Clinical Cancer Research

Tumor Suppressor *CHK2*: Regulator of DNA Damage Response and Mediator of Chromosomal Stability

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Abstract

CHK2 is a multiorgan tumor susceptibility gene that encodes for a serine/threonine protein kinase involved in the response to cellular DNA damage. After ATM-mediated phosphorylation, the activated Chk2 kinase can act as a signal transducer and phosphorylate a variety of substrates, including the Cdc25 phosphatases, p53, PML, E2F-1, and Brca1, which has been associated with halting the cell cycle, the initiation of DNA repair, and the induction of apoptosis after DNA damage. In addition, recent work has revealed another, DNA-damage–independent function of Chk2 during mitosis that is required for proper mitotic spindle assembly and maintenance of chromosomal stability. This novel role involves a mitotic phosphorylation of the tumor suppressor Brca1 by the Chk2 kinase. On the basis of its role during DNA damage response, Chk2 has been suggested as an anticancer therapy target, but given its recently discovered new function and its role as a tumor suppressor, it is questionable whether inhibition of Chk2 is indeed beneficial for anticancer treatment. However, investigators may be able to exploit the loss of *CHK2* in human tumors to develop novel therapies based on synthetic lethal interactions. *Clin Cancer Res; 17(3); 401–5. ©2010 AACR.*

Background

DNA damage checkpoint

To maintain genome integrity, eukaryotic cells have evolved signaling pathways that are activated in response to genotoxic damage. These so-called checkpoint pathways halt the cell cycle to provide extra time for DNA repair or, if the damage cannot be repaired, to induce apoptosis (1). Failure to respond properly to genotoxic insults inevitably results in an accumulation of genetic alterations, which is directly associated with tumorigenesis. The DNA damage checkpoint pathway involves the function of the checkpoint kinase Chk2 (also designated as hCds1 or Chek2) and the structurally distinct but functionally similar Chk1 kinase (2).

Chk2 kinase functions in the DNA damage response pathway

Depending on the type of DNA damage that occurs, the Chk2 and Chk1 kinases are phosphorylated and thereby activated by the ataxia telangiectasia mutated (ATM) or ATM- and Rad3-related (ATR) kinases, respectively. These sensor kinases are recruited to DNA strand breaks by DNA damage sensor complexes, the so-called Mre1-Rad50-Nbs1 (MRN) and ATR-interacting protein (ATRP) complexes. ATR mainly phosphorylates and activates Chk1 after single-strand breaks, whereas Chk2 is mainly activated by ATM in response to double-strand breaks, mediated by phosphorylation of threonine-68 of Chk2. After the initial phosphorylation of Chk2 by ATM, Chk2 homodimerizes and achieves its full activation by *trans*-phosphorylation of the threonine-383 and -387 residues within the activation loop of the kinase (Fig. 1; refs. 3, 4).

Once activated, Chk2 can phosphorylate several key substrates, including Cdc25C, Cdc25A, p53, Brca1, the promyleocytic leukemia protein (PML), and E2F-1, which is required to mediate cell cycle arrest, DNA repair, and apoptosis (2–4). Chk2 phosphorylates the dual-specificity phosphatase Cdc25C on serine-216, which promotes its binding to the 14–3-3 protein and results in its sequestration into the cytoplasm. Because Cdc25C is required to activate CDK1 at the G2/M transition in the nucleus, this leads to a cell cycle arrest in the G2 phase and protects cells from entering mitosis in the presence of DNA damage (5). Similarly, Chk2 phosphorylates the related CDK2 phosphatase Cdc25A, resulting in a cell cycle arrest in G1. In this scenario, Chk2 phosphorylates Cdc25A on serine-123, -178, and -292, which in turn promotes its binding to the $SCF^{\beta\text{-}TrCP}$ -ubiquitin ligase complex and causes its subsequent proteasomal degradation, preventing the activation of CDK2 at the G1/S transition (6).

Of interest, despite this reported importance of Chk2 for G1 and G2 cell cycle arrest, no gross effect on cell cycle arrest

