Growth Factor Receptor Signaling, DNA Damage Response, and Cancer Cell Susceptibility to Chemotherapy and Relapses

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Abbreviations

Ask	Apoptosis signal regulated kinase
BER	Base excision repair
ErbB/Her	Tyrosine kinase receptor of the EGFR family
ERCC1	Excision repair cross-complementing gene 1
Erk	Extracellular signal regulated kinase
Gadd45	Growth arrest and DNA damage 45
JNK	c-jun N-terminal kinase
MAPK	Mitogen-activated protein kinase
NER	Nucleotide excision repair
Sapk	Stress-activated protein kinase

1 Introduction

Tumor relapse following primary chemotherapy treatment is an omnious event in most cancer patients undergoing treatment and represents a major clinical challenge in part because relapsed tumors often express aggressive behavior and develop cross-resistance to a wide range of structurally and functionally unrelated agents, which limits the benefit of alternative regimens. In the case of chemotherapy drugs targeting DNA, e.g., alkylating agents and platinums, drug resistant cells develop an impressive arsenal of constitutive and inducible DNA-damage response mechanisms with a broad impact on cell cycle checkpoint and DNA repair mechanisms to

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escape chemotherapy-induced cell death. In many instances, DNA damage response signals originate at the plasma membrane as a result of growth factor receptor activation and the signals are then propagated via signal transduction cascades involving a high level of cross talks and feedback loops among distinct signaling pathways. It is therefore predictable that the overexpression of growth factor receptors frequently seen in cancer greatly impacts on chemotherapy response and relapses.

Mechanisms by which growth factor receptor-coupled signaling promote chemotherapy resistance are multifactorial and deregulation of DNA repair pathways represents a major mechanism for certain DNA-interacting drugs, in particular alkylating agents and platinums (cisplatin and carboplatin). The great progress in the characterization of the cell's major DNA repair processes, namely, base excision repair, nucleotide excision repair, double-strand break repair, and recombination repair revealed that most of the DNA repair pathways have protein kinase components directly modulating their activity and are regulated by upstream growth factor receptors, as well as by epigenetic mechanisms [1]. This chapter focuses on DNA damage-activated signaling cascades coupled to growth factor receptors and their connection to chemotherapy-induced DNA damage response and drug resistance. A particular emphasis is given to the family of mitogen activated kinases (Mapk) known to regulate DNA repair mechanisms. The potential impact of Mapk signaling inhibitors on the modulation of DNA damage response and DNA repair in the context of overcoming drug resistance is discussed.

2 Growth Factor Receptor-Coupled Signal Transduction Pathways that Are Points of Convergence for DNA Damage Response and DNA Repair

DNA damage response comprises a network of integrated signaling pathways that regulate a multifaceted response, and its components can be broadly divided as sensors, transducers, and effectors (Fig. 1). Sensors are believed to sense aberrant DNA structures and initiate the global DNA damage response. Unlike yeast, the identity of DNA damage sensors in mammalian cells remains partially understood although Atm, Brca1, the Nbs1-Mre11-Rad50 complex, and some mismatch proteins have been implicated (reviewed in 2). The transducers and effectors involved in regulating the cellular response to DNA damage stress include a variety of kinases and substrates implicated in the regulation of DNA repair, transcription, chromatin remodeling, and cell cycle checkpoints; together they constitute the core of the DNA damage response network. In this context, deregulation of cell transduction pathways secondary to deregulation of upstream growth factor receptors greatly impact on the DNA damage response to promote chemotherapy resistance.

Among various growth factor receptors commonly deregulated in cancer, aberrant expression of EGFR/ErbB receptors (most commonly overexpression/amplification) and/or their ligands has been widely investigated in relation to relapses and progres-

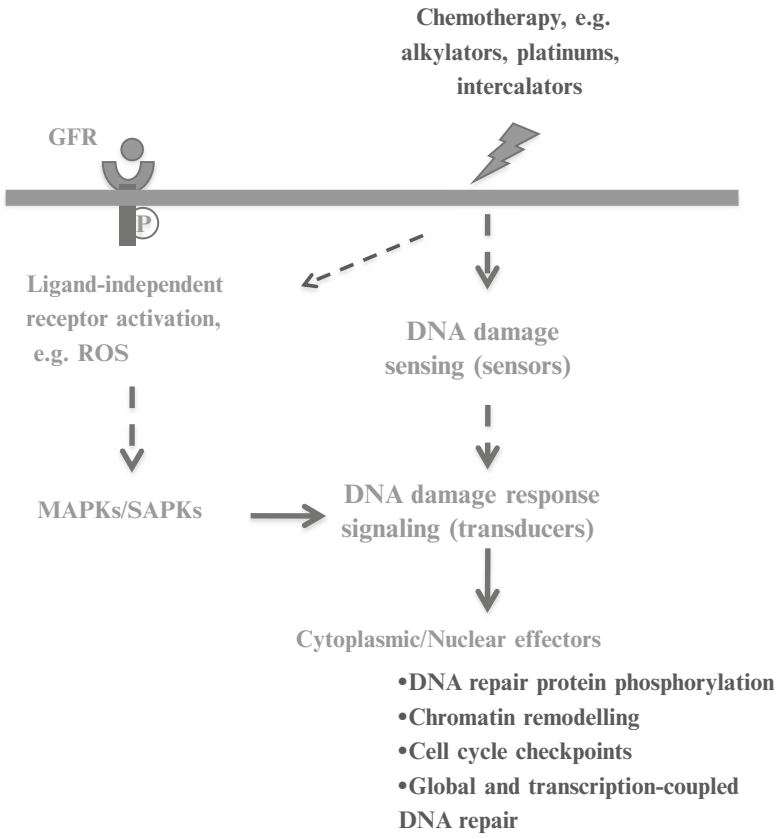


Fig. 1 Tumor cell response to DNA-interacting chemotherapy drugs. The scheme shows major mechanisms by which chemotherapy initiate the global DNA damage response, including DNA lesion sensing by sensors, regulation of DNA damage-associated cell signaling (transducers) and effectors; the later include chromatin remodeling, cell cycle checkpoints, and global and transcription-coupled DNA repair. Growth factor receprtor signaling can contribute to DNA damage response via modulation of DNA damage signaling). Moreover, chemotherapy can active growth factor receptors in a ligand independent manner, e.g., via ROS, or induces growth factor shedding , e.g., pro-EGF. Chemotherapy can also promote receptor nuclear translocation, e.g., phospho-EGFR, leading to regulation of DNA repair enzymes such as DNA-PK. In this context, deregulation of cell transduction pathways secondary to deregulation of upstream growth factor receptors can greatly impact on the DNA damage response including DNA repair to promote either chemotherapy sensitivity or resistance

sion. The EGFR receptor family includes EGFR (ErbB1), ErbB2, ErbB3, and ErbB4 receptors. The existence of a multitude of ErbB receptor ligands (e.g., EGF, HB-EGF, heregulins, BTC, and EPR) and the propensity of these receptors to homo- and heterodimerize lead to the activation of a broad and diverse signaling network [3, 4], which extends beyond members of the ErbB family to include cross talks with receptors such as G protein-coupled receptors [5–7], IGFR [8–10], PDGFR [11, 12]; interleukin receptors [13], and the urokinase-type plasminogen activator (uPAR) [14, 15].

Among ErbB receptors, overexpression of ErbB-2, the preferential dimerization partner for the other ErbB members, has been shown to deregulate the kinetics of MAPK activation and to deactivate in particular the Ras-Raf-ERK and JNK pathways [16], and promotes chemotherapy resistance [17, 23]. The Raf-MEK-ERK, p38, and JNK pathways have been involved in various contexts in the regulation of DNA damage response and DNA repair mechanisms [24]. Not surprising, combination of chemotherapy with anti-monoclonal ErbB receptors or anti-kinase small molecules sensitizes tumor cells to chemotherapy both in experimental models and patients [21, 22, 25–27]. We and others have shown an association between ErbB2 hyperactivation and upregulation of cell repair activity following exposure to cisplatin [18–20, 28, 30–32]. In addition, exposure of cancer cells to the anti-ErbB2 antibody, Trastuzumab, delayed the repair of cisplatin-induced interstrand cross links, which are believed to be critical for cisplatin anticancer activity in contrast to intrastrand cross links [29]. As well, the combination of trastuzumab and cisplatin in clinical trials results in response rates higher than that reported for either single agent alone [27]. This synergistic activity involving DNA repair modulation was also demonstrated using the high-energy α-particle emitting radionuclide (212)Bi (212)Pb-TCMC-trastuzumab [30].

