mediates cancer progression, metastasis, and response to therapies is still not clear, pharmacologic or biologic inhibition of MK2 pathway signaling has shown promise in decreasing proliferation and slowing tumor progression in multiple cancer models.[11,13,14,234–237]

5.1 | Gastrointestinal cancers

MK2 and its downstream targets have been implicated in gastric and colorectal cancers in human and mouse models.[13,14,234,235,238] Human gastric tumor tissues had higher levels of MK2-mediated inflammatory cytokines compared to normal tissues, and high levels of MK2 in gastric cancer tumors were associated with a significantly increased rate of metastasis. Furthermore, levels of cytokines IL-1β, IL-6, and TNFα are higher in primary tumors that have metastasized to the lymphatic system compared to non-metastatic primary tumors.[234]

Inflammation in the colon contributes to higher rates of colorectal cancer among patients with inflammatory bowel diseases compared to healthy individuals.[239] Some data suggest that inflammatory cytokine signaling by way of MK2 may contribute to colorectal cancer development and progression.[13,14] In an azoxy-methane (AOM)/DSS mouse model of colon cancer, MK2 knockout mice had decreased levels of tumor derived inflammatory cytokines IL-1α, IL-1β, IL-6, and TNFα. Compared to control mice, MK2 knockout mice,[13] or mice treated with an MK2 inhibitor[14] had decreased tumor incidence and tumor volumes compared to control mice. These authors also found decreased cytokine response and decreased macrophage production in response to AOM/DSS treatment in MK2 knockout mice compared to wild-type mice.[14] These findings suggest that the reduction in MK2-mediated inflammatory signaling decreases tumor incidence and proliferation and points toward cytokine signaling as a potential mechanism by which MK2 mediates tumor growth in colorectal cancer models.

The *Apc* mutant mouse spontaneously develops several intestinal tumors and is often used as a model of colorectal cancer.[240] When crossed with MK2 knockout mice, *Apc* mutant mice had decreased tumor incidence and decreased tumor volumes compared to *Apc*/MK2 wild-type mice.[235] Furthermore, inhibition of MK2 in *Apc* mutant mice reduced tumor formation, abrogated tumor proliferation, and increased expression of the apoptotic marker cleaved caspase-3.[235] Similar findings in the AOM/DSS mouse model of colon cancer demonstrated that MK2 inhibition decreased tumor volumes and cytokine levels in vivo, and suppressed colon cancer cell invasion in vitro.[14]

An important stromal cell type which contributes to colon cancer tumorigenesis is the macrophage. Colon cancer cells when treated with an MK2 inhibitor had significantly decreased expression of the chemokines MCP-1, Mip-1α, and Mip-2α,[238] all of which are involved in macrophage recruitment.[241,242] Similarly, decreased chemokine levels were detected in colon cancer cell-derived tumors treated with MK2 inhibitor compared to

vehicle, and macrophage recruitment to the tumors was significantly decreased in MK2 inhibitor treated mice. Tumor chemokine levels were rescued in MK2 inhibitor-treated tumors upon the addition of macrophages. Furthermore, treatment with an MK2 inhibitor decreased tumor growth in vivo whereas treatment with MCP-1, Mip-1α, and Mip-2α increased tumor volumes. Interestingly, in tumors treated with MK2 inhibitor the addition of these chemokines rescued tumor growth.[238] These findings suggest that MK2 may regulate macrophage chemokine expression and macrophage recruitment in colon cancer. While this work demonstrates that functional MK2 is necessary for stromal-mediated tumorigenesis, it remains unknown whether overexpression of tumor MK2 can compensate, thereby allowing these tumors to continue growing

5.2 | Head and neck cancers

MK2 has recently been shown to be a potential mediator of disease in head and neck cancers.[12,243,244] In a small clinical study, high levels of phosphorylated MK2 (p-MK2) were associated with lower overall survival.[243] A larger tissue microarray analysis showed that in p16-negative disease, high levels of p-MK2 were associated with worse cancer-specific survival compared to patients with low p-MK2 levels.[12] Compared to normal tissues and noncancerous cell lines, levels of p-MK2 protein expression and expression of RNA binding proteins such as HuR are increased in head and neck squamous cell carcinoma (HNSCC) tumor specimens and in HNSCC cell lines.[244]

As mentioned previously, chronic-tonic activation of the p38-MK2 signaling axis through a continued positive inflammatory cytokine feedback can allow for a persistently inflamed, protumorigenic microenvironment. This in turn may drive tumor progression and/or resistance to treatment in head and neck cancers. However, the precise mechanisms by which MK2 potentially mediates disease progression and ultimately patient outcomes in HNSCC, have yet to be elucidated. There is evidence that cytokines contribute to tumor cell migration and invasion in HNSCC; and mRNA levels of several inflammatory cytokines (IL-6, IL-1α, IL-1β, TNFα) and angiogenic factors (HIF-1α, VEGF) are increased in cancer cells and tumor tissues.[244–246] The inflammatory cytokines IL-1α, IL-1β, IL-6, and TNFα are regulated in part by MK2.[10] High expression levels of IL-6 are associated with worse overall survival in oropharyngeal squamous cell carcinoma (OSCC) patients. A larger dataset of HNSCC patients confirmed the finding that high IL-6 expression was associated with worse overall survival.[247] High pretreatment blood IL-6 levels served as a predictor of worse survival outcomes and greater incidence of cancer recurrence in HNSCC patients.[248] In Cal27 HNSCC cells, overexpression of IL-6 exacerbates tumor growth and metastasis compared to nontransfected Cal27 cells,[249] whereas inhibition of IL-6 with the chemotherapeutic drug Bazedoxifene (BZA) sensitized HNSCC cells to cisplatin treatment and radiation therapy (RT) in vitro and in vivo.[250] The regulation of IL-6 by MK2, and the involvement of IL-6 in head and neck cancers suggests that cytokine activation and expression may be a mechanism by which MK2 is involved in cancer progression and poor clinical outcomes.

