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Review

Beyond ATM: The protein kinase landscape of the DNA damage response

Ariel Bensimon [a,b,*], Ruedi Aebersold [a,b,c], Yosef Shiloh [d,*]

[a] Institute of Molecular Systems Biology, Department of Biology, ETH Zurich, Switzerland
[b] Competence Center for Systems Physiology and Metabolic Diseases, ETH Zurich, Switzerland
[c] Faculty of Science, University of Zurich, Switzerland
[d] The David and Inez Myers Laboratory for Cancer Genetics, Department of Human Molecular Genetics and Biochemistry, Sackler School of Medicine, Tel Aviv University, Tel Aviv 69978, Israel

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ABSTRACT

The DNA of all organisms is constantly subjected to damaging agents, both exogenous and endogenous. One extremely harmful lesion is the double-strand break (DSB), which activates a massive signaling network – the DNA damage response (DDR). The chief activator of the DSB response is the ATM protein kinase, which phosphorylates numerous key players in its various branches. Recent phosphoproteomic screens have extended the scope of damage-induced phosphorylations beyond the direct ATM substrates. We review the evidence for the involvement of numerous other protein kinases in the DDR, obtained from documentation of specific pathways as well as high-throughput screens. The emerging picture of the protein phosphorylation landscape in the DDR broadens the current view on the role of this protein modification in the maintenance of genomic stability. Extensive cross-talk between many of these protein kinases forms an interlaced signaling network that spans numerous cellular processes. Versatile protein kinases in this network affect pathways that are different from those they have been identified with to date. The DDR appears to be one of the most extensive signaling responses to cellular stimuli.

1. The protein kinase core of the DNA damage response

The genomes of all living organisms constantly suffer deleterious attacks. Of the many types of DNA lesions, one the most harmful is the double-stranded break (DSB). DSBs are caused by exogenous agents such as ionizing radiation (IR) and radiomimetic chemicals, or by endogenous agents, mainly reactive oxygen species. DSBs are also generated during the normal processes of meiotic recombination and V(D)J recombination [1]. Failure to repair DSBs, or their misrepair, may result in cell death or chromosomal rearrangements, including deletions and translocations, which in turn may promote neoplastic transformation. In order to cope with this lesion, cells activate a complex network of interacting pathways that lead either to damage repair and resumption of the normal cellular life cycle or to programmed cell death. This network, called the DNA damage response (DDR), coordinates the activation of cell cycle checkpoints, the appropriate DNA repair pathways, and numerous other responses [2].

Timely cellular response to DSBs requires that the DNA damage signal be conveyed swiftly and precisely to numerous processes across the cell. The signal transduction mechanism that disseminates the DNA damage alarm begins with sensor proteins that sense the damage or chromatin alterations emanating from it and mediate the activation of transducers, which in turn convey the alarm to numerous downstream effectors involved in specific pathways [2]. The primary transducer of the DSB alarm is the serine–threonine protein kinase ataxia telangiectasia mutated (ATM), which phosphorylates numerous key players in the various branches of the DDR [3,4].

ATM is a member of the phosphoinositide 3-kinase (PI3K)-related protein kinase (PIKK) family, which also includes ATM and Rad3-related protein (ATR), the catalytic subunit of DNA-dependent protein kinase (DNA-PKcs), hSMG1, and mammalian target of rapamycin (mTOR) kinases [5]. DNA-PK is a major player in the repair of DSBs induced by genotoxic stresses or during V(D)J recombination, via non-homologous end-joining (NHEJ) [6,7]. ATM and ATR transduce a complex signaling response to various stimuli, but most prominently to damage to DNA. ATM has been documented primarily as a critical component of the response to DSBs, but has recently emerged also in the general response to reactive oxygen species [8–12]. ATM is largely nuclear, but there is evidence that a cytoplasmic fraction of ATM is involved in

* Corresponding authors. Address: Institute of Molecular Systems Biology, Department of Biology, Eidgenössische Technische Hochschule Zürich, 8093 Zürich, Switzerland. Fax: +41 44 6331051 (A. Bensimon), +972 3 6407471 (Y.Shiloh).
E-mail addresses: Bensimon@imsb.biol.ethz.ch (A. Bensimon), yossih@post.tau.ac.il (Y. Shiloh).

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various pathways, some related to the DDR and others involved in metabolic processes [9,13–18].

ATR is activated mainly by single-stranded DNA (ssDNA) ends that are generated following the induction of DNA adducts or during the processing of DSBs or collapsed replication forks. Their length as well as ssDNA–dsDNA junctions are key factors in ATR's activation [19–23]. Evidence of ATR being activated by other mechanisms independent of ssDNA has also been obtained [24].

ATM and ATR show functional redundancy and share overlapping substrate specificity; both preferentially phosphorylate serine or threonine residues that are followed by glutamine (''SQ/TQ'' motifs) in their substrates [3,4,19,20,24,26]. Matsuoka et al. [27] identified more than 700 proteins containing the ATM/ATR phosphorylation motif (SQ/TQ) that are inducibly phosphorylated in response to IR. We assume that most of these potential substrates will turn out to be physiological. One reason for this multitude of substrates is that ATM phosphorylates many targets within each ATM-dependent pathway, and fine-tunes various processes by modulating a number of pathways within the same process [28]. A typical example is the DNA damage-induced activation and stabilization of the p53 protein, which ATM modulates by phosphorylation of p53 itself as well as many of its regulators [28–35]. Importantly, some of the ATM/ATR substrates are themselves protein kinases that target downstream effectors, most notably CHK1 and CHK2 [36–38].

The functional relationship between ATM and ATR in the DSB response is complex. It is generally assumed that after the rapid activation of ATM in response to DNA damage and the subsequent phosphorylation of its numerous substrates, ATR is triggered and maintains phosphorylation of some of these substrates [28]. Recently, it was shown that the ATM–ATR switch is driven by the length of ssDNA ends formed as a result of end resection at DSB sites [21]. In response to UV or replication stress, ATR mediates downstream activation of ATM [39]. On the other hand, during the S and G2 phases of the cell cycle, the response of ATR to DSBs that are not part of the replication process is dependent on ATM [40,41]. ATM is involved in the activation of ATR, at least by phosphorylation of the ATR activator topoisomerase II binding protein 1 (TopBP1) [42]. The downstream target kinases of ATR and ATM, CHK1 and CHK2, are also activated as a consequence of the cross-talk between ATM and ATR. Both ATM and ATR are required for CHK1 activation in response to IR, and both are required for CHK2 activation in response to UV and replication stress [39,41,43,44], since CHK2 cannot be activated by ATR alone [45–47]. CHK1 phosphorylation and subsequent activation in cells is ATR-dependent, and ATR was recently shown in a reconstituted system to directly phosphorylate CHK1 [48,49]. ATM can activate directly CHK2, but the full activation of CHK2 is a multi-step process that also requires polo-like kinase 3 (PLK3)-mediated phosphorylations, autophosphorylations and CHK2 oligomerization [46,50,51]. Both CHK1 and CHK2 also antagonize their own activities via regulatory feedback loops involving phosphatases [52,53], and both are promoted to dissociate from the chromatin in response to DNA damage [54,55]. Less is known about the direct functional relationships between DNA-PK and the other PIKK family members. In response to DSB induction, DNA-PKcs is extensively autophosphorylated [6,7], and undergoes phosphorylation on Thr^{2609} and Thr^{2647} in an ATR-dependent manner in response to UV but not IR, and in an ATM dependent manner in response to IR [56,57]. The autophosphorylation of DNA-PK at Ser^{2056} occurs at different kinetics according to DNA damage inducer [58]. Notably, cells depleted of ATM exhibit lower levels of IR-induced phosphorylation of CHK1 and CHK2, of which only CHK1 phosphorylation is abrogated completely by the addition of a DNA-PK inhibitor [59]. In certain cell lines, CHK2 phosphorylation in response to IR was impaired in cells with defective DNA-PK, or in the presence of a DNA-PK inhibitor [60]. These complex relationships among the canonical protein kinases in the DDR exemplify an intricate level of functional interactions among protein kinases in all tiers of this network.