Of relevance to DNA damage response, UV light irradiation of cells can activate EGFR in a ligand-independent manner via a mechanism involving reactive oxygen intermediates [31]. EGFR activation was shown to promote nonhomologous end-joining (NHEJ) DNA repair via MAPK activation and DNA repair activity can be prevented when EGFR signaling is blocked by cetuximab or erlotinib [32]. Moreover, expression of the EGFR occurring mutant EGFRvIII in cancer cells was associated with accelerated repair of DNA double-strand breaks attributed to a mechanism involving the DNA-dependent protein kinase catalytic subunit (DNA-PKcs) since EGFRvIII failed to regulate DNA repair and confer radio-resistance in DNA-PKcs-deficient cells [33].

An alternative mechanism by which ErbB receptors can regulate DNA repair mechanisms is via cell cycle checkpoints. For instance, stimulation with EGF produces proliferative signals in large part due to the activation of the transcription factor AP-1 [34, 35]. The cylin dependent kinase inhibitor $p21^{waf1}$,which is positively regulated by EGFR, is involved in the resistance to bulky adducts induced by cisplatin and its disruption preferentially sensitizes some cell types to cisplatin and nitrogen mustard [36]. However, the relationship between EGFR expression and resistance to cisplatin or -radiation seems to depend on cellular contexts and it has been proposed that a critical level of EGFR signaling, including MAPK activation, is necessary for the regulation of the switch between repair of cisplatin adducts and apoptosis in tumor cells [37–40].

3 Signal Transduction Pathways that Regulate Effectors of the DNA-Damage Response

The protein kinases that are coupled to growth factor receptors to phosphorylate DNA repair and effectors of cell cycle arrest checkpoints can be divided in two major groups. The first group includes kinases activated by damaged DNA and associated with inherent

DNA repair and cell cycle arrest disorders. As such, deficiencies in the gene products of *a*taxia *t*elangiectasia *m*utated (Atm), its homologue Atr, or the *DNA*-dependent *p*rotein *k*inase (Dna-pk) predispose to cancer and correlate with high radiosensitivity and abnormal cell cycle arrest. The role of these kinases in the DNA damage-induced checkpoints has been extensively reviewed [2], but as described in some of the accompanying chapters there is a growing body of information expanding our understanding of the roles of these kinases in the regulation of DNA repair processes. A second very broad group includes the kinases of MAPK and stress-activated signal transduction pathways that are activated by several stress stimuli, including chemotherapy. These kinases include Erks (Fig. 2a, b) as well as the p38 and Sapk serine/threonine kinases (Fig. 3a–d). Depending on the stress, activation of the Sapks of the Mapk superfamily can be the result of growth factor receptor activation, cytoskeletal alterations, or of the signals emanating from the damage-activated kinases, e.g., via the Atm ⇒ Abl ⇒ Map3k pathway. It is therefore evident that the cellular response to stress depends on a multitude of factors, including the unique characteristics of the stress itself, as well as the expression patterns of a vast number of proteins with highly integrated yet often opposing functions. The pathways described herein reflect the complexity and the diversity of phosphorylation-dependent mechanisms that mammalian cells use to deal with chemotherapy-induced DNA damage response.

3.1 Sapk/Mapk Transduction Pathways and the Stress Response

The stress-activated protein kinase (Sapk) has been generally referred to as the c-*j*un *N*-terminal *k*inases (Jnks) and p38. The Jnk (henceforth referred to as Sapk) and p38 kinases are members of the Mapk superfamily. The hierarchical nature of signaling through the superfamily is illustrated by the *r*eceptor *t*yrosine *k*inase (RTK) ⇒ *E*xtracellular signal *r*egulated *k*inase (Erk) pathway (Fig. 2a). In the prototypical cascade, ligand binding stimulates receptor activation (e.g., through dimerization) which results in auto- and trans-phosphorylation of multiple tyrosine residues. These residues are bound by adapter proteins such as the SH2-containing *g*rowth factor *r*eceptor *b*ound protein-*2* (Grb2). Grb2 is bound to *s*on *o*f *s*evenless (Sos) via SH3 domains, and the latter acts as a *g*uanine nucleotide *e*xchange *f*actor (GEF), stimulating the exchange of GDP for GTP bound by Ras, resulting in activation of this kinase. Ras is a farnesylated protein and therefore membrane-bound; upon its activation, it becomes an adaptor itself, recruiting Raf to the membrane. The precise mechanism of Raf-1 activation by Ras is not yet clear, but localization to the membrane as well as other signals emanating from activated Ras are necessary. Raf-1 represents the first component of the Mapk core pathway, a signaling module that is reiterated in several parallel forms responding to a variety of stimuli. The highest-level component of this module is variously labeled Mapkkk, Map3k, or Mekk, and, in the case of Raf-1, its activation results in the amplification of the extracellular signal through Mek1/2 and Erk1/2. As noted above, aberrant growth factor receptors can result in signal amplification and provides upstream control points to modulate both the duration and specificity signaling.

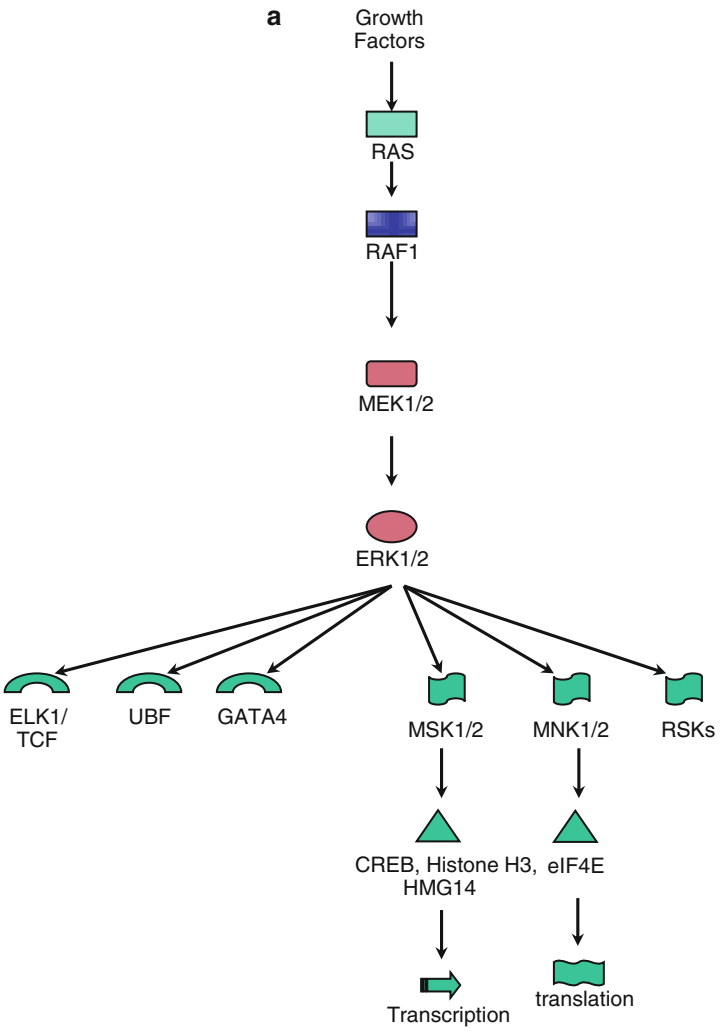


Fig. 2 (**a**) A pared-down representation of the MAP3K>MEK>MAPK cassette. (**b**) Inhibitors of the ERK pathway include a number of MAPK phosphatases, the commonly used MEK1 inhibitor PD98059, and several effector kinases activated by the p38 pathways, such as PRAK and MAPKAP-K2. Note also that PP1 and PP2A have been reported as targets of p38 (see Fig. 3c)