MK2 also drives expression of IL-1α, as seen by MK2 knockout mice having significantly decreased IL-1α compared to wild-type mice in a mouse model of colorectal cancer.[13]

Therefore, IL-1α is another cytokine that may drive cancer progression by way of the p38/MK2 pathway. High tumoral levels of IL-1α mRNA is associated with significantly reduced distant metastasis-free survival compared to tumors expressing low levels of IL-1α in HNSCC. Furthermore, tumors from patients with distant metastasis secreted significantly more IL-1α protein compared to patients without distant metastasis.[245] When cocultured with IL-1α-expressing OSCC cell lines, cancer associated fibroblasts (CAFs) express significantly greater levels of IL-1α receptor (IL-1αR), and CAFs treated with IL-1α proliferate significantly more than untreated CAFs and this proliferation was blocked upon treatment with an IL-1α neutralizing antibody.[251] Additionally, cocultured OSCC cell lines and CAFs secreted high levels of other cytokines including CXCL1 and IL-8, with the effect shown to be dependent upon IL-1α.[251] These findings suggest that IL-1α activity in tumor and stromal compartments in HNSCC may contribute to enhanced cytokine activity and disease progression in HNSCC.

TNFα is another cytokine whose synthesis is regulated by MK2 and is relevant in head and neck cancer progression and outcomes. High levels of plasma TNFα were correlated with increased incidence of cachexia,[252] and is associated with worse overall survival in head and neck cancer patients.[253] Treatment with TNFα resulted in migration and invasion in HNSCC cells in vitro.[254] TNFα synthesis is significantly decreased in MK2 knockout mice,[28,155,255] likely due to loss of inhibitory regulation of TTP. Conversely, in the presence of MK2 activity, MK2 phosphorylates TTP preventing its binding of the ARE of TNFα mRNA, allowing for TNFα protein translation.[103,144]

Inflammatory signaling by downstream targets of MK2 such as TNFα, IL-6, and IL-1β are involved in EMT.[256–259] Overexpression of EMT markers is associated with disease progression[260] and decreased survival in head and neck cancers. Zheng[254] and colleagues found that expression of both SNAI1 (also known as Snail) and SNAI2 (also known as Slug) was associated with worse survival in tongue cancers. Knockdown of either SNAI1, Slug, or both, decreased migration and invasion in Cal27 HNSCC cells. The Notch signaling pathway, known to be involved in EMT[200] and in migration and invasion of HNSCC cancer cells, was found to be upregulated at later disease stages, and was overexpressed in metastatic tissue from HSNCC patients.[261] Zhou[256] and colleagues found increases in the mesenchymal cell marker vimentin and decreased epithelial marker E-cadherin following treatment with TNFα in HNSCC cell lines. Furthermore, they found that TNFα stabilized the EMT transcription factor SNAI1 through activation of NF-κB. Similarly, TNFα treatment was found to stabilize Slug, also by way of NF-κB activation, and blocking NF-κB destabilized Slug.[124] Treatment of Cal27 cells with IL-6 induced increased expression of the EMT markers vimentin (VIM) and Snail; overexpression of IL-6 in Cal27 HNSCC cells resulted in enhanced migration in vitro, and increased locoregional (lymph node) and distant (lung) metastasis in vivo.[262] These data suggest a potential mechanism by which activation of MK2 contributes not only to tumor inflammation, but also to migration, invasion, and metastasis through cytokine induced EMT signaling in HNSCC.

Treatment resistance and loco-regional disease failure contribute to the poor long-term overall survival for patients with p16-negative, smoking associated head and neck cancer and remains a significant unaddressed problem.[263] RT is a mainstay in the treatment

for early stage head and neck cancers and in cases of locoregional disease combined chemoradiotherapy is often indicated to improve patient outcomes.[264] However, some data suggest that RT can activate the TME to promote tumor inflammation,[265] EMT[12,266] and rapid tumor repopulation,[266–268] which can drive locoregional and/or distant metastasis. Therefore, a better understanding of the mechanisms underlying radiation-induced treatment failure in head and neck cancer is needed.

In vitro and in vivo models of head and neck cancer demonstrate that radiation induced EMT may be a potential mechanism of tumor repopulation in head and neck cancers.[12,266] Irradiation of Tu167 and HN11 head and neck cancer cells significantly increased the EMT markers vimentin, ZEB2 and Snail, and chronic irradiation resulted in increased ZEB2, VIM, and TWIST1 gene expression.[266] This group found that following irradiation of either the tumor or its stromal compartment could induce rapid HNC tumor cell repopulation in vivo. Blockade with a hedgehog pathway inhibitor could abrogate this radiation-induced tumor repopulation effect.

RT activates the p38/MK2 pathway and mediates radiation-induced inflammation and EMT gene expression in head and neck cancers. RT has been shown to increase MK2 phosphorylation in established head and neck cancer cell lines in vitro and similarly in vivo in multiple head and neck PDX lines. Radiation therapy led to significant MK2-mediated gene expression of inflammatory cytokines (IL-1α, IL-1β, and IL-6), and the EMT markers (SNAl1, SNAI2, VIM). Both pharmacologic (i.e., PF3644022) and genetic (i.e. siRNA) inhibition led to an abrogation of the radiation-induced increases in cytokine and EMT gene levels.[12] Finally, treatment with combined RT and MK2 inhibitors decreased tumor volumes and increased survival in p16-positive and p16-negative PDX HNSCC models compared to monotherapy. Interestingly, levels of tumor-derived IL-1α, IL-1β, and IL-6 were also decreased with combined treatment compared to treatment with either RT or MK2 inhibitor alone[12] and may suggest these same inflammatory cytokines may stimulate tumor (re)growth in vivo similar to rectal cancer.[14] These findings suggest that MK2 is a mediator of radiation-induced inflammatory and EMT signaling in head and neck cancers.