2. Expanding the kinase landscape

We [61] and Bennetzen et al. [62] recently reported studies exploring the DNA damage-induced phosphoproteome, and provided a broader perspective of the signaling dynamics elicited by radiation [62] or radiomimetic [61] damage. The relatively small proportion of phosphorylation events that occurred on the SQ/TQ motifs in these studies attests to the extended scope of damage-induced phosphorylation events that was uncovered. The use of an ATM inhibitor in our study [61] provided an assessment of the degree of ATM dependence of cellular protein phosphorylation response to radiomimetic damage. Although ATM is a major regulator of this response, we identified a substantial fraction of ATM-independent events – about 40% of all damage-induced phosphorylation events. Together with the modest proportion of SQ/TQ phosphorylations suggests that the DDR may involve an extensive kinase network, beyond ATM. However, it is also possible that other kinases respond to DNA lesions other than DSBs, while the DSB response is still largely controlled by ATM. The plethora of DNA base lesions induced by IR or reactive oxygen species (ROS) induced by IR in cells is probably a relevant example. Here, we intend to review the published evidence for the involvement of protein kinases other than ATM/ATR in the DDR, with special attention to those that are activated or inhibited following DNA damage induction. Since DSBs are induced by a variety of chemicals as well as IR, our list will be permissive and include kinases that were activated by various chemicals. We did, however, exclude kinases shown to be induced by UV damage only. The five most prominent DDR kinases – ATM, ATR, DNA-PK, CHK1 and CHK2 – have been extensively reviewed recently [3,4,6,19,24–26,36–38,63–67] and therefore will not be discussed here in detail. The functional interactions between them and the expanding network of substrates, within and across pathways, are constantly being explored, but the relationships between them and many of the kinases mentioned below remain largely elusive. We categorized these protein kinases according to cellular processes and kinase families. However, we believe that the extensive cross-talks between these proteins (Fig. 1) attest to an interlaced signaling network that spans numerous cellular processes, in which versatile protein kinases can affect pathways that are beyond the functions and classes with which they have been identified to date. In the following text we will discuss protein kinases with ample information on their involvement in the DDR, and mention others more briefly in Table 1.

2.1. Cell cycle-regulating protein kinases

A major arm of the DDR activates cell cycle checkpoints, which temporarily stop cell cycle progression while the damage is assessed and processed [38,68–70]. It is not surprising therefore that the large number of kinases involved in cell cycle regulation also respond to DNA damage. This begins with the cyclin-dependent kinases (CDKs) themselves: in response to several DNA damaging agents, CDK1 and CDK2 phosphorylation at Tyr^{15} were up-regulated [71–73]. However, in cisplatin-treated H1299 cells, if CDK1 was depleted, CDK2 was not phosphorylated and retained kinase activity [73]. Depletion of WEE1, the kinase that phosphorylates CDK1 and CDK2 on Tyr^{15}, led to an activated DDR due to intrinsic DNA damage as a result of deregulation of CDKs, and was accompanied by activation of CHK1 [74,75]. Other DNA damage-induced