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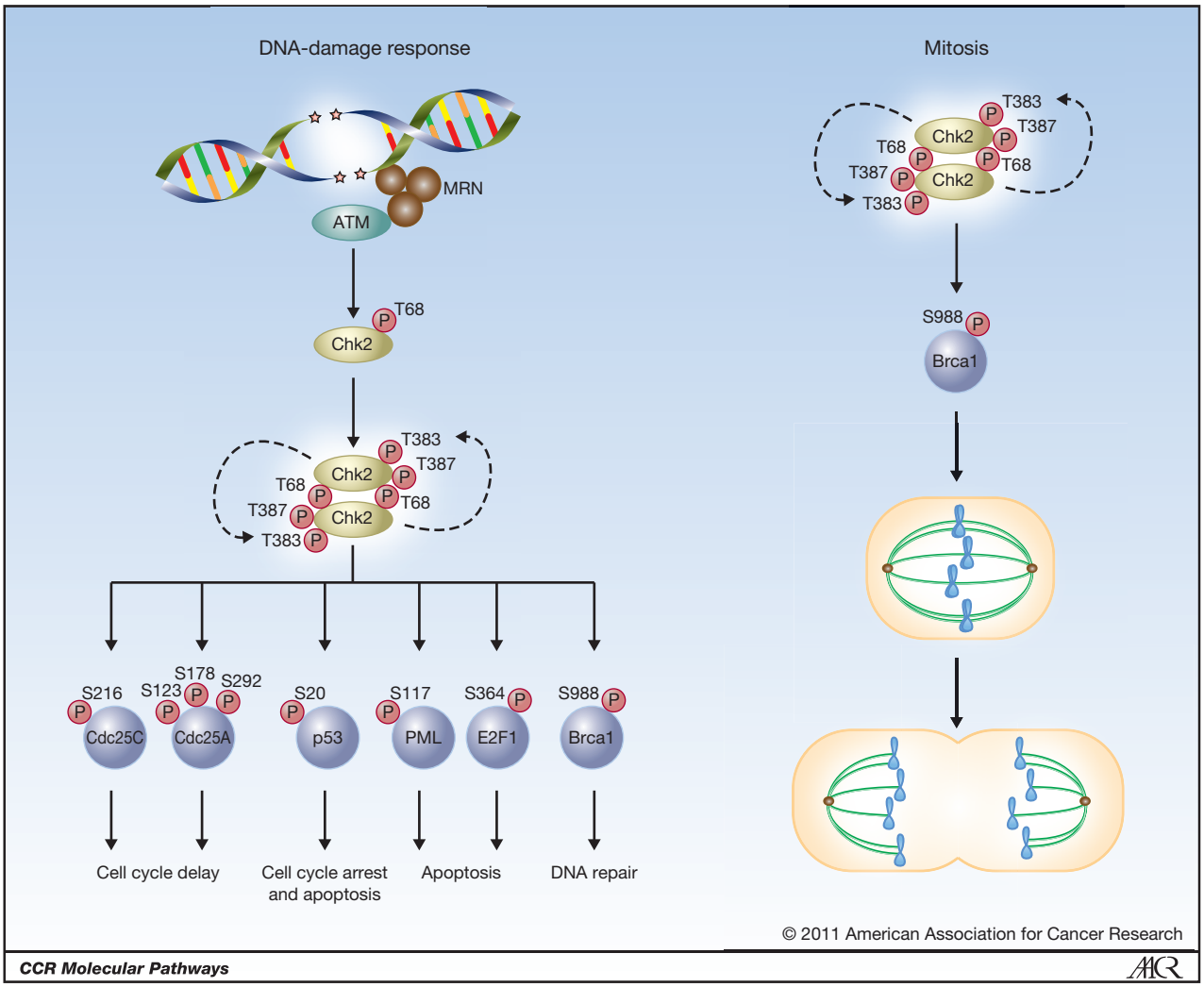

Figure 1. The role of Chk2 in DNA damage response and regulation of mitosis. Left panel: The Chk2 kinase is activated by the ATM kinase by phosphorylation of the threonine-68 residue in response to DNA double strand breaks. Chk2 achieves its full activation after homodimerization by *trans*-phosphorylation of the threonine-383 and -387 residues located within the activation loop. Subsequently, Chk2 can phosphorylate several key substrates, including Cdc25C (on Ser-216), Cdc25A (on Ser-123, Ser-178, and Ser-292), p53 (on Ser-20), PML (on Ser-117), E2F-1 (on Ser-364), and Brca1 (on Ser-988). These phosphorylations are required to mediate cell cycle delay, DNA repair, and apoptosis in response to DNA damage. Right panel: During mitosis and in the absence of DNA damage, the active Chk2 kinase can phosphorylate the tumor suppressor Brca1 on serine-988. This phosphorylation promotes the accurate assembly of a normal mitotic spindle, which is a prerequisite for faithful segregation of the sister chromatids and maintenance of chromosomal stability.

after DNA damage is observed in *CHK2*-deficient mice, suggesting that this role of Chk2 is not essential (7). Moreover, investigators have questioned the function of Chk2 in G1 and G2 in human colon carcinoma cells, where no effect on cell cycle arrest or the stability of Cdc25A is observed after homozygous deletion or siRNA-mediated depletion of *CHK2* (8, 9). A possible explanation for these observations is that the partially redundant function of Chk1 may share overlapping substrates, including Cdc25A and Cdc25C.