5.3 | Breast, bladder, and other cancers

The p38/MK2 pathway has also been implicated in preclinical models of breast cancer and breast cancer metastasis, with some work showing that this involvement is particularly crucial in the TME. Alspach and colleagues demonstrated that inhibition of p38/MAPK factors in CAFs decreased the growth of HaCaT cells in coculture with CAFs.[269] Furthermore, they showed that inhibition of p38 in patient derived CAFs coinjected with breast cancer tumor cells inhibited tumor growth in vivo.[269] These findings suggest that specific interactions between the TME and the p38 pathway, and possibly downstream molecules such as MK2, contribute to tumor growth and metastasis in breast cancer models.

Despite the success of p38 inhibitors in preclinical models of breast cancer, the side effect profile of p38 MAPK inhibitors prevent their application for widespread clinical use. Therefore, downstream effectors of p38 MAPK, including MK2, have been examined in breast cancer models. In agreement with previous studies of p38 MAPK inhibition and decreased tumor progression, Murali and colleagues (2018)[11] inhibited p38 and found

significantly decreased bone and visceral metastasis in mouse models of breast cancer. Interestingly, however, they found that neither pharmacological inhibition nor short hairpin RNA (shRNA) knockdown of p38 MAPK resulted in decreased tumor growth. To determine if MK2 inhibition, rather than p38 inhibition, could similarly reduce metastasis and to examine the effect of MK2 on tumor proliferation, mice were treated with the MK2 inhibitor ATI-450. Inhibition of MK2 did not abrogate tumor growth in vitro or in vivo; similarly, MK2 knockdown in tumor cells did not decrease tumor cells growth in vitro or in vivo.[11] However, MK2 inhibition or MK2 knockdown did significantly decrease bone and visceral metastasis to a similar extent compared to pharmaceutical or genetic manipulation of p38 MAPK.[11] These authors conclude that because inhibition or knockdown of MK2 or p38 did not lead to decreased tumor growth but did decrease metastasis, the mechanism by which MK2 or p38 inhibition decreases metastasis resides in the activity of this pathway in the TME/stroma specifically.[11] That MK2 inhibition successfully decreased metastatic burden in this model is advantageous from a translational standpoint because it points toward the ability to avoid the toxicity associated with p38 MAPK inhibition while still achieving positive outcomes.

The p38 MAPK-MK2 pathway may also mediate bladder cancer proliferation and invasion. Kumar and colleagues[16] demonstrated that inhibition of p38 decreased bladder cancer cell proliferation and DNA synthesis. Furthermore, inhibition of p38 MAPK caused G2/M arrest and G1 arrest in the bladder cancer cell lines HTB9 and HTB5, respectively. To further elucidate the mechanism by which inhibition of p38 MAPK interfered with bladder cancer cell proliferation, these authors examined the roles of MK2 and MMPs known to be involved in tumor progression[270] and which are downstream of p38 MAPK in bladder cancer cell invasion and proliferation.[16] Inhibition of p38 MAPK inhibited MMP2 and MMP9 activity in HTB9 bladder cancer cells, and blockade of MMP2 decreased cancer cell invasion. Furthermore, MMP transcript stability was decreased in cells treated with a p38 MAPK inhibitor. In investigating whether MK2 played a role in bladder cancer invasion, Kumar and colleagues[16] showed that cells expressing an MK2 kinase-inactive mutant had significantly decreased MMP mRNA levels, and significantly decreased invasion compared to wild-type MK2 cells. These findings suggest that the inhibitory effects of p38 blockade on bladder cancer cell invasion are mediated through MMPs via MK2.

MK2 may also be relevant in hematologic cancers. High MK2 expression is associated with worse event-free and overall survival in multiple myeloma.[237] MK2 knockdown or overexpression significantly decreased and increased proliferation in multiple myeloma cell lines, respectively. When combined with common systemic treatments for multiple myeloma, MK2 inhibitor further abrogated cell death in vitro. Furthermore, mice treated with an MK2 inhibitor had increased survival compared to control mice.[237]

Common cancers harboring KRAS-mutations include lung, colorectal, and pancreatic.[271,272] These cancers have poor prognosis, and MK2 may play a role in tumorigenesis and cancer outcome. Using a computer software-based analysis, Dietlein and colleagues examined a panel of 96 cancer lines and identified those cell lines that would be most susceptible to combined checkpoint inhibition and MK2 inhibition. The software predicted that cell lines harboring KRAS mutations had the greatest sensitivity of dual checkpoint and

MK2 inhibition.[129] To experimentally confirm these analyses, KRAS mutant cell lines were treated with a Chk1 inhibitor, an MK2 inhibitor, or both; survival was significantly decreased in dual-treated cells compared to treatment with Chk1 or MK2 inhibitor alone. Furthermore, shRNA experiments also demonstrated that cell survival was significantly decreased when both Chk1 and MK2 were knocked down, but not when either was knocked down individually. These findings were confirmed in vivo in xenograft models of KRAS-mutant tumors with combined Chk1 and MK2 inhibition decreasing tumor volumes compared to monotherapy.[129]