The Sapks (Fig. 3a, b) and p38 (Fig. 3c, d) are strongly activated by cellular stresses, including DNA damage by chemotherapy drugs, oxidative stresses, hyper- and hypoosmolarity, heat shock, anisomycin, heavy metals, and other insults. Indeed, the c-jun N-terminal kinase, Jnk1, was cloned and identified as a kinase phosphorylating c-jun on Ser-63 and Ser-73 [41] following UV irradiation. A simplified impression is that Erk activation results from growth factor stimulation and promotes survival/proliferation, whereas cytotoxic agents activate the Sapks,

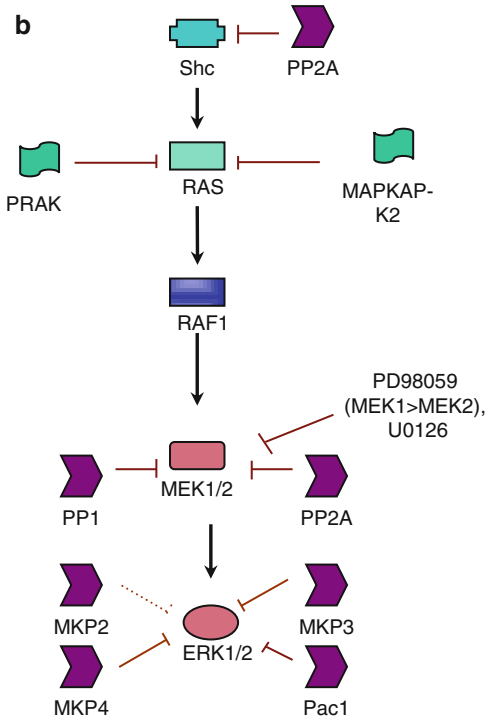


Fig. 2 (continued)

leading to "damage control" or apoptotic responses. Unfortunately, there is a great deal of reiteration between the various pathways, each making distinct (though not yet fully resolved) contributions to survival in response to various stress conditions. Furthermore, a broad "stress," such as chemotherapy, is often multifactorial. These stimuli, for instance, all have concomitant elements of oxidative stress, which also modulate SAPK activation.

Common laboratory models provide a second example of the complexity of DNA damage response . For instance, UV can potentially activate Sapks through at least three mechanisms: direct DNA/protein damage; as a consequence of RTK oligomerization; or via inactivation of phosphatases or other effects of oxidative stress. These phenomena were examined in Rat1 fibroblasts [42, 43] treated with UVB (λ 280–320 nm), with the goal of discerning the contribution of oxidative stress to Sapk activation. Interestingly, the induction of Sapkγ activity was strong and rapid in response to UVB, and the kinetics of this response were similar to those seen upon treatment with the ribotoxin anisomycin, but differed from the slower and more gradual induction seen upon arsenite treatment (an inducer of oxidative stress). These kinetics were mimicked by those of Sek1activation (Sapk activator). Further, the activation of Sapkγ in response to UVB, anisomycin, and IL-1α was not blunted by 30 mM n-acetyl cysteine (NAC) pretreatment, though this was sufficient to completely ablate the

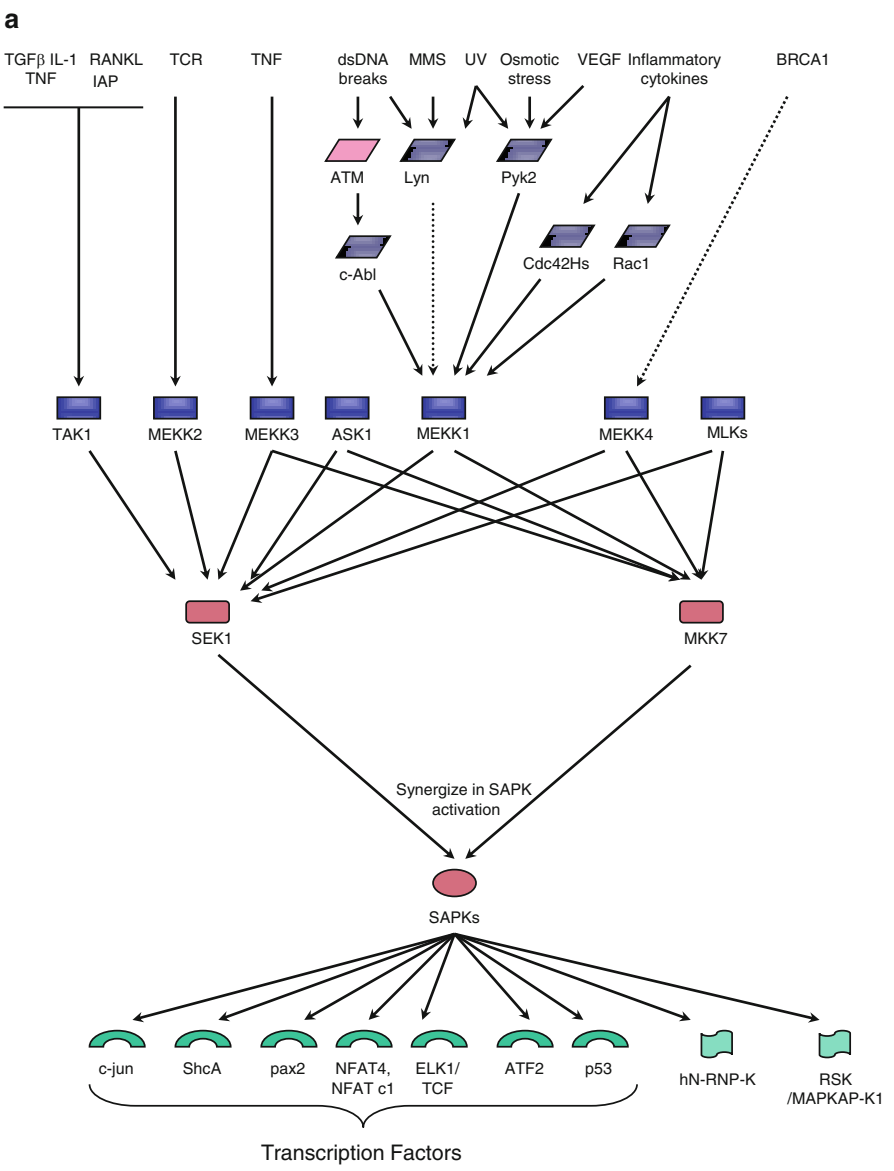
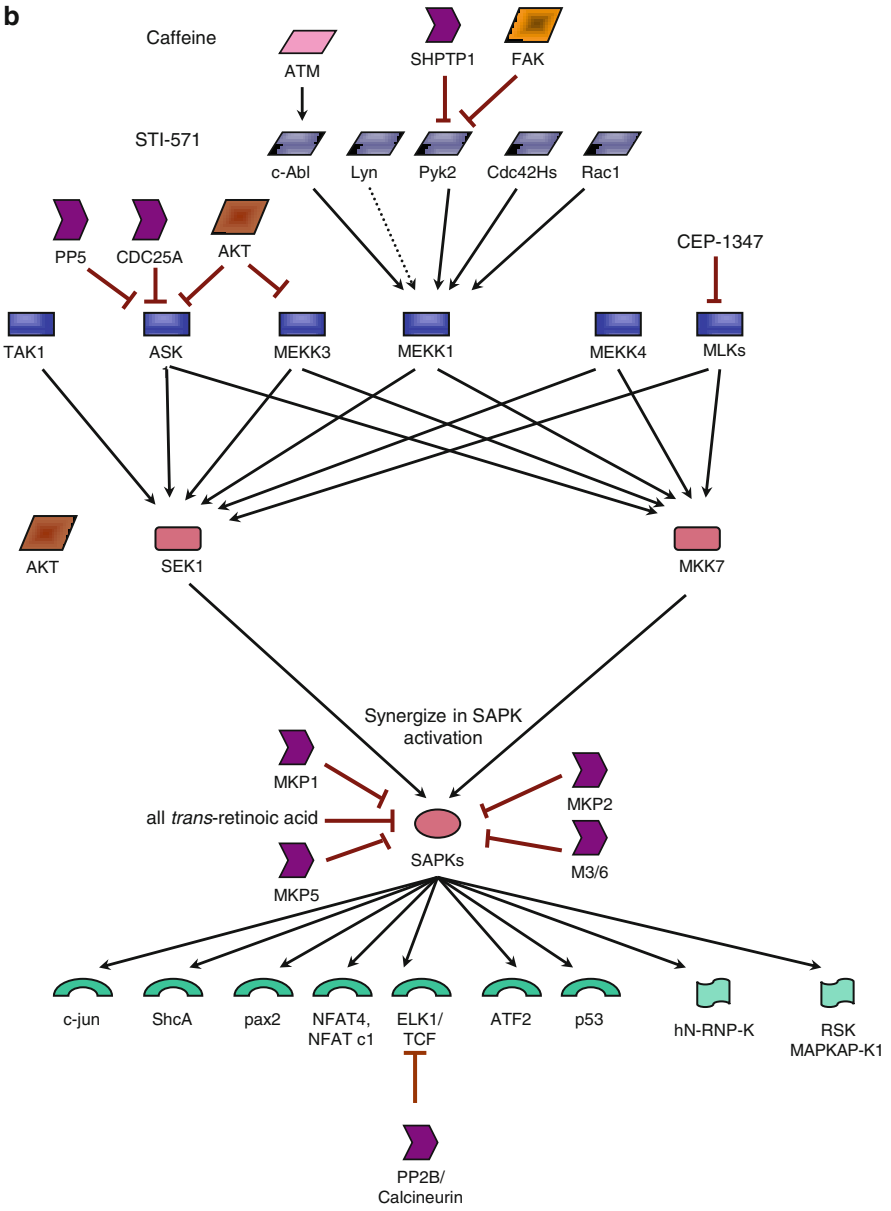