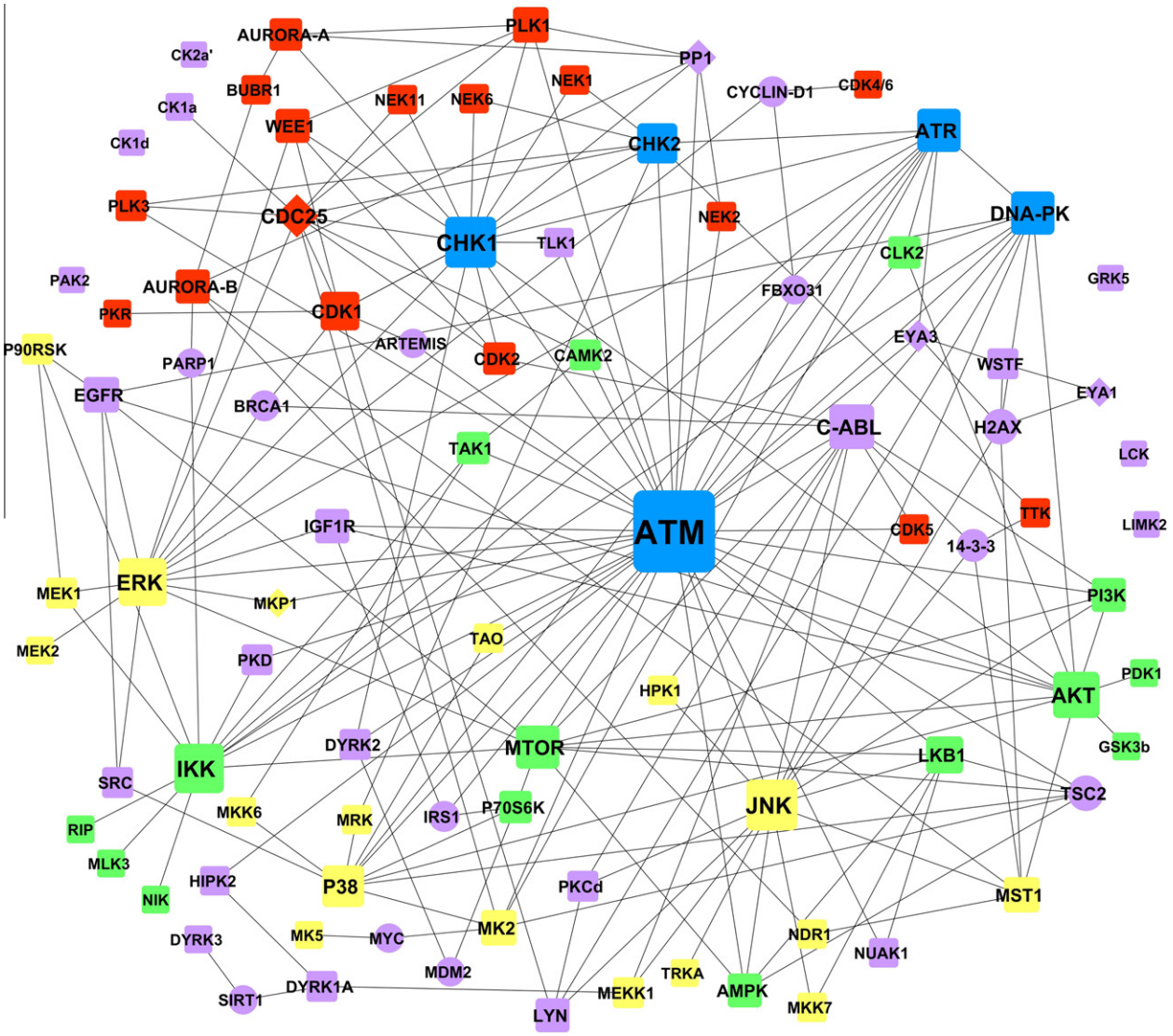

Fig. 1. The expanding protein kinase landscape of the DNA damage response. This diagram depicts proteins discussed in the text but not those that were identified in high-throughput screens (Table 2). Nodes represent protein kinases (squares), phosphatases (diamonds) and other proteins mentioned in the text (circles). Colors denote pathways by which kinases were described: blue – DNA damage response; red – cell cycle control; yellow – MAPK pathways; green – Akt, NFkB, mTOR pathways. Nodes sizes are proportional to the number of edges. Functional cross-talks (dependency, activation, inhibition, or physical interaction) which are mentioned in this text were depicted as edges between the proteins. The figure was prepared using Cytoscape [25].

phosphorylation events also contribute to the regulation of CDK1/2. In IR-treated chicken DT40 cells, the activity of CDK2 was enhanced through Thr^{160} phosphorylation in a CHK1-dependent manner, which played a role in controlling centrosome amplification [76]. CDK1 protein and activity levels were reduced in response to doxorubicin, in part due to phosphorylation of CDK1 at Tyr^{4} by double-stranded RNA (dsRNA)-activated protein kinase (PKR) [77]. Finally, c-Abl down-regulated the activity of CDK2 in response to IR, leading to growth arrest [78]. The ATM/CHK2, the ATR/CHK1, and p38/MK2 pathways converge to control CDK1/2 by inactivation of the CDC25 phosphatases (reviewed in [79]). Another mechanism by which ATM controlled CDK1 activity was via phosphorylation of Artemis, which in turn modulated the formation of CDK1–cyclin B complex and controlled recovery from the DNA damage-induced G2 arrest [80]. CDK1 also regulates CHK1 and CHK2: in cells depleted of CDK1, the phosphorylation of CHK1 on Ser^{317} following cisplatin treatment was impaired, and so was the BRCA1-regulated phosphorylation of CHK1 and CHK2 on Ser^{317} and Thr^{68}, respectively, following IR [73]. Irrespective of DNA damage, CDK1 phosphorylated CHK1 at Ser^{286}/Ser^{301} during mitosis, promoting sequestration of CHK1 to the cytoplasm and enabling timely activation of CDK1 itself [81]. This feedback loop is likely to be modulated in response to DNA damage.

CDK4/6 are inhibited in response to DNA damage, and this is one of the pathways that lead to the G1/S checkpoint. Similar to the p53-mediated pathway that contributes to this checkpoint, this one is ATM-dependent: it relies on ATM-mediated phosphorylation of the F-box only protein 31 (FBXO31), which mediates the degradation of cyclin D1 [82]. Inhibition of MAPK/ERK kinase (MEK1/2) also inhibited IR-induced cyclin D1 degradation, likely because of inhibition of IR-induced extracellular-signal regulated kinase (ERK) activation [82,83]. ERK can induce cyclin D1 degradation via F-box/WD repeat containing protein 8 (FBXW8), but depletion of FBXW8 did not modulate IR-induced cyclin D1 degradation, so it would seem that the IR-induced activation of MEK/ERK pathway was involved differently [82]. CDK5 was found to be involved in the DDR in a high-throughput screen for proteins whose loss is synthetic lethal with inhibition of poly(ADP-ribose) polymerase (PARP), together with other kinases, including ATM, ATR, CHK1, polo-like kinase 3 (PLK3) and p38γ. CDK5 depletion demonstrated

its involvement in the intra-S and G2/M checkpoints in response to IR [84]. In post-mitotic neurons, CDK5 activity was up-regulated in response to DNA damage, and it was implicated in ATM activation by phosphorylating it on Ser^{794} and in cell cycle re-entry in response to DNA damage [85]. Of note, c-Abl can phosphorylate CDK5 at Tyr^{15}, thereby promoting CDK5 kinase activity [86]. CDK5 activity was considerably up-regulated in response to CPT in the nuclear compartment to which c-Abl is translocated, suggesting a putative interplay between the two protein kinases in the DDR [85–87].

Polo-like kinases (PLKs) regulate mitotic entry, spindle pole checkpoints and cytokinesis [88], and of these PLK1 and PLK3 have been implicated in the DDR. PLK1 is activated following phosphorylation by Aurora-A on Thr^{210}, which promotes entry into mitosis [89]. In response to IR and other DNA damaging agents, PLK1's activity was inhibited by down-regulation of Thr^{210} phosphorylation, which was implicated in cell cycle arrest [90,91]. Depletion or inhibition of ATM, CHK1 or protein phosphatase 2A (PP2A) abrogated PLK1's response to damage [91–94]. In cells treated with doxorubicin at G2, PLK1 was degraded, which was required for the cells to maintain an efficient G2 checkpoint. Degradation was mediated via the anaphase-promoting complex/cyclosome (APC/C). Impaired degradation of PLK1 reduced the levels of CHK1 phosphorylation on Ser^{317} and reduced the levels of the WEE1 kinase [95]. PLK1 phosphorylates CDC25C on Ser^{198}, thereby promoting nuclear accumulation of the phosphatase, and this phosphorylation event is likely to be regulated also in the DDR [96]. PLK3 was phosphorylated in response to IR in an ATM-dependent manner [97]. PLK3 phosphorylated CHK2 on Ser^{62}/Ser^{73}, and participated in CHK2 activation in vivo; these phosphorylation events primed CHK2 for full activation by ATM [46,97]. Similar to CHK1 and CHK2, PLK3 inactivated CDC25C by phosphorylating it on Ser^{216} according to some labs, [98,99], or Ser^{191} according to another lab, leading to its nuclear accumulation [100]. PLK3 also phosphorylated CDC25A on Ser^{513} and Ser^{519}. Substitutions of these serine residues by alanines prevented IR-induced degradation of this phosphatase [101].