The tumor suppressor p53 has been reported to be another key target of Chk2 in response to DNA damage. In fact, studies in knockout mice showed that Chk2 phosphorylates p53 on serine-20, and that this phosphorylation disrupts the p53-MDM2 interaction leading to the stabilization and accumulation of p53 after DNA damage (10, 11). Chk2 was therefore implicated as a direct regulator of p53 and suggested to mediate p53-dependent cell cycle arrest and apoptosis after genotoxic damage. However, other studies using knockout mice or *CHK2*-deficient human cell lines challenged these results and showed no requirement of Chk2 for the stabilization of p53 after DNA damage (8, 12, 13). Thus, given these conflicting results, the role of Chk2 in regulating Cdc25 phosphatases or p53 is presently unclear; however, taken together, the results suggest that Chk2 is not essential for cell cycle arrest in response to genotoxic damage.

Role of Chk2 in DNA repair and apoptosis

In human cells, Chk2 appears to be involved in DNA repair by phosphorylating and regulating the tumor suppressor breast cancer 1 (Brca1). When DNA damage occurs, Chk2 phosphorylates Brca1 on serine-988, causing its dissociation from nuclear foci. The soluble and active Brca1 then mediates the error-free homologous recombination (HR) DNA repair pathway while repressing the error prone non-homologous end joining (NHEJ) (14–16). To facilitate DNA repair via HR, Brca1 forms a protein complex together with Brca2, which can directly interact with the Rad51 recombinase, a key component of the HR DNA repair pathway (17–19). Presumably, the regulation of Brca1 by Chk2 assists the switch from NHEJ to HR (15). However, this pathway operates only during S-phase and G2 when the DNA is duplicated and sister chromatids are available. Of interest, Brca1 also associates with DNA mismatch repair proteins, such as the Msh2-Msh6-complex (20), and Chk2 also interacts with Msh2 (21), suggesting a possible but as yet undefined involvement of Chk2 and Brca1 in DNA mismatch repair.

When DNA damage cannot be repaired, the damaged cell can initiate apoptosis, which may also be regulated by the Chk2 kinase. In fact, it has been suggested that by regulating p53, Chk2 is required for the induction of p53-dependent apoptosis (12). In addition, Chk2 may also support p53-independent apoptosis by phosphorylating the transcription factor E2F-1 on serine-364, which is associated with its stabilization, transcriptional activation, and the induction of apoptosis in a p53-independent manner (22). Moreover, Chk2 can also phosphorylate the tumor suppressor PML on serine-117, which promotes its pro-apoptotic activity in a p53-independent manner (23).

Chk2 is required for the maintenance of chromosomal stability and functions during mitotic spindle assembly

In addition to the established role of Chk2 after DNA damage, recent work from our laboratory revealed a new and DNA-damage–independent function of the Chk2 kinase in mitosis that is required for the maintenance of chromosomal stability (Fig. 1; ref . 24). This novel function of Chk2 may be of particular interest because chromosomal instability (CIN), which is defined as the perpetual gain or loss of whole chromosomes, is a major characteristic of human cancer and can directly contribute to tumorigenesis and tumor progression (25). Of importance, the loss of *CHK2* or impairment of its kinase activity is sufficient to induce CIN in diploid human somatic cells, which places *CHK2* in the squad of the very few genes associated with CIN in human cancer (24). Because chromosomal segregation defects take place during mitosis, it is conceivable that Chk2 could play an important role during mitotic cell division. In fact, Chk2 is required for the proper and timely assembly of the mitotic spindle apparatus, which is a prerequisite for both the accurate attachment of chromosomes to the mitotic spindle and the subsequent faithful segregation of sister chromatids onto the two daughter cells (24). Thus, *CHK2* is a key tumor suppressor gene that is involved in the proper assembly of mitotic spindles and the maintenance of chromosomal stability.

Of interest, the tumor suppressor protein Brca1 is a direct target of the Chk2 kinase and is phosphorylated on serine-988 not only after DNA damage but also during mitosis in the absence of damage. Intriguingly, this mitotic phosphorylation of Brca1 mediates the mitotic role of Chk2. Indeed, loss of *BRCA1* or impairment of its Chk2-mediated phosphorylation causes an improper mitotic spindle assembly and induces CIN in human somatic cells (24). In line with a possible mitotic role, Brca1 localizes to mitotic centrosomes, where it may regulate centrosome integrity and spindle assembly, possibly by regulating the ubiquitination of γ-tubulin (26, 27).