Fig. 3 (**a**) Major activators of SAPK pathways. Activators stimulate MAP3Ks either directly or via kinases upstream of the prototypical MAP3k>MEK>MAPK cassette. A given genotoxic/chemothereapeutic agent may activate one or several MAP3Ks. MEKK1 represents a major point of convergence for signals arising from genotoxic agents. Signals are then transmitted to SEK1 and MKK7 which synergize in the activation of the SAPKs, resulting in effects on transcriptional activity via SAPK-target transcription factors. (**b**) Inhibitors of the SAPK pathway and upstream kinases include physiological inhibitors such as phosphatases and kinases, as well as pharmacological inhibitors. (**c**) Many of the MAP3Ks that stimulate SAPK activation appear to be shared with the p38 pathway, e.g., ASK1, MEKK3, MEKK4, TAK1. Each of these activates MKK3 or MKK6 (or both). MKK3 appears to activate p38α and -β, while MKK6 activates all four p38 isoforms.



SEK1 has also been reported to activate p38s; its upstream activators are shown in Fig. 3a. p38 kinases exert their impact via several mechanisms, including activation of transcription factors, effector kinases, and phosphatases. In the case of Cdc25, phosphorylation results in inactivation and degradation. (**d**) Inhibitors of the p38 pathway include a wide array of MAPK phosphatases, kinases, and pharmacological inhibitors such as the CSAIDs. A notable characteristic of the CSAIDs is that they inhibit p38α and -β, but have little activity towards p38γ or -δ (i.e., they inhibit the same subset of isoforms activated by MKK3)

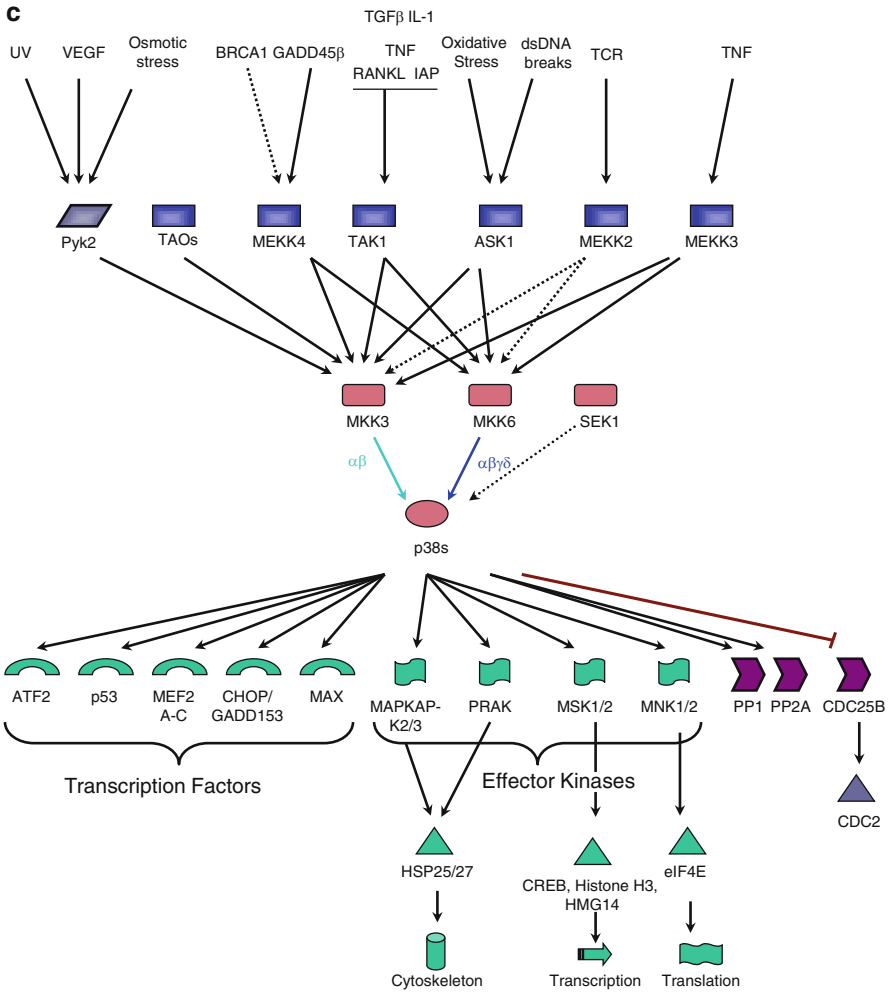


Fig. 3 (**c**) (continued)

arsenite and cadmium chloride stimulation of the enzyme. Thus it appears that oxidative stress does not play a substantial role in Sapkγ activation by UVB, but rather that the activation may be via another mechanism such as direct ribotoxicity.

In the case of platinums (cisplatin and carboplatin), a survey of the literature indicates a broad and varied activation of Mapk/Sapks in response to different chemotherapeutics and DNA-damaging agents. Mitogen-activated protein kinase (MAPK) pathway and DUSP6, a phosphatase involved in dephosphorylation of extracellular signal-regulated kinase (ERK) were reported to regulate the induction of the NER gene, ERCC1,following exposure to cisplatin in melanoma resistant cells [44]. Furthermore, prolonged activation of c-jun N-terminal kinase activity was reported in cells treated with cisplatin but not with transplatin (a therapeutically inactive isomer of cisplatin) [45]. While transplatin

