Supplementary Table 1 Logical functions of the model

Logical function	Time scale value	Explanation and references
1. camptothecin · topoisomeraseI → DNA SSBs	1	Camptothecin causes DNA single-strand breaks (SSBs) by inhibiting topoisomerase I (Pommier 2006).
2. SN38 · topoisomeraseI → DNA SSBs	1	SN38 causes SSBs by inhibiting topoisomerase I (Pommier 2006).
3. bleomycin → DNA DSBs early	1	Bleomycin causes DNA double-strand breaks (DSBs) (Povirk et al 1996). In the model, there are two components representing DSBs: 'DNA DSBs early' designates DSBs in the early phase of the DNA damage response (time scale value '1'), when DSBs have functions partially different from that in the later phase of the DNA damage response (time scale values '2' and '3') ('DNA DSBs late').
4. HU → DNA DSBs early	1	Hydroxyurea causes DSBs by blocking replication fork progression (Feng et al 2009, Saintigny et al 2001).
5. IR → DNA DSBs early	1	Ionizing radiation causes mainly DSBs by causing blockade of replication fork progression (Ward et al 1988, Löbrich et al 1995).
6. daunomycin · topoisomeraseII → DNA DSBs early	1	Daunomycin (daunorubicin) causes DSBs by inhibiting topoisomerase II (Andoh and Ishida 1998).
7. doxorubicin · topoisomeraseII → DNA DSBs early	1	Doxorubicin (adriamycin) causes DSBs by inhibiting topoisomerase II (De Beer et al 2001).
8. VP16 · topoisomeraseII → DNA DSBs early	1	VP16 (etoposide) causes DSBs primarily by inhibiting topoisomerase II (Baldwin and Osheroff 2005).
9. DNA SSBs → DNA DSBs early	1	During replication, SSBs can be transformed into DSBs (Strumberg et al 2000, Jackson and Bartek 2009).
10. DNA DSBs early → DNA DSBs late	2	DSBs in the early phase of the DNA damage response have roles different from that in the later phase.
11. DNA DSBs early → Ku	1	The Ku dimer becomes activated by binding to DSBs sites (Dong et al 2010).
12. Ku · PP5 → PARP1-PAR	1	The Ku dimer stimulates poly-ADP-ribosylation of PARP1; this depends on dephosphorylation of PARP1 by PP5 (Dong et al 2010).
13. !DNA SSBs · !DNA DSBs early → PP2A-Bx	1	PP2A-Bx ("Bx" designates the unknown identity of subunit B of the complex) is active in the absence of DNA damage, but inactive in the early phase of the response to SSBs or DSBs (Feng et al 2009, Leung-Pineda al 2006); compare logical function 77.
14. DNA SSBs · TopBP1 · !PP2A-Bx · PP5 → RPA-P-ATR-ATRIP-P	1	RPA and the ATR-ATRIP complexes bind to SSBs sites (Zou and Elledge 2003, Zhang et al 2005); this binding, as well as ATR kinase activity depends on catalytic activity of PP5 (Zhang et al 2005), ATR activation depends on TopBP1 (Liu et al 2006, Blackford et al 2010); in the late phase of the DNA damage response, PP2A-Bx inactivates the RPA-P-ATR-ATRIP-P complex by dephosphorylating RPA at threonine 21 and serine 33 (Feng et al 2009).
15. DNA SSBs → Cdc7	1	Cdc7 becomes activated in response to SSBs (Kim et al 2008).
16. DNA DSBs early → Cdc7	1	Cdc7 becomes activated in response to DSBs (Kim et al 2008).
17. nuclear c-Rel · Cdc7 → claspin-P	1	c-Rel expression is not induced by DNA damage, but constituitively active (Xu et al 2008, Radiation Genes Database); c-Rel in turn mediates constitutive expression of claspin (Kenneth et al 2010); Cdc7 actviates claspin by phosphorylation (Kim et al 2008).