CHK2 alterations in human cancer

Several studies have identified *CHK2* as a multiorgan cancer susceptibility gene that is mutated in both somatic and hereditary human cancers, including breast, colon, prostate, and lung carcinomas, albeit at low frequencies (3, 28). In addition, investigators have reported a loss of the *CHK2* locus on chromosome 22q13 in breast, colorectal, ovarian, and brain tumors (29–31), and epigenetic silencing of *CHK2* expression in lung cancer (32). Point mutations at I157T and the deletion mutation 1100delC encoding a truncated Chk2 protein with a reduced or absent kinase activity were shown to be main mutations in human tumors, increasing the risk to develop breast and prostate cancers (33–35), as well as thyroid, bladder, kidney, ovarian, and colorectal cancers (36–38). Furthermore, germline mutations of *CHK2* have been found in families with Li-Fraumeni syndrome that do not harbor mutations in *TP53*, suggesting that Chk2 could act as an upstream regulator of p53 (39). However, *CHK2* mutations do not account for the cancer predisposition phenotype of Li-Fraumeni syndrome as originally thought (40), and concomitant mutations in *CHK2* and *TP53* have been reported in colon and breast cancer, arguing against an exclusive role upstream of p53 (41, 42). In support of this notion, the mitotic function of Chk2 required for maintenance of chromosomal stability also appears to be independent of p53 (24). Furthermore, a loss of *CHK2* was found in the majority of human lung adenocarcinomas (24). This result may be particularly important in light of the finding that lung adenocarcinomas were prominently induced after experimental induction of CIN in various mouse models (43).

Clinical-Translational Advances

Targeting the Chk2 kinase for anticancer therapy

On the basis of its reported functions during cellular DNA damage response, it has been suggested that inhibition of Chk2 might increase the therapeutic index of DNA-damaging drugs. Indeed, antisense inhibition of *CHK2* was

shown to enhance the apoptotic activity of γ-irradiation and treatment with the topoisomerase I inhibitor camptothecin (44). Similarly, Chk2 inhibition with siRNA or dominant-negative mutants was shown to enhance adriamycin-induced apoptosis in a colon carcinoma xenograft model by preventing the release of survivin from the mitochondria (45). According to these results, one might expect small-molecule inhibitors of Chk2, including NSC-109555, debromohymenialdisine (DBH), VRX0466617, and EXEL-9844, to also show therapeutic efficacy during anticancer treatment (46–49), and in fact several Chk2 inhibitors, such as AZD7762, PF447736, and XL844, have been evaluated in phase I clinical studies (48). Unfortunately, most Chk2 inhibitor compounds suffer from unspecificity and also inhibit the Chk1 kinase, which serves distinct functions in the G2 DNA damage checkpoint (50, 51). Thus, the anticancer efficacy of Chk1/Chk2 inhibitors may not be related to a sole inhibition of Chk2. In contrast to a possible role of Chk2 inhibition in enhancing chemotherapy responses, it has been shown that inhibition of Chk2 can lead to a protection from radio- or chemotherapy (46, 52), which may indicate that targeting of Chk2 may not be beneficial for anticancer treatment. Furthermore, given the latest results regarding the mitotic role of Chk2 (24), we should also consider the possibility that the inhibition of Chk2 is associated with an increase in chromosome missegregation, which may contribute to de novo tumorigenesis in response to therapy.

Treatment of *CHK2*-deficient human tumors

Despite the conflicting results regarding the therapeutic value of Chk2 inhibition, a key issue is whether the frequent loss of *CHK2* in human cancer, especially in lung adenocarcinomas (24), can be exploited for therapeutic purposes. One possible approach may be to use poly-(ADP-ribose) polymerase (PARP) inhibitors to prevent the repair of DNA single-strand breaks via base excision repair and instead trigger the Brca1-mediated HR pathway of DNA repair. If both repair pathways are suppressed, cells cannot respond to DNA damage any more and undergo apoptosis. This concept, known as "synthetic lethality," was validated by the use of small-molecule inhibitors of PARP (KU0058684 and KU0058948) that selectively inhibit the cell growth of *BRCA1*-deficient cells (53). Moreover, because the function of Brca1 in HR requires its phosphorylation by Chk2 (15), PARP inhibitors can result in synthetic lethality with *CHK2* deficiency (54). Thus, lung adenocarcinomas, which frequently show a loss of *CHK2*, might particularly benefit from treatment with PARP inhibitors. This notion remains to be tested in clinical trials.

Given the novel function of Chk2 in mitotic spindle assembly, antimitotic drugs that target the dynamics of microtubules might also exhibit synergistic effects with *CHK2* deficiency in cancer cells. These drugs include taxanes, epothilones, and *Vinca* alkaloids, and are frequently used for anticancer treatment (55). It would be of great interest to investigate whether these drugs show an enhanced efficacy in *CHK2*-deficient cancer cells that already show an impaired formation of mitotic spindles. This attractive hypothesis should be addressed in future experiments and possibly in clinical trials.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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