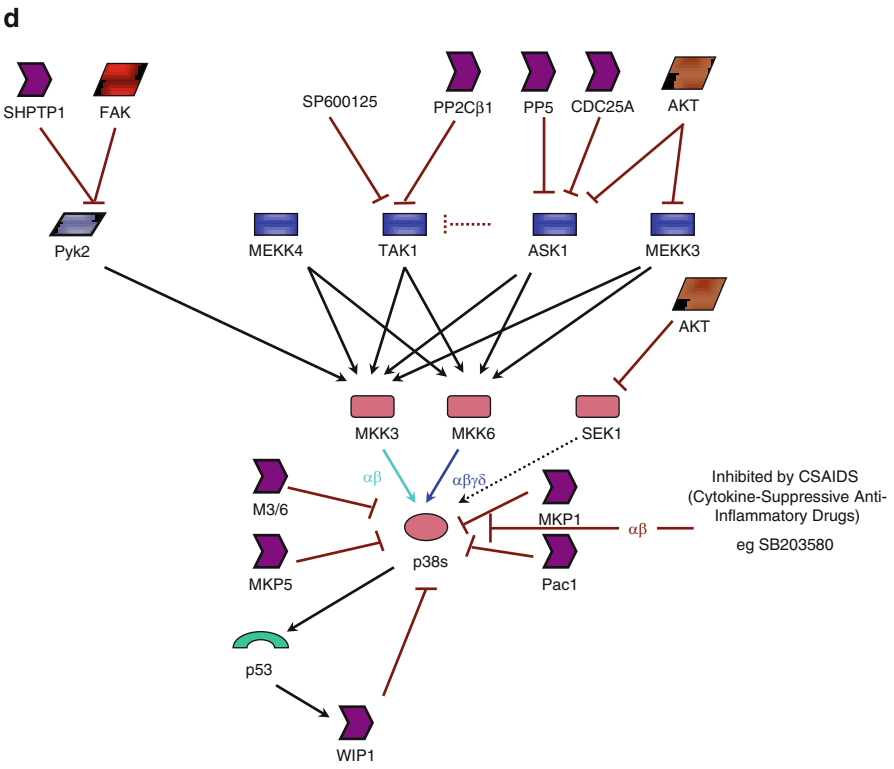


Fig. 3 (**d**) (continued)

produced a rapid and transient increase in c-jun phosphorylation, cisplatin stimulated a more prolonged increase. Furthermore, transplatin was a very effective inducer of MKP-1, (a dual-specificity phosphatase which inactivates p38 and Sapk), while cisplatin induced only a marginal increase in MKP-1 protein levels.

The amplitude of Sapk activation by cisplatin may vary depending on cell lines used, but most reports indicate a similarly prolonged Sapk activation in response to this drug [45–47]. In contrast to the c-jun kinases, there are discrepancies with respect to the reported effects of cisplatin on p38 activity. While some studies reported no effect [48], others observed a strong induction of p38 [46], notably p38γ [49]. This induction is significant with respect to analyses of Sapk pathways because, although it is often considered a minor isoform, p38γ has been suggested to be more efficient in phosphorylating ATF2 than p38α [50, 51]. Equally important, inhibition of the p38 mitogen-activated protein kinase signal, or knockdown of p38 expression was reported to significantly decrease etoposide-induced ERCC1 protein levels and DNA repair capacity in lung cancer cells [52]. Noticeable, the *c*ytokine-*s*uppressive *a*nti-*i*nflammatory *d*rugs (CSAIDs) such as SB203580, which are commonly used to inhibit the p38 kinases, do not inhibit p38γ or -δ, but rather exert their effect exclusively through the predominant isoforms, p38α and -β [51]. Furthermore, the

emerging role for p38 as a principal mediator of UV-induced G2/M arrest deserves particular attention when it comes to DNA interacting chemotherapy [53].

Another step in the pathway from DNA damage to Sapk activation has recently been filled in with the finding that cells from c-Abl$^{-/-}$ mice are defective in Sapk activation in response to cisplatin and ionizing radiation (IR), but not inflammatory cytokines [54]. c-Abl was shown to physically associate with Mekk1, a Map3k upstream of Sek1 and Sapk. This association was inducible in the nucleus upon treatment with DNA damaging agents. Furthermore, a cellular inhibitor of Sapk activation, Jip-1, can inhibit Bcr/Abl-induced transformation [55]. Rac1 and Cdc42Hs are kinases upstream of Mekk1, and the expression of dominant negative mutants of these enzymes ablate Sapk activation in response to cytokines [56]. They do not, however, affect Sapk activation upon treatment with IR [54], indicating that the Mekk1 sits at a point of convergence in the regulation of Sapk responses to various stresses (Fig. 3a). This is further supported by the observation that UV stimulates Sapk activation through a Pyk2 ⇒ Mekk1 pathway [57].

Phosphorylation of c-Abl by the DNA damage-signaling kinase Atm has also been proposed, with the further suggestion that c-Abl may be involved in the down-regulation of Dna-pk activity [58]. This would indicate that double-stranded DNA breaks induce Sapks via the pathway Atm ⇒ c-Abl ⇒ Mekk1 ⇒ Sek1 ⇒ Sapk.

A final example of Sapk pathway activation by chemotherapy agents can be found in the *a*poptosis *s*ignal regulated *k*inase-1 (Ask1). Ask1 lies upstream of both the Sapk and p38 kinases, and is a MAP3K. It is strongly induced by cisplatin treatment of Ovcar3 ovarian carcinoma cells with kinetics similar to those observed for Sapk activation in response to cisplatin [59]. Interestingly, Ask1 has also been shown to associate with and phosphorylate Cdc25A [60] (Fig. 2b), a proto-oncogene which is overexpressed in several cancers. In this case, however, the interaction between Cdc25A and Ask1 appears to be independent of the former enzyme's phosphatase activity. Overexpression of Cdc25A or phosphatase-deficient Cdc25A (C430S) resulted in decreased activation of Ask1 in response to the oxidant H_2O_2. This also led to suppression of Sapk and p38 activation in response to this stress. This apparent inhibition of Ask1 by Cdc25A may be a negative feedback mechanism for p38 or Sapks. Though Cdc25A is predominantly nuclear, it has previously been shown to associate with cytoplasmic Raf1 [61], and all three Cdc25 isoforms conditionally associating with 14-3-3 proteins, with the phosphorylation and nuclear export of Cdc25A being a mechanism of Chk1 and Chk2 regulation of its activity in response to UV and γ-radiation, respectively [62, 63]. Furthermore, p38 phosphorylates Cdc25B in the cytoplasm at the G2/M checkpoint in response to UV [53]; thus all three Cdc25 isoforms could potentially participate in cytoplasmic interactions to regulate Sapk signaling.

In summary, the activation of multiple Sapk/Mapks in response to chemotherapy stress can trigger multiple signals whose specificity is often cell type-dependent. The precise role of each kinase in the DNA damage response is, however, somewhat more difficult to discern. This is further complicated by the broad range of DNA damage types induced by anticancer drugs, the high degree of cross talk between the mitogen- and stress-activated protein kinase pathways as well as by the cell heterogeneity observed in cancer tissue.

3.2 Biological Significance of SAPKs Activation to Chemotherapy Response

As seen above, DNA damaging agents, including chemotherapy drugs, produce strong activation of Sapk/Mapks through a number of different mechanisms. The activation of these kinases modulate DNA damage response to contribute to either cell death or survival, depending on the context. Expression of a dominant negative (dn) (non-phosphorylatable) c-jun construct was shown to sensitize a cisplatin-resistant cell line proposed to be the result of a repair defect in the dn-c-jun-expressing cells; this association was not observed with the therapeuticaly inactive analogue transplatin [64]. The lack of induction of c-jun kinase activity by transplatin conflicts with the result of Sanchez-Perez et al. [45], though this is in agreement with Hayakawa et al. [47], suggesting that differences in cell lines and assay conditions may be responsible for some of the discrepancy. Of particular relevance, activation of SAPK/JNK was reported to be induced by non-repaired cisplatin adducts in transcribed genes and this led to activation of DNA repair factors including Ataxia telangiectasia mutated- and Rad3-related kinase, and replication protein A [65]. In contrast to the suggested protective role of c-jun in response to cisplatin, a paper by Sanchez-Perez et al. [66] indicates a pro-apoptotic role for c-jun in response to cisplatin. Using a knockout mouse embryonic fibroblast cell model, the authors show that c-jun$^{-/-}$ cells are resistant to cisplatin, but can be sensitized by restoration of c-jun by transfection.

Clearly, some of the effects of Sapk/Mapk activation in response to DNA damaging agents remain to be established, with particular attention given to choice of the cell line, method measuring kinase activation and mechanism of pathway inhibition. The importance of the latter issue is emphasized by the disparate results of studies using dominant negative mutants [47, 64] or knockout cell lines [66] to study the function of jun in response to cisplatin. Moreover, the effect of Sapk can be complicated by the impact on other DNA damage responsive genes such as the *G*rowth *a*rrest and *D*NA *d*amage 45 (Gadd45), a stress-inducible protein regulated by Sapk/Mapks and implicated in G2/M checkpoints, and possibly in DNA repair by modifying chromatin structure [67, 68].