MK2 may also mediate treatment resistance in pancreatic cancer. Kopper[273] and colleagues found that MK2 is a mediator of gemcitabine sensitivity in pancreatic cancer cell lines via the DNA damage response. Inhibition of MK2 decreased activation of the DNA damage response marker H2AX (histone variant 2AX) and resulted in increased cell proliferation in gemcitabine-sensitive pancreatic cancer cell lines. Similarly, MK2 has been shown to mediate radiation sensitivity in pancreatic cancer by way of DNA damage response mechanisms. Ataxia-telangiectasia group D-associated gene (ATDC, also known asTRIM29) is overexpressed in pancreatic cancer[274] and confers radiation and chemotherapy (gemcitabine) resistance in pancreatic cells lines, but knockdown of ATDC in xenograft models resulted in enhanced radiation sensitivity.[113] MK2 phosphorylates ATDC by way of upstream activation of the DNA damage response effector ATM (and its subsequent activation of p38 MAPK, and MK2 phosphorylation-site mutants) or knockdown of MK2 abrogated radiation resistance in ATDC overexpressing cell lines.[113]

Finally, there is evidence that MK2 may be involved in preventing the immune system from mounting a defense through supporting the expression of PDL1 and an immunosuppressive phenotype. In colorectal and lung tumors, KRAS associated ROS accumulation led to enhanced TTP phosphorylation at MK2 inhibitory sites. This suggested persistent MK2 activation inhibited TTP, which increased the stability of PDL1 mRNA and reduced antitumor activity.[275] It is therefore possible that in addition to modulating survival through checkpoint arrest, enhancing cytokine release and promoting migration, MK2 may also provide tumor cells protection from attack by the immune system.

5.4 | Potential therapeutic uses of MK2

Acute and chronic Inflammation both contribute to the pathobiology of many oncologic and non-oncologic human diseases.[1] While p38 MAPK is considered a central player in regulating inflammation, cell differentiation, proliferation, apoptosis, senescence and RNA biology, attempts to regulate p38 MAPK clinically have largely been unsuccessful.[3] However, an immediate downstream substrate of p38 MAPK is MK2. With its powerful effects on the inflammatory process, cellular migration, and cell survival, this protein appears to be an attractive target for intervention. However, to date, there is a substantial dearth of MK2 specific clinical inhibitors being explored in the oncologic domain.

The data is promising that targeting MK2 (pharmacologic or genetic) causes inhibitory effects on the release of cytokines that may aid the maintenance and growth of cancer tissues to stimulate a persistent inflammatory microenvironment. Since many of the cytokines released through MK2 actions support its own stimulation, it appears that MK2 may

function in a positive feedback loop exacer-bating inflammation. The consequence of aberrant MK2 pathway activation may promote metastasis through increased motility, cell survival and angiogenesis. Therefore, one might expect that reducing the persistent activity of MK2 would counteract the positive feedback and reduce tumor inflammation and growth. Several preclinical studies have demonstrated efficacy with research grade MK2 inhibitors thus providing proof of principle of MK2 as an attractive target for limiting tumor inflammation.

Reducing inflammation on its own is unlikely to inhibit tumor growth completely but the effect of MK2 on checkpoint arrest offers other avenues to combat tumor growth. The idea of SL of certain tumor models with adjuvant MK2 suggests a pathway into the clinic using combination therapies against p53 mutant tumors, which account for over 50% of all tumors.[276] It was shown in p53 mutant cancers that utilizing MK2 in combination with CHK1 inhibition caused death by mitotic catastrophe. Potentially using an MK2 inhibitor to further short circuit a tumors already compromised repair mechanism in combination with traditional chemotherapy and/or radiotherapy would be a novel way to destroy rapidly proliferating cells to improve therapeutic outcome.[126] Studies will hopefully discover more checkpoint molecules that could be used in conjunction with MK2 as a therapy. For example, in addition to CHK1, the DNA repair protein XPA has shown efficacy in enhancing the SL of MK2 in p53 negative tumors.[130] As we increase our knowledge of the cell cycle and DNA repair further, combined therapies either with traditional cytotoxic chemotherapies or novel targeted agents may enhance this killing depending on the molecular mechanisms of the tumor.

MK2 inhibition has also shown efficacy with radiotherapy in preclinical work demonstrating that the combination reduces tumor growth more than monotherapy indicating synergy.[12] It is possible that radiotherapy along with the combinatorial treatment of MK2 inhibition with CHK1 or XPA antagonists might improve responses even further. Certainly, radiotherapy is a very efficient method of introducing DNA damage and blocking cell cycle arrest after radiotherapy may improve current treatment modalities. Given the propensity of radiotherapy to generate fibrosis and the emerging roles of MK2 in wound healing, it is not clear whether it would exacerbate or reduce unwanted side effects. Conflicting reports leaves the role of MK2 in wound healing and collagen deposition uncertain.[10,231,277] A better understanding of MK2 function in fibrosis and wound healing is necessary to direct its use in treatments and whether it is better suited for aiding chemotherapy or radiotherapy.

The action of MK2 on migration and EMT gene changes implicate its ability to control metastasis by increasing its invasive potential through motility and differentiation. Because metastasis is the main cause of mortality in cancer finding treatments to block this hallmark of cancer biology is paramount. Preclinical models have demonstrated the potential benefit of blocking MK2 and reducing cancer metastases.[11,234] However, whether this is applicable to one group of cancers versus all cancers has not yet been realized. It is reasonable to assume that MK2 is likely to contribute globally to tumor migration, invasion and metastases and therapeutically targeting MK2 may be an important future clinical direction that will need to be explored.

6 | CONCLUSION

The effects of MK2 are diverse and are centered around responding to stress, facilitating survival, migration, repair, and regrowth. Many aspects of its function arise from its ability to modulate mRNA stability for cytokines and other factors that control cell survival. The observation that the stability mRNA for PDL1 begs the question of how many more mRNA moieties are regulated in this fashion and what that means for the mechanism of MK2 action.[275] The regulation of PDL1 expression by MK2 hints at a role for MK2 in immunosuppression and tumor survival leading to potential clinical applications in immunological tumors that have evaded killing mechanisms of the immune system. As we learn more about the functions of MK2 in inflammation, wound healing, and tumor growth we will be better served to understand how to deploy pharmacological intervention of MK2 in the patient setting. Much of this will also rely on the development of specific inhibitors of MK2 that have high efficacy and are well tolerated.