Aurora-A and Aurora-B, which regulate chromosome segregation and cytokinesis, are both inhibited by DNA damage to ensure blocking of mitosis. In etoposide-treated cells, Aurora-A's activity was inhibited while the protein levels increased in a CHK1-dependent manner [102]. Aurora-B activity was also inhibited in response to IR, depending on protein phosphatase 1 (PP1) and possibly PARP-1 [103,104]. PP1 is also involved in the regulation of Aurora-A, since IR treatment of cells entering mitosis led to rapid PP1-mediated dephosphorylation of Aurora-A on the activating phosphorylation Thr^{288} [105,106]. Importantly, IR-induced activation of PP1 was mediated by an ATM phosphorylation of an inhibitory unit, I-2, which led to dissociation of the complex and dephosphorylation of PP1 itself [103]. I-2 can also regulate Aurora-A activity directly [106]. Thus, PP1 can act as an ATM effector to control Aurora kinases as well as other kinases. Irrespective of DNA damage, depletion of myosin-phosphatase targeting subunit 1 (MYPT1), a PP1 regulator, increased phosphorylation of PLK1 at Thr^{210} [107,108]. PP1 also mediated an ATM-dependent inhibition of activity of NIMA kinase 2 (NEK2) in response to IR [109,110]. The NEK kinase family includes several kinases involved in cell cycle regulation, and, apart from NEK2, other kinases in the NEK family are also modulated by the DDR. Cells depleted of NEK1 failed to activate cell cycle checkpoints in response to IR, and the activating phosphorylation sites of CHK1 and CHK2 were impaired, resulting in persistent DNA damage [111]. The activity of NEK1, which translocated to the nucleus, did not depend on ATM or ATR, but was required to maintain chromosomal stability and suppress

Table 1
Additional protein kinases implicated in the DDR.

Protein kinase	Brief summary	Reference
CK1α	IR-induced CDC25A degradation is regulated by casein kinase 1α (CK1α)-mediated phosphorylation	[279]
NEK6	In response to IR, NEK6 was phosphorylated, possibly by CHK1 or CHK2	[280]
BUBR1	BUBR1 +/− cells failed to arrest at the G2/M checkpoint in response to DNA damage, and exhibited lower levels of H2AX phosphorylation compared to WT cells	[281]
TTK/MPS1	TTK phosphorylated CHK2 on Thr^{68} and was phosphorylated by CHK2 onThr^{288}. TTK-depleted cells were impaired in maintaining the IR-induced G2/M checkpoint	[282,283]
GRK5	GRK5 promoted inhibition of cisplatin-induced apoptosis by phosphorylation of p53 on Thr^{55}	[284]
MK5	MK5 was involved in the regulation of miR34c-modulated Myc expression, a process that is also controlled by MK2 is response to DNA damage	[285]
p21-activated kinase 2 (PAK2/γPAK)	PAK2 kinase activity was up-regulated in response to IR, in a wortmannin dependent manner. Activation of PAK2 by UV or cisplatin was wortmannin independent	[286]
Tropomyosin related kinase A (TrkA)	Following CPT treatment, JNK modulated the activation of TrkA, a tyrosine kinase receptor involved in cell death. In SY5Y cells, ectopic expression of TrkA increased NHEJ efficiency, possibly following elevation of the cellular amount of the NHEJ player XRCC4	[287,288]
Mixed lineage kinase 3 (MLK3)	Silencing of MLK3 resulted in elevated basal NF-κB signaling, thereby rendering cells more resistant to etoposide treatment and indicating that MLK3 had an inhibitory effect on IKK and promoted an apoptotic signal	[289]
NUAK1	Irrespective of DNA damage, The senescence-regulating kinase NUAK1 was activated by LKB1 kinase. NUAK1 is regulated by Akt, and promoted ATM activity, implicating NUAK1 in the DDR	[290,291]
Protein kinase D (PKD)	In neuronal cells, PKD was rapidly phosphorylated on its activation loop in response to etoposide, in an ATM-independent manner. It was suggested that the antioxidant resveratrol blocks NF-κB activation in response to various stimuli, including oxidative stress, by blocking this phosphorylation, thereby modulating the interaction of PKD with IKK	[292,293]
IKKε	The IKKε kinase was implicated in the DNA damage-induced NF-κB response. Following DNA damage it translocated to the nucleus, phosphorylated the PML protein, and was then retained in the nucleus in PML nuclear bodies, contributing to the anti-apoptotic response of NF-κB	[294]
Tousled like kinase 1 (TLK1)	TLK1 activity was inhibited in response to various DNA damaging agents in an ATM-, NBS1- and CHK1-dependent manner. CHK1 phosphorylated TLK1 on Ser^{695}. A TLK1 isoform lacking the N-terminus was translated in response to IR and had a radio-protective effect, facilitating damage repair, at least by phosphorylating RAD9	[295–300]
CK 1δ	CK1δ translocated to the nucleus and mediated p53 phosphorylation on Thr^{21} in response to doxorubicin	[301]
Lyn	The src-like tyrosine kinase Lyn was activated in response to IR and associated with CDK1. Lyn interacted with DNA-PK and PKCδ and modulated their activities, and also regulated the JNK pathway	[157,302,303]
Lymphocyte-specific tyrosine kinase (LCK)	LCK's activity was up-regulated in response to IR. The oncogenic variant of LCK, with an F505Y mutation, was associated with impaired DNA repair and chromosomal instability	[304–306]
LIM domain kinase 2	Expression of the isoform LIMK2b is induced by IR in a p-53 dependent manner. LIMK2b-depleted cells exhibited an early exit of the IR-induced G2/M arrest	[307]

lymphomagenesis [112,113]. NEK11 kinase activity was up-regulated in response to etoposide, cisplatin and IR, and was activated by a CHK1-mediated phosphorylation on Ser^{273} [114,115]. NEK11 phosphorylated CDC25A to regulate its degradation, and mutation of the kinase at Ser^{273} to alanine or kinase-dead stabilized the protein level of CDC25A [115].

2.2. MAP kinases

The mammalian mitogen-activated protein kinases (MAPKs) are a family of serine/threonine kinases with crucial roles in relaying extracellular stimuli such as growth factors, cytokines, hormones and various stresses into a variety of cellular processes affecting cellular growth and proliferation, differentiation, and inflammation [116–118]. They are divided into three major groups: the extracellular signal-regulated kinases (ERKs), the c-Jun N-terminal kinases (JNKs, also known as the stress-activated protein kinase or SAPK group), and the p38 MAPKs family. Each of these kinases exists in several isoforms and each MAPK signaling axis comprises at least three kinase components: MAPK kinase kinases (MAP3Ks) regulate MAPK kinase (MAP2Ks), which in turn regulate the MAPK family as well as other kinases. The involvement of the MAPK family in genotoxic responses has been reviewed [119,120], and here we will mention the involvement of the he ERK, JNK and p38 kinases, as well as upstream regulators.

ERK1/2 was activated, as measured by its state of phosphorylation, in response to etoposide, adriamycin and IR, in a manner dependent on ATM and the upstream kinase MEK1, and was involved in DNA damage-induced apoptosis [121]. The IR-induced activation resulted in IR dose-dependent oscillations of ERK1/2 phosphorylation, which was dependent on EGFR and Src, and was partially blocked by wortmannin [122]. As part of these oscillations, the transient dephosphorylation of ERK1/2 was mediated by an ATM-dependent regulation of the MAPK phosphatase 1 (MKP1) [123]. In turn, ERK1/2 facilitated etoposide/IR-induced ATM activation, as indicated by p53 and CHK2 phosphorylation, CDC25C phosphorylation, and G2/M cell cycle arrest [124,125]. Inhibition of ERK1/2 impaired IR-induced ATR, CHK1 and WEE1 activity, as well as ATM autophosphorylation and homologous recombination repair (HRR) [125,126]. ERK1/2 was also involved in regulating the stability of breast cancer type 1 susceptibility protein (BRCA1) after IR, while BRCA1 depletion impaired ERK phosphorylation after IR [127].