3.3 Modulation of Sapk/Mapk Activation by DNA Damage, the Case of p53

p53 regulation (via phosphorylation) by Sapks has broad implications for the regulation for DNA damage response, including DNA repair. The multifunctional tumor suppressor p53 is involved in both DNA repair and cell cycle arrest [69]. Transcriptional control of gene expression by p53 [70] is essential for the cellular response after DNA damage and phosphorylation is limiting to this regulation. In DNA-damaged cells, p53 is phosphorylated on many Serine/Threonine residues resulting in modulation of its affinity for different transcriptional targets. For example,

phosphorylation of Ser15 is increased following UV-induced DNA damage and correlates with nuclear shuttling of p53 [71]. Phosphorylation on Ser residues enhances transcription of the Cdk inhibitor $p21^{waf1}$, which contributes to cell cycle arrest [72]. This implies that this is one mechanism by which deficiencies in kinases upstream of p53, such as Atm and Chk2, result in impairment of DNA damaged-induced cell cycle arrest [73]. Also, loss of p53 function can compromise induction of apoptosis and DNA damage repair resulting in drug resistance, increased mutation, and neoplastic progression.

During genotoxic stress p53 is subject to multiple phosphorylations. Sapk phosphorylation of p53 on Thr-81 is important for p53 stabilization and for its transcriptional activities in response to stress [74]. Both Erk1/2 and p38 have been implicated in the regulation of p53 function in response to NO [75]. However, the phosphorylation of p53 by Pka, Sapks, and CKII is conformation-dependent [76]. The mutations affecting the p53 tumor suppressor genes in Li-Fraumeni syndrome and more than 50% of all sporadic cancers are clustered in the DNA binding domain and affect the transcriptional activity and conformation which in turn is likely to affect its phosphorylation, resulting in inactive forms of p53 [76]. Furthermore, viral oncoproteins functionally inactivate p53 in a large proportion of tumors with genetically intact p53 locus [77–79]. Notably, p53 was shown to enhance sensitivity to EGFR inhibitors via induction of cell-cycle arrest, apoptosis, and DNA damage repair [80]. As such, p53-dependant pathways are attractive targets to manipulate cancer cell response to chemotherapy drugs.

The association of p38 and Erks with p53 in untreated UVB- and UVC treated cell lysates has been reported [81, 82], while the dissociation of p38 from p53 following UV or cisplatin [83] has also been observed. As is often the case, some of these differences may be due to the particular cell lines studied or to the types of UV (UVB versus UVC) used. The most significant difference, however, is that one report suggests p38 and Erk phosphorylation of p53 Ser15 in response to UV and cisplatin [81], while another states that the phosphorylation is primarily on Ser33, not Ser15 [82]. While the former study shows that p38 and Erk can co-precipitate p53, and that their inhibition blocks phosphorylation of p53 on Ser15, the latter shows a similar co-precipitation, and an absence of kinase activity towards an artificial p53 substrate consisting of the first 25 aa of this protein. The solution to the apparent conflict seems to lie in the phosphorylation of Ser33 by p38, which appears to be required for phosphorylation at surrounding sites. In a similar vein, another study examined the effect of Erk inhibition on p53 Ser15 phosphorylation in response to cisplatin [84]. This report suggests that the MAPK/ERK inhibitor PD98059 is more effective than wortmannin (DNA-PK, Atm inhibitor), caffeine (Atr inhibitor) or the p38 inhibitor SB202190 at inhibiting phosphorylation of p53 at Ser15. Further, PD98059 completely ablates both p21waf1 and Mdm2 induction following cisplatin treatment, suggesting a strong effect on p53 transactivation. Again, however, these extensive inhibitor studies involve mostly whole-cell treatments with inhibitors, supporting the conclusion of Bulavin et al. [82], namely, that Mapk phosphorylation of p53 Ser33 coordinates further N-terminal phosphorylations.

The involvement of other Sapks in the response to cisplatin was further investigated using dn-Sek1 to inhibit the Sapk pathway, and SB202190 or SB203580 to inhibit p38α/β [46]. Neither of these treatments had an observable effect on apoptosis, indicating that Erk, but not Sapk or p38, plays a role in inducing apoptosis in response to cisplatin. As is often the case, however, these results do not apply to all cell lines, as PC3 cells show no effect of Erk inhibition on apoptosis, and the in fact these results conflict with the above studies using dn-c-jun and c-jun knockouts [47, 64, 66]. Interestingly, the fact that PC3 cells are p53 mutant may suggest that the mechanism of Erk-dependent apoptosis is via p53, as suggested for p38, and as would be expected given the results of Persons et al., [84] as noted above. This too, must be appraised cautiously, however, given the contrasting findings that PD980159 *sensitizes* Caov-3 (p53 mutant) and A2780 (p53 wt) ovarian carcinoma cells to cisplatin [47], as well as C8161 melanoma cells (p53 wt) [85].

3.4 p38 As a Checkpoint Kinase: Regulation of Two Steps

Consequent to DNA damage, the dual-specificity phosphatase Cdc25A is rapidly degraded, resulting in maintenance of inhibitory phosphorylation on Cdks and delayed transition from G1 to S phase. In the absence of functional p53, the cell cycle resumes concomitant with restoration of Cdc25A expression while arrest can be completely avoided by Cdc25A overexpression [62]. This arrest is therefore reinforced by p53-dependent $p21^{waf1}$ expression, which similarly targets the Cdks, resulting in Rb hypophosphorylation. Phosphorylation of Cdc25 phosphatases creates 14-3-3 binding sites leading to their sequestration in the cytosol following various stresses [86]. Chk1, Chk2, and p38 have been shown to phosphorylate the various Cdc25 isoforms in response to several cellular stresses (reviewed in [87]). In response to ionizing radiation, Cdc25A is phosphorylated by Chk2, while Chk1 phosphorylates Cdc25C [88]. In contrast, upon UV irradiation, Cdc25A is phosphorylated in a Chk1-dependent fashion, representing the first wave of a bipartite G1/S checkpoint [62]. Cdc25B is phosphorylated by p38 following UV treatment, initiating the G2/M checkpoint [53]. As mentioned above, UV-induced checkpoints are reinforced by p38 phosphorylation of p53, coordinating subsequent phosphorylations around the N-terminus of p53. Similarly, p38, Chk1, and Chk2 play a dual role in phosphorylating both p53 and Cdc25s.

In a negative feedback loop, p53 downregulates Chk1 transcription [89], while p38 is inactivated by the p53-inducible Wip1 [90]. Repression of Chk1 by p53 requires p21waf1, since p21waf1 alone is sufficient for this to occur and cells lacking p21waf1 cannot downregulate Chk1[89]. Interestingly, pRb is also required for Chk1 downregulation. p53 and Chk1 play interdependent and complementary roles in regulating both the arrest and resumption of G2 after DNA damage [89]. p53/p21waf1/pRb are also required for maintenance of G2 arrest [91, 92]. Another transcriptional target of p53, the 14-3-3 phospho-binding proteins, is involved in the initiation and maintenance of the G2 arrest by sequestering Cdc25C in the cytoplasm [93]. Although 14-3-3 proteins are not kinases, their cell cycle arrest function

relies mostly on kinase activities since they bind phosphorylated proteins with much greater affinity. Thus, the Mapk/Sapks are emerging as regulators of this pathway at several points. Erk and p38 can phosphorylate p53 [81–84], resulting in induction of p21, as well as Gadd45, which is proposed to regulate the G2/M checkpoint by disruption of the Cdc2–cyclinB1 complex [94]. Gadd45 induction following UV is also proposed to be directly mediated by Sapks and Erks, though not p38, in a p53-independent manner [67]. We therefore see each of the major Mapk/Sapk family members playing an important role in checkpoint regulation: Sapk and Erks through Gadd45 induction, p38 and Erks through p53 phosphorylation, and p38 through Cdc25B phosphorylation. Additional effects of these kinases on apoptosis (terminal cell cycle exit), are also apparent, but are beyond the scope of this chapter.