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No datasets were generated or analyzed during the current study.

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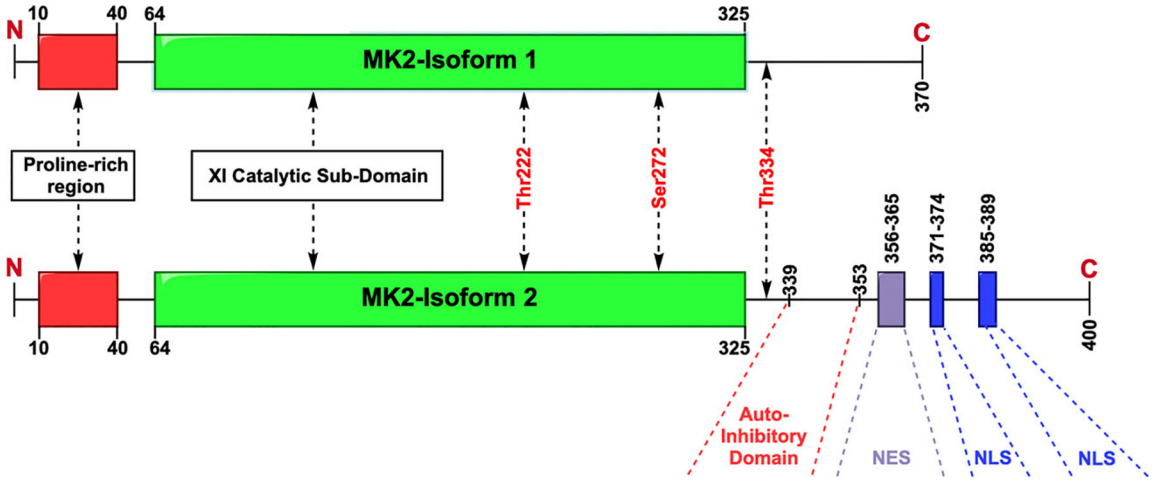

FIGURE 1.

A schematic diagram of the two known transcripts for MK2. Isoform 1 is the shorter version shown above which contains an N-terminus proline rich region, the catalytic domain and a truncated C-terminus. The longer isoform 2 also contains the N-terminus proline rich region and the catalytic domain but also includes an auto-inhibitory domain, nuclear export sequence (NES), and two nuclear location sequences (NLS). The sites phosphorylated by p38, which is required for activation, are labeled in red. MK2, mitogen-activated-protein-kinase-activated-protein-kinase-2

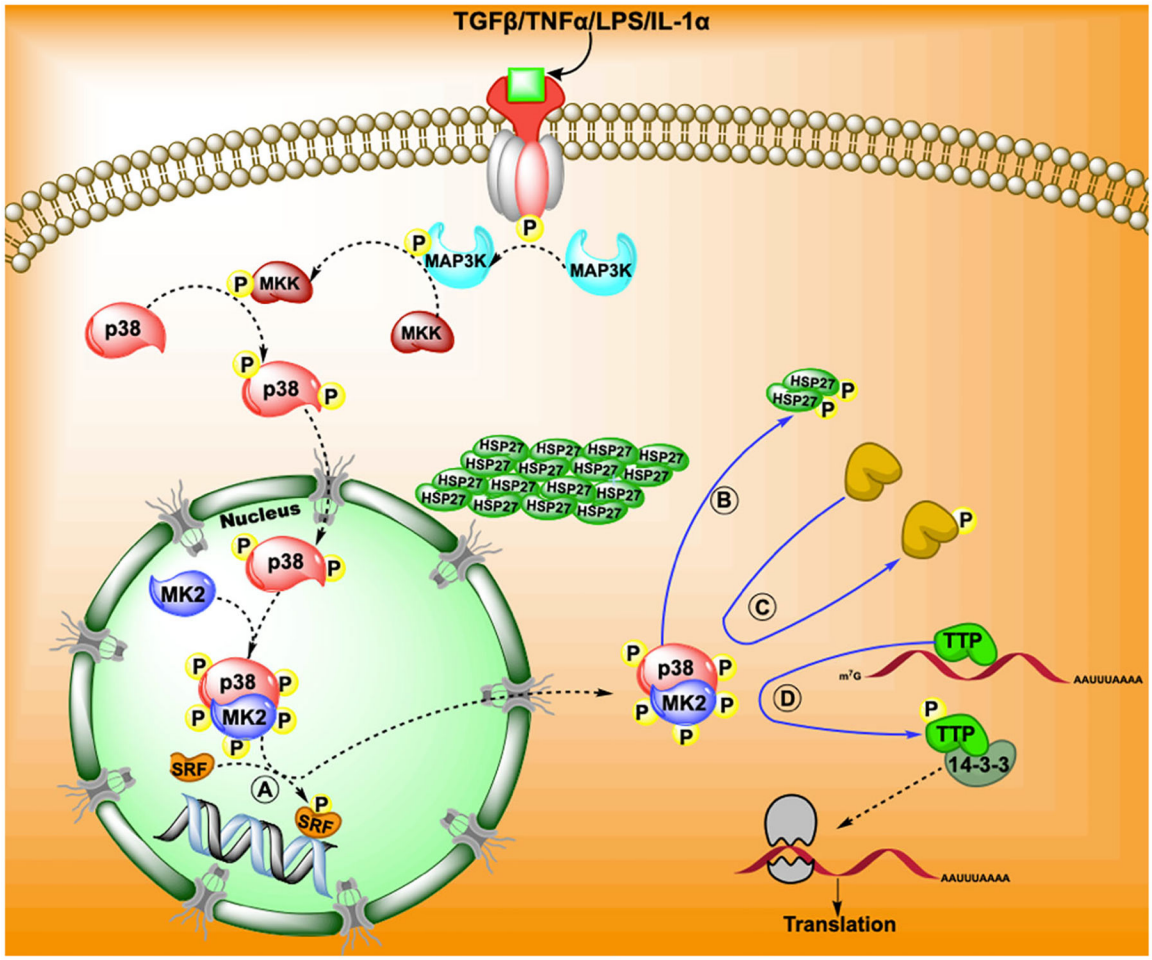

FIGURE 2.