Two upstream MAPK kinases, MEK1 and MEK2, which can phosphorylate ERK1/2, were activated by IR, and blockage of MEK2 activation through the use of dominant negative kinase increased sensitivity of the cell to IR and decreased the cellular recovery from the G2/M cell cycle checkpoint arrest [128]. Possibly related, in Xenopus egg extracts, ERK mediated phosphorylation of CDC25 phosphatases, irrespective of DNA damage [129,130]. Downstream of MEK1, IR induced a transient increase of p90RSK which was MEK1 and EGFR dependent [131]

p38 MAPK enzymatic activity was induced in response to various DNA damaging agents [132]. Of note, UV irradiation activated p38 more vigorously than IR, and activation induced by cisplatin but not UV was c-Abl dependent [132,133]. UV-activated p38 phosphorylated CDC25B, modulating its interaction with 14-3-3 and facilitating the initiation of a G_2/M checkpoint [134]. This occurred in part through its ability to activate MAPK-activated protein (MAPKAP) kinase-2 (MK2). MK2, like CHK1 and CHK2, phosphorylated CDC25B and CDC25C [135], and their involvement in cell cycle regulation has been reviewed recently [79,136].

p38 and MK2 were activated in response to several DSB-inducing agents as indicated by phosphorylation of MK2 on Thr^{334} and phosphorylation of p38 on Thr^{180}–Tyr^{182} [137]. Activation of MK2 was ATR-dependent in response to doxorubicin, cisplatin and CPT, but ATM-dependent only in response to doxorubicin. Importantly, depletion of MK2 in $p53^{-/-}$ mouse embryonic fibroblasts (MEFs) resulted in mitotic catastrophe after DNA damage and diminished cell survival, since MK2 was required for the G2/M checkpoint in these cells [137]. MK2 depletion impaired CDC25A degradation in response to cisplatin, and CDC25B binding to 14-3-3 in response to doxorubicin [137,138]. Following DNA damage induction, the p38/MK2 complex undergoes nuclear export, and in the cytoplasm it is involved in maintenance of the G2/M checkpoint via stabilization of specific mRNAs achieved by phosphorylation of players in this process [138]. MK2 in the DDR was also demonstrated in the repression of Myc through an MK2-dependent induction of miR-34c in response to etoposide, which led to S-phase arrest [139]. Several kinases upstream of p38 MAPK were implicated in the DDR. In response to IR, MAPK kinase 6 (MKK6) was activated [140], as was MLK-related kinase (MRK, also known as MLTK), which was autophosphorylated and contributed to phosphorylation of CHK2. It was required for cell cycle arrest, and for IR-induced p38γ activation but not p38α, [141,142]. Thousand and one amino acid (TAO) kinases are MAP3Ks that activate p38 MAPK. TAOs were shown to be activated by IR and required for p38 activation. IR activation of TAOs was abrogated in ATM-deficient cells, and TAO1 and TAO3 were shown to be phosphorylated in response to IR [133]. Phosphorylation of TAO3 on Ser^{324} was ATM-dependent and required for p38 MAPK activity [133]. Notably, evidenced by a fluorescent reporter, MAP3Ks were activated in the nucleus in response to etoposide, but not UV [143].

Relationships between ATM and p38 MAPK have been demonstrated in relation to oxidative stress regulation, in addition to ROS-driven activation of ATM [8–12]. The self-renewal capacity of hematopoietic stem cells (HSCs) was found to depend on ATM-mediated modulation of the response to oxidative stress [144]. In $Atm^{-/-}$ but not $Atm^{+/+}$ mice, elevation of ROS levels led to p38 activation and resulted in HSC exhaustion, which was averted when p38 MAPK was inhibited, or upon treatment with the antioxidant N-acetyl cysteine (NAC) [145]. Similarly, treatment of $Atm^{-/-}$ neuronal stem cells with NAC or with a p38 MAPK inhibitor improved their proliferation [146]. Treatment of $Atm^{-/-}$ mice with NAC reduced the acute sensitivity of these mice to IR, prevented lymphomagenesis, and, interestingly, restored aberrant DSB-repair dependent processes such as V(D)J recombination [147]. One level at which these signals may converge is the mTOR pathway discussed below, since both ATM and p38 MAPK/MK2 can signal to tuberous sclerosis 2 protein (TSC2), which in turn modulates mTOR signaling in response to ROS [16,148,149]. Inhibition or depletion of p38 MAPK also attenuated the doxorubicin-induced response of the mTOR substrate p70 ribosomal S6 kinase [150].

Another member of the MAPK family, c-Jun kinase (JNK), is activated by IR [151], in an ATM-dependent manner [152,153]. Timely activation of JNK was regulated also by the MAPK kinase kinase 1(MEKK1), MKK7, c-Abl, DNA-PK, Lyn tyrosine kinase and protein kinase Cδ (PKCδ) [154–157]. IR also promoted an interaction between JNK and the PI3K subunit p85α [151], and JNK promoted c-Abl translocation into the nucleus in response to adriamycin, by phosphorylation of 14-3-3, which retains c-Abl in the cytoplasm [87]. Finally, JNK was recruited to H2AX phosphorylated on Tyr^{142}, possibly to induce pro-apoptotic functions, but substrates or relationships with other kinases recruited at the sites were not demonstrated [158]. The MKK7–JNK pathway and the MKK3/6-p38-MAPK pathway exhibit antagonistic roles in cell proliferation and senescence [159,160]. The activation of JNK in response to doxorubicin was dependent on 5′-AMP-activated protein kinase (AMPK), and was abolished in the presence of the antioxidant NAC, while in drosophila, MKK7 and JNK mediated apoptotic cell death induced by LKB1 [161,162]. According to tissue specific inactivation of MKK7

in a murine cancer model, MKK7 acted as a tumor suppressor by affecting p53 stability, DDR signaling, and cell cycle arrest [163].

The mammalian sterile 20-like kinase 1 (MST1) is activated during apoptosis and can promote apoptotic chromatin fragmentation by activating JNK. JNK in turn phosphorylates MST1 to further promote its activation. In response to etoposide, MST1 activation was required for apoptotic DNA fragmentation, accompanied by H2AX phosphorylated on Ser^{139}, which MST1 could phosphorylate in vitro [164–166]. MST1 promoted apoptosis by translocating to the nucleus, a process that was repressed by its Akt-mediated phosphorylation [167]. In response to IR, MST1 activation coincided with the activation of another downstream kinase, nuclear Dbf2-related 1 (NDR1) kinase [168]. NDR1, which was associated with lymphomagenesis, was involved in centrosome duplication and the regulation of the G1/S cell cycle transition [168–170]. MST1 and NDR1 are involved in the correct alignment of mitotic chromosomes through regulation of aurora B activity [171,172].