4 Kinases Involved in Phosphorylation of DNA Repair Proteins

In general, mammalian DNA repair proteins are not thought to be transcriptionally inducible, though some show minor induction in specific circumstances. This may be because basal levels of genomic insult are sufficient to require a constantly functioning repair system. It is also logical that DNA repair proteins are primarily regulated posttranscriptionally, since DNA lesions would impede their expression. ERCC1, for example, is induced following cisplatin treatment of A2780 ovarian carcinoma cells, reportedly by a combination of increased transcription and mRNA stabilization [95]. Additionally, some of the enzymes providing the basic building blocks required for repair may be induced following UV irradiation [96]. However, it is likely safe to assume that the major part of repair activity modulation derives from posttranslational modification or association with proteins (e.g., p53), which are stabilized in response to genotoxic insult. Indeed, posttranslational modification of cell cycle checkpoint and DNA repair proteins can stimulate arrest and repair via several mechanisms [97, 98]. The phosphorylation status of these proteins can modulate their stability [99], complex formation, subcellular localization [100, 101], catalytic activity [102], DNA binding affinity and transcriptional activity [103], as well as structural remodeling affecting both the protein and chromatin structure [104, 105]. As such, the kinases of the signal transduction pathways activated by genotoxic stress will directly or indirectly modulate DNA repair and cell cycle.

Nucleotide excision repair (NER) is modulated by phosphorylation and kinase inhibitors.

Activation of p53 by phosphorylation is important for efficient DNA repair. To date, however, little is know regarding the modulation of DNA repair activities due to phosphorylation of DNA repair proteins per se. It has been shown that nucleotide excision repair is inhibited by phosphorylation (via CAK phosphorylation of repair components) and that the inhibition of CAK by the cyclic nucleotide protein kinase inhibitor, H-8, restores the NER activity to original levels [106], suggesting that the activity of the NER can be downregulated by phosphorylation. This is an important finding to understand the controversial role of the p53-regulatory pathway and specifically its downstream

effector, $p21^{waf1}$, in the regulation of NER. The role of CAK in NER provides a link between $p21^{waf1}$ and NER since high levels of $p21^{waf1}$ can inhibit CAK in vivo [92], which in turn should increase NER activity. This model would support studies describing the contribution of $p21^{waf1}$ in NER [107, 108]. This is in apparent contrast with other studies showing that $p21^{waf1}$ has little effect [108–110] or an inhibitory role in NER [111]. In addition, a recent study showed by LM-PCR that basal levels of $p21^{waf1}$ inhibited NER in a p53-deficient background [112]. This deficiency in NER may be interpreted on the basis of the CAK/NER complex interaction.

The inhibition of NER has been used as an approach to improve cisplatin-based chemotherapy, particularly in cisplatin resistant tumors. Unfortunately, treatment with cisplatin and other bulky adduct inducing drugs, e.g., alkylating agents, is inconsistently successful despite frequent low NER capacity in tumor cells due to p53 deficiencies (50% of all cancers) which impairs both global genomic NER [113] and transcription–coupled NER [114]. Other repair pathways such as base excision repair (BER) can act on damage preferentially repaired by NER, perhaps representing a mechanism by which to overcome NER-deficiency. It should be noted, however, that p53 plays a direct role in BER by stabilizing the interaction between DNApolβ and abasic DNA [115, 116]. Therefore, p53 deficiencies would compromise BER as well, and this repair mechanism is unlikely to compensate for NER lost in a p53 deficient background.

4.1 p53-Dependent DNA Repair

Gadd45 and $p21^{waf1}$ are two DNA-damage inducible genes that can be induced via both p53-dependent and –independent pathways. Many studies implicate those two stress-inducible proteins in NER and apoptosis [117]. In vivo $p21^{waf1}$ can be phosphorylated by protein kinase B (Akt/Pkb) [118], an anti-apoptotic kinase. Both Gadd45 and $p21^{waf1}$ interact with PCNA [119, 120], which is known to affect cell cycle progression by supporting DNA repair and, indirectly, survival. An additional function of Gadd45 is to bind to UV-damaged chromatin, which affect lesion accessibility [117]. A direct role for $p21^{waf1}$ phosphorylation in NER has not been addressed; however, phosphorylation by mitogen-activated protein (MAP) kinases is involved in the induction of the Gadd45 promoter after DNA damage [67]. Similarly, inhibition of Sapkγ and Erk kinase activities either by expression of a dominant negative mutant Sapkγ or by treatment with a selective chemical inhibitor of Erk (PD098059) substantially abrogates the UV induction of the Gadd45 promoter [67]. P53-independent induction of Gadd45 [121] and $p21^{waf1}$ [122] has been described following DNA damage, including treatment with cisplatin [123]. Notably, colon carcinoma is characterized by frequent p53 and mismatch repair deficiencies. The p53-dependent upregulation of human mismatch repair gene MSH2 in UV-irradiated colon carcinoma cells depends on a functional interaction with c-jun [124],(Although UV is not a therapeutic agent, some of its properties may reflect those of more relevant chemotherapeutic agents). As described above, the c-jun kinases (Sapks) are activated by many cellular stresses, including cisplatin.

4.2 Replication Protein A

Among the many proteins involved in NER, replication protein A (RPA) is one factor known to be phosphorylated after DNA damage, though the kinase(s) responsible have not yet been determined. The single stranded DNA binding protein RPA is a multifunctional hetero-trimer involved in NER [106, 125] replication, and repair of strand breaks [126, 127]. RPA is modified by phosphorylation during replication [128] and the DNA damage response [129]. In particular, the 32-kDa subunit is phosphorylated following UVC [130]. Hyperphosphorylation of RPA has been observed in cells from patients with either GGR or transcription-coupled repair (TCR) deficiency (A, C, and G complementation groups of Xeroderma pigmentosum and A and B groups of Cockayne syndrome, respectively). This excludes both intermediates in the NER pathway and signals from stalled transcription as essential signals for RPA hyperphosphorylation. However, UV-sensitive cells deficient in NER and TCR require lower doses of UV irradiation to induce RPA32 hyperphosphorylation than normal cells, suggesting that persistent unrepaired lesions contribute to RPA phosphorylation. UVC irradiation experiments on nonreplicating cells and S-phase-synchronized cells emphasize a role for DNA replication arrest in the presence of UV-induced lesions in RPA UV-induced hyperphosphorylation in mammalian cells [130]. One might therefore speculate that inhibition of RPA phosphorylation could improve treatments inducing NER-substrate lesions.

4.3 O^6-alkylguanine-DNA Alkyltransferase

The expression of O^6-alkylguanine-DNA alkyltransferase (AGT) (26) a DNA repair protein that confers tumor resistance to many anticancer alkylating agents is upregulated in the absence of p53 [131] and frequently overexpressed in oral cancer cells genetically and functionally deficient for p53 [132]. p53 thus acts as a repressor of AGT expression, whereas the activators of Pkc, phorbol-12-myristate-13-acetate (PMA), and 1,2-diacyl-sn-glycerol (DAG), as well as the protein phosphatase inhibitor, okadaic acid (OA), increase the transcriptional level of AGT(27). The activity of AGT is inhibited by phosphorylation that can be catalyzed by Pka, Pkc, and/or CKII [133]. Thus the activation of these kinases may impair the elimination of akylated DNA lesions.

4.4 Blm Helicase

Bloom's syndrome (BS), a rare genetic disease, arises through mutations in both alleles of the Blm gene which encodes a 3′-5′ DNA helicase. BS patients exhibit

a high predisposition to development of all types of cancer affecting the general population and Blm-deficient cells display a strong genetic instability. Blm participates in the cellular response to ionizing radiation. The Blm defect is associated with a partial escape of cells from the γ-irradiation-induced G2/M cell cycle checkpoint. In response to ionizing radiation, Blm protein is phosphorylated and accumulates through an Atm-dependent pathway [134]. Caffeine, by inhibiting Atm and its homologue Atr [135, 136] enhances the radiosensitivity of cells in part by altering the phosphorylation of Blm, in addition to its effects on Chk1 and Chk2, as outlined above.