A brief overview of the canonical pathway for p38 MAPK-MK2 pathway and the downstream effects following MK2 phosphorylation. The pathway may involve the binding of a cytokine or growth factor to a cell membrane receptor which results in a sequence of kinase chains through MAP3K to MKK to p38 MAPK. The phosphorylation of p38 MAPK stimulates its migration into the cytosol where it binds and phosphorylates MK2. Phosphorylated MK2 is then activated and may further phosphorylate (A) transcription factors and co-factors that initiate transcription. Phosphorylation of MK2 results in exposing its nuclear export sequence which facilitates the movement of p38 MAPK-MK2 complex into the cytosol. Here, MK2 further phosphorylates targets such as (B) heat shock proteins, (C) enzymes (e.g., 5-lipoxygenase) and (D) binding proteins and chaperones (TTP or 14-3-3) to elicit responses. The figure shows that the migration of MK2 and thus p38 are required for their full function

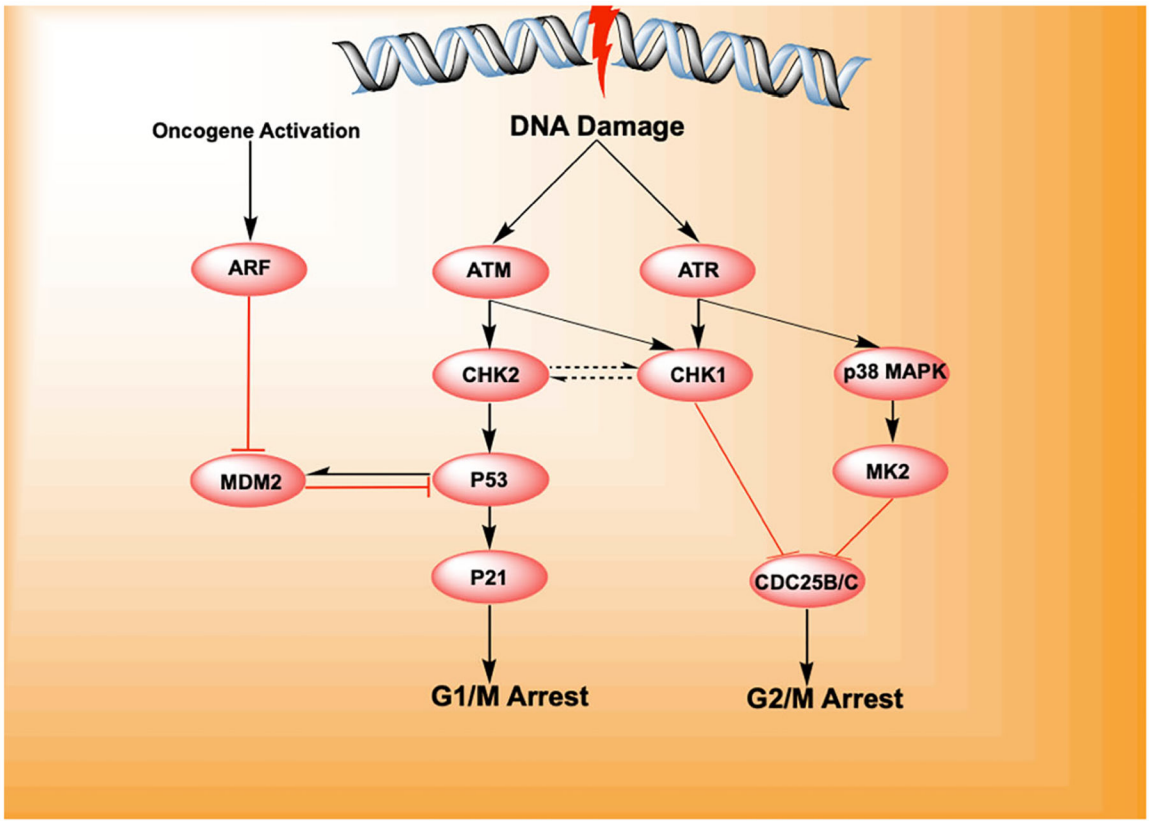

FIGURE 3.

DNA damage initiates the DNA damage response through the activation of the kinases ATM and ATR that activate the checkpoint proteins CHK1 and CHK2. These proteins initiate cell cycle arrest by activating p53 (which dissociates from its inhibitory factor (HDM2/MDM2) followed by p21 that causes arrest in the G1/M phase of the cell cycle. In the absence of p53, it was noticed that signaling through p38 MAPK activated MK2, which lead to the phosphorylation of the CDC25 phosphatases arresting the cell cycle in the G2/M checkpoint. Cancers with inactive p53 were susceptible to death by mitotic catastrophe when exposed to DNA damage in the presence of CHK1 and MK2 inhibition.[119]