2.3. The Akt-mTOR-NF-kB connection

Akt (protein kinase B) is a kinase involved in cell cycle regulation, cell survival and proliferation, and is activated downstream of PI3K signaling [173]. In response to various stimuli, Akt is activated and this activation is associated with its phosphorylation on Thr^{61} by 3-phosphoinositide-dependent protein kinase 1 (PDK1) and on Ser^{473}, and may be followed by translocation to cellular compartments [174,175]. Full activation of Akt, as measured by the phosphorylation of Ser^{473}, was ATM-dependent in response to IR [176]. In contrast, Kwon et al. [177] reported that phosphorylation of Akt, as well as Akt's substrate glycogen synthase kinase 3β (GSK-3β), could be induced in response to IR to a similar extent in ATM-deficient and -proficient cell lines. In murine $Atm^{-/-}$ thymocytes, the basal phosphorylation level of Akt was higher than that in $Atm^{+/+}$ thymocytes [178]. Ser^{473} of Akt can be phosphorylated by DNA-PK as well as mammalian target of rapamycin complex 2 (mTORC2) in a signal context-dependent manner [179–183]. Inhibition of mTOR by rapamycin led to the activation of Akt in an IGF1R-, PI3K-dependent manner [184,185]. Activation of Akt by PDK1, and DNA-PK was critical for the correct regulation of p21 protein levels, and when mis-regulated, led to increased apoptosis in response to IR [181].

Akt is involved in G2/M checkpoint and can phosphorylate CHK1 on Ser^{280}, which may be inhibitory since expression of activated Akt inhibited IR-induced CHK1 activity [186,187]. In response to IR, Akt phosphorylated CLK2, a kinase involved in alternative splicing regulation and cell cycle progression [188–190]. Interestingly, CLK2 is the human homolog of the budding yeast protein Tel2, involved in telomere length regulation, PIKK stability, and localization of the ATM homolog TEL1 to DSBs [191–193]. Inhibition of p38 MAPK or the upstream c-Src kinase impaired the activation of Akt in response to IR [150,194], via an unknown mechanism. A possible mechanism of this inhibition may come from a study of the protection offered by the scatter factor (SF) against adriamycin-induced damage: intricate relations were disclosed in this regard between numerous kinases, including Src, Akt, MKK3/6 and p38 MAPK, TAK1 and NIK and the NFκB pathway [195].

The mammalian target of rapamycin (mTOR; FRAP1), a member of the PIKK family of protein kinases, is a cytoplasmic-nuclear shuttling protein kinase that exists in two distinct multi-protein complexes, TORC1 and TORC2. It regulates protein synthesis and ribosome biogenesis as well as autophagy in response to various stimuli and functions as a sensitive sensor of nutrient and redox balances [196]. In murine $Atm^{-/-}$ thymocytes, mTOR signaling was mis-regulated as evidenced by phosphorylation of its substrate eukaryotic initiation factor 4E (eIF4E)-binding protein (4EBP1); and inhibition of mTOR with rapamycin attenuated the elevated phosphorylation and significantly delayed thymic lymphoma development in $Atm^{-/-}$ mice [16,178]. IR treatment was shown to lead to ERK- and ATM-dependent transient increase in cap-dependent mRNA translation that was associated with increased phosphorylation of mTOR on Ser^{2448} [197]. Several hours after IR, protein synthesis was inhibited in a p53-dependent manner. Transient increase of p70 S6 kinase activity, an mTOR substrate, was found in a breast carcinoma cell line and depended on PI3K and EGFR [131]. However, the fine-tuning and timing of this damage response may be cell line- and damage type-dependent, since mTOR activity in other cell lines was inhibited in a p53- and AMPK-dependent manner, accompanied by a reduction is p70 S6 kinase activity [198–200]. On the other hand, in response to doxorubicin, p70 S6 kinase was activated in an mTOR – p38α-dependent manner, and phosphorylated MDM2 on Ser^{163}, which inhibited MDM2 nuclear entry [150].

Putatively linked, mTOR was shown to be repressed in response to an increase in ROS levels or IR, in a mechanism involving ATM-dependent TSC2 activation via the LKB1/AMPK metabolic pathway in the cytoplasm [16]. LKB1 was phosphorylated in response to IR on Thr^{366} in an ATM-dependent manner, and although the function of this phosphorylation event remains to be elucidated, mutation of the site to alanine/glutamate moderately reduced the ability of LKB1 to suppress cell growth [201,202]. LKB1 activated AMPK by phosphorylating it on Thr^{172}, which led to TSC2 phosphorylation and down-regulation of mTOR [203,204]. There is evidence of the involvement of this signaling mechanism in the DDR: AMPK phosphorylation was moderately induced in response to etoposide, in an ATM-dependent manner, which promoted mitochondria biogenesis [15]; and LKB1 and AMPK were inducibly phosphorylated on Ser^{428} and Thr^{172}, respectively, in response to doxorubicin [162]. AMPK was also activated in an ATM-dependent/LKB1-independent manner in certain cell lines [205]. In B cells, DSBs induced by etoposide or by activation-induced cytidine deaminase (AID) activated ATM, which signaled through LKB1 to inactivate CRTC2, which controls cell proliferation, self-renewal, and differentiation – all involved in lymphomagenesis [206].

The core IκB kinase (IKK) complex, which activates the NF-κB transcription factor family [207], consists of two catalytic subunits, IKKα/IKK1 and IKKβ/IKK2, and a regulatory subunit, IKKγ/NEMO (NF-kB essential modulator). Activated IKK phosphorylates IκB to cause its ubiquitin-proteasome-mediated degradation, which in turn releases NF-κB to the nucleus for transcriptional regulation. The involvement of the NF-κB pathway in the cellular response to genotoxic stresses, including DSBs, has been reviewed [208,209], so we will focus on the roles of kinase cross-talks in this context. In response to IR, ATM was demonstrated to be essential for the activation of the NF-κB pathway, including IKK activation, IκBα degradation, and induction of NF-κB DNA binding activity [210].

In response to DNA damage, a small fraction of ATM associated with IKKγ/NEMO exited the nucleus and associated with IKK catalytic subunits [211], a process in which PARP1 plays an important role [212]. Importantly, activation of ATM by oxidative stress could also lead to NFκB activation, while induction of DSBs per se by restriction enzymes was insufficient to lead to activation [213]. On the other hand, NF-κB response to AD288, a topoisomerase II inhibitor that does not induce DSBs, was mediated by DNA-PK and not ATM [214]. GSK-3β phosphorylation and activation in response to IR contributed to an ATM-independent transcriptional response of NF-κB, although the ATM-dependent pathway was likely to be the more prominent one [177]. GSK-3β may explain the observation that IR-induced activation of IKK in A-T lymphoblasts was reduced and delayed but not abolished. ATR also interacted with IKKγ in response to replication stress: it did not seem to

phosphorylate it, and, rather, antagonized ATM-dependent NF-κB activation [215]. TGFβ-activated kinase (TAK1) was involved in IKK activation in response to multiple stimuli; and, irrespective of DNA damage, it was also able to phosphorylate MKK6, leading to activation of the JNK pathway, which is also involved in the DDR [216]. TAK1 was activated in response to etoposide, and was required for activation of the IKK complex [217]. ATM regulated the activation of TAK1 through the phosphorylation of IKKγ, and through the regulation of ELKS, which interacted with TAK1 [217]. In response to IR and doxorubicin but not etoposide, the NF-κB response was modulated by the inhibition of MEK1, indicating this kinase may also be involved [218,219]. The NF-κB response to doxorubicin may also involve p90RSK, since expression of a dominant negative form delayed IκBα degradation [214]. Doxorubicin-induced NF-κB response was also inhibited by the addition of rapamycin, suggesting the involvement of an mTOR complex in IKK activity like that previously shown irrespective of DNA damage [220,221].