18. RPA-P-ATR-ATRIP-P · claspin-P · Timeless-Tipin · !PP2A-Bx · Hsp90 → Chk1-P	1	ATR phosphorylates Chk1 at serines 296, 317 and 345, this depends on claspin (Kim et al 2008, Adams et al 2006, Zhao et al 2001, Petermann et al 2008, Pedram et al 2009) and on the Timeless-Tipin complex (Kemp et al 2010); PP2A-Bx deactivates Chk1 by dephosphorylating at least serines 317 and 345 (Leung-Pineda et al 2006); Hsp90 stabilizes Chk1 (Arlander et al 2003, Tse et al 2009).
19. RPA-P-ATR-ATRIP-P · FHIT · !Wip1 → Chk2-P	1	ATR phosphorylates Chk2 at threonine 68 (Wang et al 2006, Helt et al 2005), this depends on FHIT (Yutori et al 2008), Wip1 deactivates Chk2 by dephosphorylating it at threonine 68 (Fujimoto et al 2006).
20. 2 !ATM-P · !RPA-P-ATR-ATRIP-P · !Chk1-P · !Chk2-P → PP1	1	PP1 dephosphosphorylates p53 constitutively, thereby reducing its transcriptional activity; thus, kinases phosphorylating p53 in the early DNA damage response temporarily outcompete phosphatase PP1 (Li et al 2006a).
21. DNA DSBs early · MRN · PP5 · PP2A-B55 · !Wip1 → ATM-P PP2A-B55 in this function is only included in the *GINsim* model, but not in the *CNA* model, because the algorithms function differently. The inclusion of PP2A-B55 allows for basal activation of ATM, leading to inhibition of PP2A-B55, as defined by logical function 22.	1	The MRN complex binds to DSBs sites and facilitates autophosphorylation of ATM at serine 1981 (Bakkenist and Kastan 2003, Dupré et al 2006, Robinson et al 2007), this is promoted by PP5 (Ali et al 2004). The main phosphatase dephosphorylating ATM at serine 1981 is Wip1 (Shreeram et al 2006). Also in response to DSBs, the ATM-antagonizing phosphatase complex PP2A-B55 (PP2A complex including the subunit B55) becomes inactivated by dissociation; this is dependent on ATM kinase activity (logical function 22). This results in increased ATM activity. Thus, ATM and PP2A-B55 antagonize each other (Guo et al 2002, Goodarzi et al 2004, Freeman and Monteiro 2010). That issue might be explained by DSBs-induced low activity of ATM (activity level '1' in the logical model, described by logical function 21), which in turn is sufficient to inactivate PP2A-B55 (logical function 22). Now, the combination of PP2A-B55 inactivity and presence of DSBs might trigger full activation of ATM (i.e., ATM gains activity level '2' in the model, as described by logical function 23). Later (at time scale value 3); well before DNA damage is fixed by repair mechanisms, PP2A-B55 again becomes active (Guo et al 2002, Goodarzi et al 2004). In the model, this reactivation of PP2A-B55 in the late DNA damage resoponse is a consequence of Wip1-mediated downgegulation of the PP2A-B55-antagonizer ATM-P (logical functions 21 and 23).
22. !ATM-P → PP2A-B55	1	
23. DNA DSBs early · MRN · PP5 · !PP2A-B55 · !Wip1 → 2 ATM-P	1	
24. 2 ATM-P · MRN → MRN-P	1	ATM-P phosphorylates the MRN complex subunit Nbs1 at serine 343 (Lim et al 2000, Kurz et al 2004).
25. 2 ATM-P · FHIT · !Wip1 → Chk2-P	1	ATM-P phosphorylates Chk2 at threonine 68 (Melchionna et a 2000); this depends on FHIT (Yutori et al 2008); Wip1 dephosphorylates Chk2 at threonine 68 (Fujimoto et al 2006).
26. 2 ATM-P → c-Abl-P	1	ATM-P phosphorylates c-Abl (Baskaran et al 1997, Foray et al 2002,

		Waning et al 2011).
27. !c-Abl-P → MDM2	1	c-Abl-P mediates phosphorylation of MDM2 at serine 397, leading to ubiquitinylation-mediated proteolysis of MDM2 (Goldberg et al 2002, Waning et al 2011).