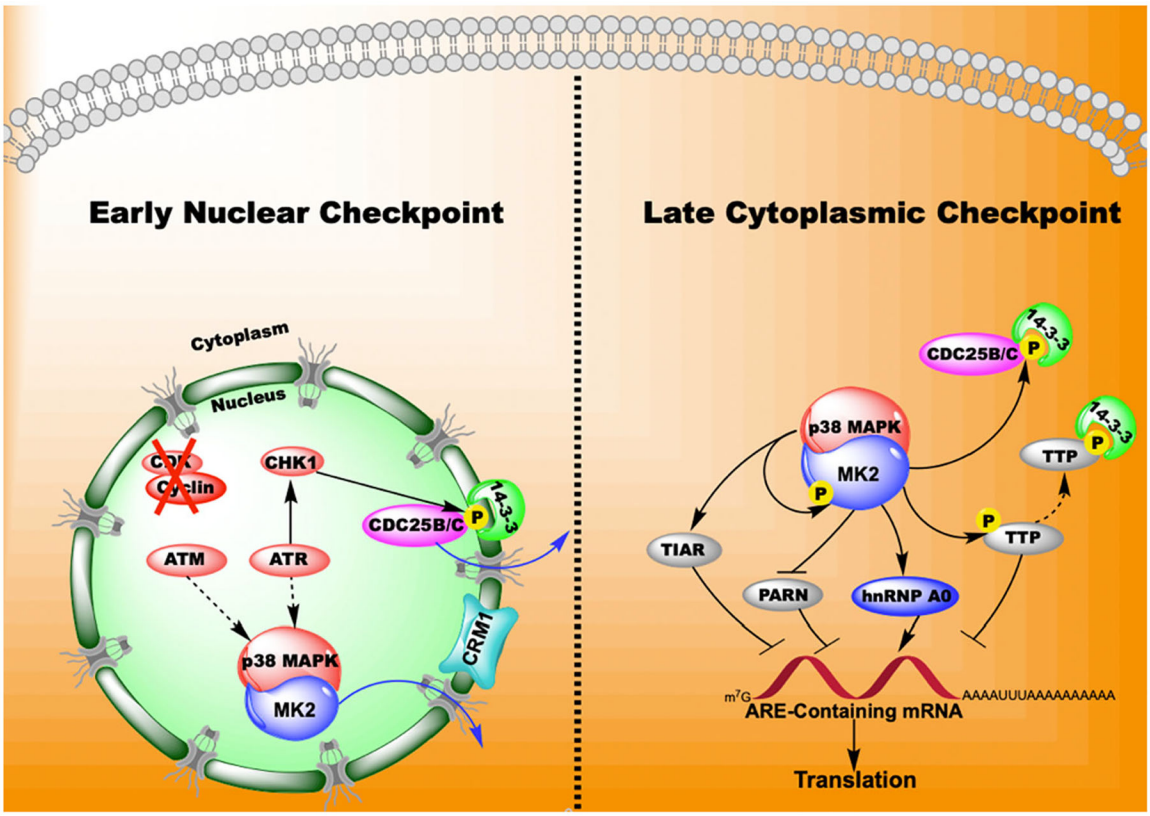

FIGURE 4.

MK2 regulates nuclear factor kappa B (NF-κB) transcription by altering the location of p38 MAPK. When p38 MAPK is activated, it translocates to the nucleus and regulates NF-κB activity through phosphorylating MSK1. MSK-1 activation initiates IF-κB transcription and the translocation of p65 out of the nucleus preventing NF-κB gene transcription. However, MK2 activity removes p38 MAPK from the nucleus, separating it from MSK-1 and preventing the inhibitory actions MSK-1 on NF-κB activity.[125]