5 Histone Modifiers Implicated in the Regulation of DNA Damage Response and DNA Repair

In response to DNA damage, detection of lesions and repair of DNA must occur in the context of chromatin ultrastructure. Folding into chromatin alters the accessibility of the DNA to proteins involved in DNA transactions. Likewise, several mechanisms have evolved to regulate the chromatin-packaged state of DNA under stress response. These include: covalent histone modifications, ATP-dependent chromatin remodeling and histone variant incorporation. In this context, genetic studies have revealed that mutants of histone modifying proteins and chromatin remodellers often show sensitivity to genotoxic agents. Covalent histone modification, including histone phosphorylation, methylation, acertylation, or ubiquitination are associated with DNA damage response, including checkpoint mechanisms. As reviewed by Costelloea et al. [137], several enzymes associated with chromatin remodeling are involved in the DNA damage response, in particular, the DNA double strand break (DSB). These include: Mec1 (Stable retention of DDR checkpoint proteins at DSB, DSB repair), CK2 (DNA damage regulated kinase that phosphorylates H4S1, linked to histone deacetylation), Dot 1 (Required for 53Bp1, Rad9 recruitment to DSB, checkpoint activation in S. cerevisiae, marks active chromatin), Set1 (Involved in checkpoint activation in *S. cerevisiae*, H3K4me2, H3K4me3, mark 5′ region of active genes, H3K4me1 localized to silenced chromatin), Esa1, Gcn5, and Hat1. For instance, extensive phosphorylation of H2A(X) is amongst the early events following DSB. γH2A(X) is necessary for the damage-induced focal accumulation of proteins involved in checkpoint signaling, DNA repair, as well as chromatin remodeling. Importantly, this modification is not needed for the initial recruitment to DSBs of key DDR proteins believed to be involved in DNA damage sensing, such as Nbs1 or 53Bp1. Some proteins, for example Mdc1, bind directly to γH2A(X) via an interaction between the Ser139 phosphate and the BRCT domains of Mdc1. However, direct interaction with γH2A(X) has not been demonstrated for all proteins recruited to the site of DNA damage. The recruitment of many of these proteins may be facilitated through other histone modifications.

6 Circumventing Chemotherapy Resistance by Targeting Signaling Molecules That Modulate DNA Damage Response and DNA Repair

The concerted role of plasma membrane growth factor receptors in the regulation of multiple proliferative and survival pathways, including response to chemotherapy-induced DNA damage and DNA repair, make growth factor receptor and their coupled signaling components attractive targets to modulate chemotherapy response in refractory/drug resistant cancer. Several anti-receptors are currently approved for clinical use, either small molecules or antibodies. Also an increasing number of novel inhibitors targeting components of downstream signaling, including Mapk/Sapk, have been identified, some of which have entered or completed clinical trials (reviewed in 138, 139). This exciting progress provides opportunities to exploit this knowledge in formulating alternative combinatorial regimens to sensitize resistant cancer cells to chemotherapy. As noted above, combination of chemotherapy with anti-monoclonal ErbB receptors or small molecule kinase inhibitors sensitize tumor cells to specific DNA-interacting chemotherapy drugs in particular platinums [21, 22, 25–27]. The anti-ErbB2 antibody,Trastuzumab, inhibited or delayed the repair of cisplatin-induced DNA damage, as well as γ-radiation, and enhanced cytotoxicity of cisplatin in preclinical models and in patients [18, 19, 27–30]. A similar result was reported for the EGFR inhibitor, Gefitinib, and cisplatin in ovarian cancer cells [140]. Modulation of DNA repair by ErbB receptors was found to be mediated, at least in part, via the MAK pathway [19, 32], suggesting that targeting MAPKs should achieve therapeutic benefit as well. Interestingly, a variety of MAPK inhibitors are being developed, including noncompetitive inhibitors of MEK1 and MEK2 such as PD98059, PD184352, and U0126; competitive inhibitors of MEK1 and MEK2 such as Ro092210 and LLZ16402; AZD6244 (Selumetinib; locks MEK1/2 into an inactive conformation to prevent ERK phosphorylation), RDEA-119 (an allosteric inhibitor of MEK1/2 with activity when administered by oral route), SP600125 which inhibits Jun-N-terminal kinase 2 (JNK2); CEP1347 (KT7515) which inhibit multiple MAPK kinases (MLK1, 2 and 3), and others targeting p38 (e.g., several p38 inhibitors are being evaluated in clinical trials mostly for rheumatoid arthritis or psoriasis, including Vertex 745 (VX745), RPR200765A, SB235699, and SCIO469. The availability of these targeted molecules certainly opens-up exciting directions to investigate their relevance to the DNA damage response and DNA repair in the context of improving therapeutic response in chemotherapy refractory cancers. In order to selectively sensitize tumors and not normal tissue to chemotherapy, the overexpression of these receptor targets for "chemosensitization" would have to be determined in the tumor. This represents an emerging theme of tumor profiling that ensures that the correct patient sub-group is treated.

The use of modulators that target directly DNA repair mechanisms has also provided encouraging results to modulate chemotherapy response. For instance, the triple-negative breast cancer (TNBC), which accounts for up to 20% of all breast cancers, is an aggressive subtype of breast cancer where targeted therapies used for hormone

receptor-positive and HER2-overexpressing breast cancers are ineffective and with a high incidence of relapse to conventional chemotherapy. DNA reacting drugs such as cisplatin have been shown to be effective in the neoadjuvant setting for TNBC but again relapses are common. The poly (ADP-ribose) polymerase-1 (PARP1), an enzyme involved in DNA repair, is significantly increased in TNBC and other cancer types [141]. Encouraging results have been achieved when chemotherapeutic agents such as platinums are combined with PARP1 inhibitors in TNBC [142]. Of note, potential benefits of a combination of EGFR antibody, Cetuximab, and PARP1 inhibitors was reported in head and neck cancer; this synergistic effects was shown to occur via modulation of nonhomologous end-joining (NHEJ)- and homologous recombination (HR)-mediated DNA double strand break (DSB) repair. Once again, profiling the tumor for the overexpression of the target will help ensure that patient selection is optimal for clinical benefit. [143].

Finally, targeting cell cycle checkpoints required for DNA repair via inhibition of checkpoint mechanisms addressed above is another potential strategy to interfere with DNA repair, e.g., p38, CDC25B, and protein kinase C to abrogate G2 arrest through a Cdc2-dependent pathway. The Atm and Atr kinases and their downstream effectors Chk1 and Chk2 all are also appealing targets to enhance chemotherapy response.

7 Concluding Remarks and Perspectives

The progress in the characterization of DNA damage response signaling and resolution of crystal structures of DNA repair proteins provides exciting avenues toward discovery of selective molecules targeting specific levels of the DNA damage response and with the potential to overcome resistance to DNA-interacting chemotherapy such as platinums, which represent a major class of anticancer agents. An alternative strategy is based on the evidence that receptor signaling-mediated chemo-resistance involves, at least in part, impaired cell cycle checkpoints, increased DNA repair, and/or downregulation of the apoptotic threshold. As noted above, growth factor receptor upregulation is a frequent cause of innate resistance in many types of cancers. Inhibition of the upstream receptors can not only interfere with the proliferative signals but also render cells more susceptible to drug-induced apoptosis. Finally, inhibitors of cell cycle checkpoints are certainly an important Achille's heel of tumor resistance to genotoxic chemotherapy drugs and therefore represent a promising avenue for future therapies. Finally, the potential of incorporating DNA damage response modulators in chemotherapy regimens for refractory or relapsed cancers is not without dilemma. Clinical experience with all anticancer drugs, including targheted agents and therapeutic antibodies revealed to cancer cells are masters of developping alteranative mechanisms to escape cell death. Resistance to inhibitors of DNA-damage associated signaling inhibitors has been documented to occurs via mutations in the target genes, feedback regulatory or compensatory mechanisms [144–148]. Also, heterogeneity in the level and activity of signaling molecules between tumor cell subpopulations can result in differential effect of the inhibitors. Therefore, resistance to

signaling molecules can underscore the potential of a combined therapeutic approach and add to the endless cycle of drug resistance. Certainly, defining genetic alterations of individual tumors is becoming prerequisite to maximizing therapeutic efficacy in the era of individualized medicine, and targeting DNA damage response signaling is no exception. Here too, the emerging tenets of personalized medicine require some means to assess tumors for the overexpression of the targets of chemosensitization, wherther by biopsy, in blood, or by a yet-to-be-defined noninvasive imaging approach, so that there is selective effects on tumor and not normal tissue.

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