28. 2 !ATM-P · !Chk2-P · !MDM2 → MDMX	1	Chk2-P phosphorylates MDMX at serines 342 and 367, ATM-P phosphorylates MDMX at serine 403; both events lead to ubiquitinylation-mediated proteolysis of MDMX (Chen et al 2005, Pan et al 2003, Pereg et al 2005). Independent of these events, the E3 ligase MDM2 polyubiquitinylates MDMX, leading to its proteolysis (Chen et al 2005, Pan et al 2003, Pereg et al 2005).
29. RPA-P-ATR-ATRIP-P · !MDMX · !MDM2 · !PP1 · PML → p53-P	1	ATR phosphorylates p53 at serine 15 (Lakin et al 1999, Zou and Elledge 2003). MDM2 and MDMX polyubiquitinylate p53, leading to its proteolysis (Chen et al 2005, Goldberg et al 2002, Brooks et al 2007). PP1 dephosphosphorylates p53 constitutively, thereby reducing transcriptional activity of p53; thus, phosphorylation of p53 in response to DNA damage temporarily outweighs its dephosphorylation (Li et al 2006a). PML stabilizes p53 (Bao-Lei et al 2006).
30. 2 ATM-P → BARD1-BRCA1-P	1	ATM-P phosphorylates serines 1387, 1423 and 1524 of BRCA1; BARD1 stabilizes BRCA1 (Fabbro et al 2004, Cortez et al 1999, Gatei et al 2000).
31. 2 ATM-P · !MDMX · !MDM2 · BARD1-BRCA1-P · !PP1 · PML → p53-P	1	ATM-P phosphorylates p53 at serine 15, this depends on BARD1-BRCA1-P (Bakkenist and Kastan 2003, Fabbro et al 2004, Li et al 2006a). See logical function 29 for effects of MDM2, MDMX, PML, and PP1 on p53.
32. Chk1-P · !MDMX · !MDM2 · !PP1 · PML → p53-P	1	Chk1-P phosphorylates p53 at serine 20 (Shieh et al 2000, Ou et al 2005). See logical function 29 for effects of MDM2, MDMX, PML, and PP1 on p53.
33. Chk2-P · !MDMX · !MDM2 · !PP1 · PML → p53-P	1	Chk2-P mediates phosphorylation of p53 at serine 20 (Shieh et al 2000, Ou et al 2005). See logical function 29 for effects of MDM2, MDMX, PML, and PP1 on p53.
34. !MDM2 → HIPK2	1	MDM2 polyubiquitinylates HIPK2, leading to its proteolysis; higher levels of DSBs lead to higher MDM2 degradation rates, such that HIPK2 becomes more stable (Rinaldo et al 2007, Dauth et al 2007). See logical function 27 for MDM2 degardation; the increase in degradation as a result of increased DNA damage is not captured by the model:
35. p53-P · HIPK2 → p53-P-PS46	1	HIPK2 phosphorylates already transription activing (and thus, phosphorylated) p53 at serine 46 (Rinaldo et al 2007, Dauth et al 2007).
36. 2 ATM-P · TopBP1 · !PP2A-Bx · PP5 → RPA-P-ATR-ATRIP-P	1	ATM-P recruits RPA-P-ATR-ATRIP to DSBs sites (Robison et al 2007, Zou and Elledge 2003, Adams et al 2006), the ATM-dependence of RPA–ATR-ATRIP recruitment to DSBs sites is also shown in fibroblasts (Jazayeri et al 2006, Reinhardt et al 2007). For TopBP1, PP2A-Bx, and PP5 see logical function 14.
37. Chk2-P → E2F-1-P	1	Chk2-P stabilizes E2F-1 by phosphoryling it at serine 364 (Stevens et al 2003).
38. !Chk1-P · !Chk2-P → Cdc25A	1	Chk1-P and Chk2-P phosphorylate Cdc25A at serines 76 and 123, respectively, leading to ubiquitinylation-mediated proteolysis of Cdc25A; Cdc25A is only stable only in absence of both, Chk1-P, and Chk2-P (Falck et al 2001, Jin et al 2008).