Cells depleted of another related kinase, receptor interacting protein (RIP), were impaired in NF-κB signaling in response to camptothecin (CPT), adriamycin and IR, but not UV [222]. Reconstitution of these cells with WT or kinase-dead RIP restored a proper NF-κB response after treatment with adriamycin [222], which also led to the ATM-dependent formation of a complex between RIP and IKKβ. NF-κB-activating kinase (NIK) is known to be able to activate the IKK complex in response to various stimuli, and expression of a dominant-negative NIK inhibited NF-κB activation in response to CPT [223].

The translocation of ATM in response to IR, as well as TAK1 phosphorylation were dependent on a steady state of calcium levels, by an unknown mechanism [17]. The nuclear export of IKKγ in response to etoposide was also regulated by calcium levels [224]. One feasible explanation of how calcium regulates TAK1 is that calcium-dependent signals are transduced to TAK1 through Ca^{2+}/calmodulin-dependent protein kinases II (CaMKII), a kinase that converts the calcium signal to a phosphorylation signal. Irrespective of DNA damage, TAK1 could be phosphorylated and activated by CaMKII [225]. The activity of this kinase was stimulated upon IR in an ATM-dependent manner, together with changes in calcium concentration, and inhibition of CaMKII increased IR- or doxorubicin-induced cell death [226–228]. CaMKII also phosphorylated CDC25C, and thus played a role in the G2/M transition, but this pathway has not been examined in the context of DSBs [229,230].

2.4. Tyrosine kinases and others

Several tyrosine kinases and dual-specificity kinases have been implicated in the DDR, c-Abl and the EGF receptor (EGFR) being prominent examples. Interestingly, tyrosine phosphorylation has not been extensively investigated in the DDR context, implying that novel DDR branches associated with tyrosine kinases remain to be discovered.

c-Abl is a non-receptor tyrosine kinase that is ubiquitously expressed and localized in both the nucleus and cytoplasm. Its activity was up-regulated following exposure to DNA damage-inducers, such as IR, cisplatin, and mitomycin C [231]. c-Abl interacted with ATM and DNA-PK [232,233]. IR-induced activation of c-Abl required ATM, and it was assumed that ATM phosphorylates c-Abl at Ser^{465}, although such phosphorylation in cells was not directly demonstrated [234]. IR led to an ATM-dependent disruption of a complex between c-Abl and BRCA1, which may be a c-Abl target [235]. In vitro, DNA-PK and c-Abl phosphorylated each other [233]. In vivo, down-regulation of DNA-PK activity several hours after IR was shown to be dependent on c-Abl [236]. c-Abl was targeted from the cytoplasm to the nucleus in response to DNA damage induced by adriamycin, and was liberated for translocation to the nucleus by JNK-mediated phosphorylation of 14-3-3 [87]. The cytoplasmic fraction of c-Abl was sequestered in the cytoplasm by 14-3-3, which bound to c-Abl via c-Abl's phosphorylation on Thr^{735}, which could be induced in cells by TTK in response to oxidative damage [237]. Cells deficient in c-Abl failed to induce a MEKK1-dependent activation of JNK after IR [231], a process regulated also by PKCδ [157]. After IR, c-Abl phosphorylated MEKK1 and PKCδ, and induced translocation of the latter to the nucleus [154,238]. c-Abl also phosphorylated and activated hematopoietic progenitor kinase (HPK1), which in turn mediated activation of JNK by c-Abl [239].

c-Abl activated by IR was also shown to mediate phosphorylation of PI 3K and mTOR, leading to the inhibition these kinases' activity [199,240]. In response to IR, EGFR translocated into the nucleus and formed a complex with DNA-PK, facilitating DNA-PK's activation and autophosphorylation [241]. Inhibition of EGFR led to reduced efficiency of the NHEJ route of DSB repair, while expression of a constitutively active variant of EGFR stimulated both the HRR and NHEJ repair pathways [242,243]. Phosphorylation of EGFR at several residues regulated the timely translocation and retention of EGFR in the nucleus following DNA damage, and depended at least in part on Src kinase [122,244,245]. Notably, Src itself was also phosphorylated after IR treatment [122].

Downstream of EGFR are several PI3K/Akt- and Ras/Raf/MEK/ERK-mediated signaling responses to IR (reviewed in [246]). Importantly, these pathways could be activated by another receptor involved in the response to IR, the insulin growth factor 1 receptor (IGF1R), which cross-talks with EGFR [247,248]. IGF1R phosphorylation was up-regulated in response to IR, and fell to baseline levels after several hours [249]. Down-regulation of IGF1R led to cellular radiosensitivity, impaired p53 stabilization in response to IR, and reduced basal levels of ATM [250]. A-T cells had low levels of IGFIR, indicating a role for ATM in regulating IGFIR expression, and their radiosensitivity was alleviated by IGF1R expression [251]. The interaction of the IGF1R substrate with ATM was up-regulated in response to cisplatin-induced DNA damage [252,253]. Irrespective of DNA damage, IRS1 can also be phosphorylated by p70S6K, leading to inhibition of IRS1, which provides a feedback response from an mTOR substrate to the upstream IGF1R signaling [254,255]. While each of these components was DNA damage responsive, how DNA damage affects these cross-talks remains to be elucidated.

Dual-specificity tyrosine-phosphorylation-regulated kinases (DYRKs) are involved in regulation of cell survival or apoptosis in response to DNA damage. DYRK2 was translocated to the nucleus and mediated phosphorylation of p53 at Ser^{46}, which potentiates induction of apoptosis [256]. ATM was required for the damage-induced nuclear translocation of DYRK2, and phosphorylated DYRK2 at Thr^{33} and Ser^{369}. This phosphorylation protected DYRK2 from MDM2-mediated degradation in the nucleus [257]. Interestingly, DYRK2 also serves as a scaffold for the EDVP E3 ligase, in a complex that includes DNA damage-binding protein 1 (DDB1), thus merging recognition of a substrate, phosphorylation and degradation of at least one substrate, Katanin p60 [258]. Since this complex was shown to play a role in regulation of mitotic transition, and DDB1 is a known DDR player which controls CHK1 stability [259], perhaps future studies will show a role for this complex in DDR. In contrast to DYRK2, DYRK1A and DYRK3 promoted cell survival by phosphorylation of SIRT1, which led to down-regulation of DNA damage-induced acetylation of p53 [260]. How these kinases are regulated in the DDR is unclear. However, DYRK1 was shown to interact with two other kinases involved in the DDR, MEKK1 and homodomain-interacting protein kinase 2 (HIPK2), via a scaffold protein anthocyanin (Han11), and DYRK1 also interacted directly with HIPK2 [261]. HIPK2 accumulated in response to IR, and could interact with and phosphorylate p53 at Ser^{46}, promoting apoptosis.