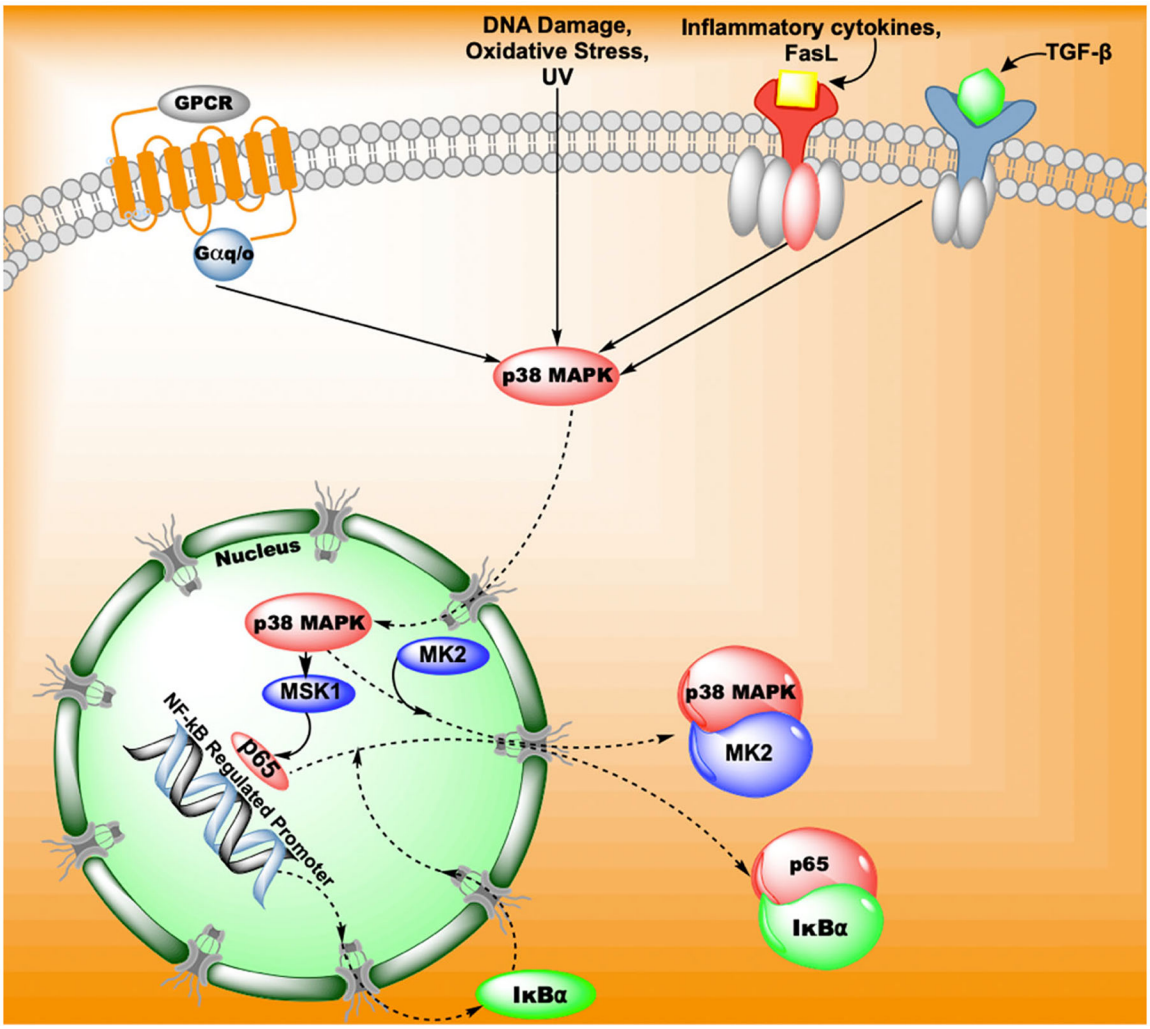

FIGURE 5.

p38 MAPK-MK2 pathway mediates the late cytoplasmic G2/M checkpoint through its actions on RBPs and 14-3-3 accessory proteins in the cytosol. ATM and ATR cause the activation of p38 MAPK that forms a complex with MK2 and translocates out of the nucleus. At this stage, CHK1 phosphorylates 14-3-3 and CDC25 proteins initiating arrest at the G2/M checkpoint. In the cytoplasm, MK2 phosphorylates PARN, hnRNP A0, TTP and 14-3-3 proteins causing the stabilization of mRNA and the subsequent transcription of genes such as GADD45α that maintain the checkpoint status. The phosphorylation of 14-3-3 also maintains the sequestration of CDC25B/C contributing to the arrest at G2/M phase.[121]

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TABLE 1

The known phosphorylation substrates of MK2

Molecule name	Function of MK2 phosphorylation	Phosphorylation site	Reference
HSP25/HSP27	Protein Stabilization, chaperoning and motility	HSP25-Ser15 Ser86	Stokoe et al. (1992)[53]
		HSP27-Ser15 Ser78 Ser82	Rouse et al. (1994)[82]
LIMK1	Cell motility	Ser323	Kobayashi et al. (2006)[83]
LSP1	cell motility	Ser243	Wu et al. (2007)[84]
NOGO-B	Motility	Ser107	Rousseau et al. (2005)[85]
KRT18, KRT20, Vimentin	Cell structure and motility	Keratin 18 (Ser52) and 20 (Ser20)	Menon et al. (2010)[86]
RCSD1/CAPZIP	Motility	Ser179 and Ser244	Eyers et al. (2005)[87]
SRF	Transcription factor	Ser103	Heidenreich et al. (1999)[88]
SRC-3	Transcription cofactor	Ser857	Shrestha et al. (2020)[89]
MRTF-A	Transcription cofactor	Ser312 and Ser333	Ronkina et al. (2016)[90]
CREB	Transcription factor	Ser133	Tan et al. (1996),[91] Iordanov et al. (1997),[92] Faust et al. (2012)[93]
HSF1	Transcription factor	Ser121	Wang et al. (2006)[94]
ALOX5	Immune response	Ser271	Werz et al. (2000),[95] Flamand et al. (2009)[96]
PDE4A	Cell signaling, immune response	Ser147	MacKenzie et al. (2011),[97] Houslay et al. (2017),[98] (2019)[99]
RPS6KA3	Cell signaling	Ser386	Zaru et al. (2007)[100]
TAB3	Cell signaling	Ser506	Mendoza et al. (2008)[101]
RIPK-1	Signaling and cell death	Ser321	Jaco et al. (2017)[102]
ZFP36/TTP	RNA binding protein	Ser52 and Ser178	Mahtani et al. (2001),[103] Ronkina et al. (2019)[104]
HNRNP A0	RNA binding protein	Ser84	Rousseau et al. (2002)[105]
NELFE	RNA binding protein	Ser51, Ser115, and Ser251	Borisova et al. (2018)[106]
RBM7	RNA binding protein	Ser136	Tiedje et al. (2015)[107]
PABPC1	RNA binding protein	unknown	Bollig et al. (2003)[108]
Dazl	RNA binding protein	Ser65	Williams et al. (2016)[109]
14-3-3ζ	Accessory binding protein	Ser58	Powell et al. (2003)[110]
PARN	mRNA stability and cell cycle control	Ser557	Reinhardt et al. (2010)[87], Duan et al., 2020)[111]
CDC25B, CDC25C	Cell cycle control	Ser169, Ser249, Ser323, Ser353 and Ser375	Lemaire et al. (2006)[112]
HDM2/MDM2	Cell cycle and DNA repair	Ser157 and Ser166	Weber et al. (2005)[51]

Molecule name	Function of MK2 phosphorylation	Phosphorylation site	Reference
ATDC/TRIM29	Cell signaling	Ser550	Wang et al. (2014)[113]
UBE2J1 ubiquitin conjugating enzyme	Posttranslational modification	Ser184	Menon et al. (2013)[114]
CEP131	Protein stability	Ser47 and Ser78	Tollenaere et al. (2015)[115]
Beclin-1	Autophagy	Ser90	Wei et al. (2015)[116]
RSK	macropinocytosis	Ser386	Zaru et al. (2007)[100]

Note: Each protein listed is confirmed to have sites phosphorylated by MK2.

Abbreviations: LSP1, lymphocyte specific protein 1; SRC-3, steroid receptor coactivator 3; SRF, serum response factor.