39. Cdc25A → Cdk2	1	Cdc25A activates Cdk2 by dephosphorylating it at tyrosine residues (Blomberg and Hoffmann 1999, Falck et al 2001).
40. Chk2-P → Cdc25C-P	1	Chk2-P phosphorylates Cdc25C at serine 216 (Matsuoka et al 1998, Pedram et al 2003).
41. DNA DSBs early · !DNA DSBs late → Cdt2-DDB1	1	DSBs trigger transient activation of the complex made of Cdt2 and DDB1. At time scale value 2, Cdt2-DDB1 is inactive (Stuart et al 2009).
42. DNA DSBs early · Hsp90 → PIDD	1	DSBs trigger activation of PIDD by autocatalytic cleavage, this depends on Hsp90 (α or β ?); activation of PIDD by DSBs in human epithelial cells is at least within the first hours after induction of DNA strand breaks independent of transactivation by p53 (Cuenin et al 2008, Tinel et al 2007, Tinel et al 2010).
43. PIDD → PIDD-RAIDD-caspase2	2	PIDD binds via RAIDD to caspase-2, which becomes activated. This occurs later than binding of PIDD to RIP1 and NEMO (logical function 44) (Cuenin et al 2008, Janssens et al 2005, Tinel and Tschopp 2004).
44. PIDD · NEMO → PIDD-RIP1-NEMO-PIASy	1	PIDD and NEMO (not bound to the IKK complex, S. Miyamoto, pers. communication) enter the nucleus and form a complex with RIP1 and PIASy (Tinel et al 2007, Janssens et al 2005, Mabb et al 2006, Wu et al 2006); a role of RIP1 in DNA DSBs-iduced NF-κB activation has additionally been shown in MEFs (Hur et al 2003).
45. PIDD-RIP1-NEMO-PIASy · !SENP2 → PIDD-RIP1-NEMO-S	1	PIASy sumoylates (SUMO-1) NEMO within the PIDD-RIP1-NEMO complex (Janssens et al 2005, Mabb et al 2006, Yang et al 2011a). SENP2 desumoylates NEMO (Lee et al 2011).
46. 2 ATM-P · PIDD-RIP1-NEMO-S → ATM-P-RIP1-NEMO-P	1	ATM-P phosphorylates sumoylated NEMO at serine 85 (Huang et al 2003, Wu et al 2006). RIP1 is bound to ATM at least until TAK1 becomes phosphorylated in the cytosol (logical function 51) (Yang et al 2011a).
47. ATM-P-RIP1-NEMO-P · cIAP1 → nuclear ATM-P-RIP1-NEMO-Ub	1	Phosphorylated NEMO within the complex becomes monoubiquitinylated at lysine 277 and lysine 309 by cIAP1 (Huang et al 2003, Wu et al 2006, Jin et al 2009).
48. nuclear ATM-P-RIP1-NEMO-Ub · Ca^{2+} → cytosolic ATM-P-RIP1-NEMO-Ub	1	Export of ATM-P-RIP1-NEMO-Ub to the cytoplasm depends on Ca^{2+}, but there is nevertheless no increase in intracellular Ca^{2+} level within 6 h post DNA breakage (Wu et al 2006, Berchtold et al 2007, Gangadharan et al 2010). RIP1 is bound to ATM at least until TAK1 becomes phosphorylated in the cytosol (logical function 51) (Yang et al 2011a).
49. cytosolic ATM-P-RIP1-NEMO-Ub · Ubc13 · XIAP → ATM-P-RIP1-NEMO-Ub-TRAF6-Ub-ELKS-Ub	1	TRAF6 becomes polyubiquitinylated dependent on ATM and Ubc13 (Hinz et al 2010); ELKS becomes polyubiquitinylated (K63-linked) dependent on ATM, Ubc13 and XIAP (Wu et al 2010); RIP1 is bound to ATM at least until TAK1 becomes phosphorylated in the cytosol (logical function 51) (Yang et al 2011a). All proteins acting in this model between cytosolic ATM and activation of the IKK complex form a complex (Mabb et al 2006, Wu et al 2006, Jin et al 2009, Stilmann et al 2009, Wu et al 2010, Hinz et al 2010).