Table 2
Protein kinases identified as putative DDR players phosphoproteomic screens [(a) Matsuoka et al. [27], (b) Bennetzen et al. [62], (c) Bensimon et al. [61]] and functional screens [(d) Paulsen et al. [308], (e) Lovejoy et al. [309], (f) O'Donnell et al. [310], (g) Hurov et al. [311], (h) O'Connell et al. [312]], and not mentioned in the text.

Gene symbol	Gene ID	Phosphoproteomic screen	Functional screen	Gene symbol	Gene ID	Phosphoproteomic screen	Functional screen
AAK1	22848		f	**NEK8**	284086		d
ACVR1	90		g	**NEK10**	152110		g
ACVRL1	94		e	**OXSR1**	9943	a,c	g
AKT3	10000	a		**PAK3**	5063		g
ALPK2	115701		g	**PAK6**	56924		f
BCKDK	10295		f	**PHKG2**	5261		f
BMPR1B	658		g	**PIM1**	5292		g
BRAF	673		f	**PIM2**	11040		g
CAMK4	814		f	**PRKAA2**	5563		g
CAMKK1	84254		h	**PRKACA**	5566		g
CDK12	51755	b		**PRKCB**	5579		g
CDK13	8621	a ,b,c		**PRKCE**	5581		f
CDK17	5128		g	**PRKCG**	5582		f
CDK19	23097		g	**PRKX**	5613		f
CDK3	1018	b		**PRPF4B**	8899	c	
CDKL2	8999		f	**RAF1**	5894	a	
CSNK1G1	53944		f	**RIOK1**	83732		g
DAPK3	1613		f	**RIOK3**	8780		g
DDR1	780		h	**RIPK2**	8767	a	g
DYRK1B	9149	b		**RIPK3**	11035		f
EPHA7	2045		f	**ROCK1**	6093	a	
ERBB4	2066		f	**ROCK2**	9475	a	f
FLT3	2322		g,h	**ROR2**	4920	a	
GAK	2580		g	**RPS6KA2**	6196		f
GRK4	2868		g	**RPS6KA3**	6197		f
GSG2	83903	a		**RPS6KA5**	9252		h
HCK	3055		h	**RPS6KB2**	6199	a	
INSR	3643		f	**SGK3**	23678		f
IRAK4	51135		f	**SIK1**	150094	a	
ITK	3702		g	**SLK**	9748	a	
KALRN	8997		g	**SMG1**	23049	a	
LATS1	9113	a		**SPEG**	10290	a	
MAP4K4	9448	a		**STK10**	6793	b	
MAPK4	5596		g	**STK24**	8428	a	
MARK2	2011		f	**STK38L**	23012		f
MAST4	375449	a	g	**TSSK4**	283629	a	
MATK	4145	a		**TYK2**	7297	b	
MELK	9833		g	**ULK4**	54986		g
MUSK	4593		f	**WNK1**	65125	a	

The activation and accumulation of HIPK2 was controlled by ATM, but not CHK2 [262].

Finally, two additional protein kinases with an emerging role in the DDR are CK2 and WSTF. Casein kinase 2 (CK2) represents a special case as it is a constitutively active kinase. CK2 is involved in the DDR from its early stages: CK2-mediated phosphorylation and eviction from chromatin of HP 1β is a very early step in the DSB response [263], and CK2 phosphorylation regulates the interaction of two DSB sensors, Nijmegen breakage syndrome 1 (NBS1) and mediator of DNA-damage checkpoint 1 (MDC1), at the DNA damage sites [264,265]. CK2 also phosphorylates several DDR proteins such as p53 and MDM2 [266]; not much is known, however, about how CK2 itself is regulated in the DDR except that in response to IR, CK2α′ translocates into the nucleus [267]. Williams–Beuren syndrome transcription factor (WSTF) interacted with H2AX and phosphorylated the histone at Tyr^{142}, and depletion of WSTF abrogated the maintenance of phosphorylation at Ser^{139} (which forms γH2AX) and maintenance of MDC1/phospho-ATM foci [268]. Tyr^{142} was dephosphorylated by one of the phosphatases eyes absent homolog 1/3 (EYA1/EYA3) in response to IR, and at least EYA3 might be regulated by an ATM/ATR-mediated phosphorylation [158]. Dephosphorylation promoted DSB repair rather than apoptosis [158]. The regulatory steps controlling WSTF kinase activity in the DDR are still not known.

2.5. Further additions to the protein kinase sub-network of the DDR

Several other kinases that have been linked to the DNA damage response are presented in Table 1. For most of them, details of how they are modulated by the DNA damage signal are largely missing. Importantly, several phosphoproteomic and functional siRNA screens performed in recent years in search of new DDR players have turned up a number of additional protein kinases. These protein kinases, which are presented in Table 2, provide numerous starting points for detailed studies of additional phosphorylation-driven DDR pathways.

3. Concluding remarks

At the systems level, the emerging picture of DNA damage-induced protein phosphorylation (Fig. 1) still places ATM in a central position, at least following the induction of DSBs. However, beyond ATM lies a landscape of numerous other kinases, some of which play critical roles in the DDR. One of the major functional principles governing the organization of the DDR is that it relies on a relatively small core of DDR-dedicated proteins, but, once DNA damage is induced, it rallies to the cause of cellular defense numerous proteins that most of the time are involved in other processes unrelated to DNA damage. In some cases these proteins acquire functions in the DDR context different from the ones they exert in ordinary times, and in other cases they continue their usual tasks but operate them in DDR pathways. In the case of protein kinases, it is safe to say they carry their kinase operations over to the DDR, but their substrate specificity and/or subcellular localization may change, often following their own damage-induced post-translational modifications. Ample examples can be found in this review. However, we cannot exclude the possibility that the action of some of these kinases has minimal or no functional consequence in the DDR.

Interesting and important players in the protein phosphorylation arena that were not discussed extensively here are protein phosphatases. Notable examples documented in the DDR are PP5 [269,270], PP2A [271–273], WIP1 [274–276], and PP1 [103,277,278]. The impact of dephosphorylation of a protein on its function may be no less that its phosphorylation. Of note, our [61] and Bennetzen et al.'s [62] phosphoproteomic screens identified a substantial number of protein dephosphorylations induced by DNA damage. The cross-talk between kinases and phosphatases in the DDR is an important area of research that is likely to shed light on the still elusive process of DDR recovery.

Additional high-throughput proteomic and functional screens related to other genotoxic stresses, and the elucidation of cross-talks among the multitude of protein phosphorylation-driven pathways in the DDR, are likely to substantiate the DDR as one of the genome's most extensive signaling networks that respond to cellular stimuli.

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