50. ATM-P-RIP1-NEMO-Ub-TRAF6-Ub-ELKS-Ub · LUBAC → ATM-P-RIP1-NEMO-Ub-TRAF6-Ub-ELKS-Ub-TAB	1	RIP1 is bound to ATM at least until TAK1 becomes phosphorylated in the cytosol (logical function 51) (Yang et al 2011a).

		All proteins acting in this model between cytosolic ATM and activation of the IKK complex form a complex (Mabb et al 2006, Wu et al 2006, Jin et al 2009, Stilmann et al 2009, Wu et al 2010, Hinz et al 2010). Dependent on ATM-P, XIAP and ELKS-Ub, NEMO becomes linearly polyubiquitinylated at K285 and / or K309 by the LUBAC (SHARP-HOIP-HOIL-1) complex in the cytosol (Niu et al 2011).
51. ATM-P-RIP1-NEMO-Ub-TRAF6-Ub-ELKS-Ub-TAB → TAK1-P	1	Phosphorylation of TAK1 depends on ATM, ELKS, Ubc13, TRAF6, TAB (TAB1 or 2 ?) and XIAP, and linearly polyubiquitinylated NEMO (Wu et al 2010, Hinz et al 2010, Jin et al 2009, Niu et al 2011). RIP1 is bound to ATM at least until TAK1 becomes phosphorylated in the cytosol (logical function 51) (Yang et al 2011a). All proteins acting in this model between cytosolic ATM and activation of the IKK complex form a complex (Mabb et al 2006, Wu et al 2006, Jin et al 2009, Stilmann et al 2009, Wu et al 2010, Hinz et al 2010).
52. RPA-P-ATR-ATRIP-P · TAK1-P → p38-P	1	Phosphorylations of p38α at T180 and Y182 depend on kinase activities of ATR and TAK1 (Yang et al 2011a, Cannell et al 2010). In response to DSBs, ATR kinase activity in turn depends on ATM-P (logical function 36) (see also Lafarga et al 2009); phosphorylated p38α is exported from the nucleus to the cytosol (Ben-Levy et al 1998).
53. p38-P → MK2-P	1	p38-P mediates phosphorylation of MK2 at threonine 334; this occurs also in presence of functional p53, as was shown in HEK293 cells (functional p53) (Yang et al 2011a, Cannell et al 2010).
54. p38-P · MK2-P → HuR	1	DSBs-induced phosphorylation of p38α leads to upregulation of Hur, this depends on MK2-P (Lafarga et al 2009).
55. MK2-P → miR-34c	1	MK2-P triggers expression of miR-34c; this occurs also in HEK293 cells (p53 wildtype) (Cannell et al 2010).
56. !miR-34c → c-Myc	1	miR-34c downregulates c-Myc expression ; this occurs also in HEK293 cells (p53 wildtype) (Cannell et al 2010).
57. !TAK1-P · !p90-P → PP1-CUEDC2	1	PP1-CUEDC2 dephosphorylates the IKK complex constitutively, thus, kinases phosphorylating the IKK complex in the DNA damage response (logical functions 62 and 63) temporarily outcompete phosphatase *PP1-CUEDC2* (Li et al 2008).
58. cytosolic ATM-P-RIP1-NEMO-Ub → MEK-P	1	cytosolic ATM-P-RIP1-NEMO-Ub mediates phosphorylation of MEK1/2, although earlier (which does not lead to activation of NF-κB, and are not included in the model) phosphorylations of MEK1/2 and ERK1/2 are independent of ATM (Panta et al 2004, Tang et al 2002, Li et al 2006b, Ahmed et al 2009).
59. MEK-P → ERK-P	1	MEK1/2 phosphorylates ERK1/2 (Panta et al 2004, Ahmed et al 2009).
60. ERK-P → p90-P	1	ERK1/2 mediates phosphorylation of $p90^{rsk1}$ (Panta et al 2004, Sturgill et al 1988).
61. IKK complex → IKK complex-P in *CNA* !TAK1-P + !p90-P → IKK-P in *GINsim*	1	The basal phosphorylation of the IKK complex is sufficient for constitutive activation of c-Rel. c-Rel in turn mediates constitutive expression of claspin (Kenneth et al 2010, see also logical functions 67 and 70).
62. p90-P · !PP1-CUEDC2 · IKK complex → 2 IKK complex-P	1	$p90^{rsk1}$ mediates activation (level ‚2') of the IKK complex subunit IKKβ above its basal activity level (level '1') by phosphorylation (Panta et al 2004, Bottero et al 2001); $p90^{rsk1}$, like other IKKβ activating kinases, outcompetes PP1-CUEDC2 phosphatase from binding to the IKK complex (Li et al 2008).
63. TAK1-P · !PP1-CUEDC2 · IKK complex → 2 IKK complex-P	1	In response to DSBs, TAK1-P mediates activation (level '2') of the IKK complex subunit IKKβ above its basal activity level (level ‚1') by phosphorylation (Berchtold et al 2007, Li et al 1998, Jin et al 2009, Perkins 2007, Wu et al 2010, Hinz et al 2010, Bottero et al 2001); TAK1-P, like other IKKβ activating kinases, outcompetes PP1-CUEDC2 phosphatase from binding to the IKK complex (Li et al 2008).
64. !IKK complex-P → 2 IκBα In *GINsim*, activity of IIκBα is not defined by means of a logical functions, but by defining all conditions under which IIκBα gains either activity level '0', '1'or '2', respectively.	1	IκBα is fully stable (activity level '2' in the model) only in absence of both, basal and stimulated activity of the IKK complex (activity level '0' in the model) (Li et al 1998, Strozyk et al 2006, Bottero et al 2001, DiDonato et al 1996).
65. !FKBP51 → IκBα In *GINsim*, activity of IIκBα is not defined by means of a logical functions, but by defining all conditions under which IIκBα gains either activity level '0', '1'or '2', respectively.	1	FKBP51 is necessary for IKK-mediated degradation of IκBα (Romano et al 2004).
66. 2 !IKK complex-P → IκBα In *GINsim*, activity of IIκBα is not defined by means of a logical functions, but by defining all conditions under which IIκBα gains either activity level '0', '1'or '2', respectively.	1	Inducers of SSBs and DSBs trigger phosphorylation of IκBα by IKK-P, leading to proteolysis of IκBα (Li et al 1998, Strozyk et al 2006, Bottero et al 2001, DiDonato et al 1996).
67. 2 !IκBα → cytosolic c-Rel	1	Constitutive low-level degradation of IκBα (driven by constitutive low activity of the IKK complex) releases c-Rel, which accordingly has a basal activity, leading to basal expression of claspin, as long as IκBα is not fully stabilized (i.e. gains activity level '2' in the model) (Hayden and Gosh 2008, Xu et al 2008, Kenneth et al 2010, RadiationGenes Database).
68. !IκBα → cytosolic p50-p50	1	Degradation of IκBα releases the NF-κB dimer p50-p50 (Hayden and Gosh 2008).
69. !IκBα → cytosolic p50-p65	1	Degradation of IκBα releases the NF-κB dimer p50-p65 (Hayden and Gosh 2008).
70. cytosolic c-Rel · importin α-1-β-1 → nuclear c-Rel	1	Released c-Rel binds prior to nuclear import to importin α-1 and importin β-1 (Hayden and Gosh 2008, Xu et al 2008).
71. cytosolic p50-p50 · importin α-1-β-1 → nuclear p50-p50	1	Released p50-p50 binds prior to nuclear import to importin α-1 and importin β-1 (Hayden and Gosh 2008, Xu et al 2008).
72. DNA DSBs early · IKKε → IKKε-P	1	DSBs trigger accumulation of IKKε in the nucleus, where IKKε becomes phosphorylated (Renner et al 2010).
73. IKKε-P · PML → PML-PS38	1	Inside the nucleus, IKKε-P phosphorylates PML at serine 38 (Renner et al 2010).
74. IKKε-P · PML-PS38 · TOPORS → IKKε-S-P	1	IKKε-P becomes sumoylated (SUMO-1) at lysine 231 by TOPORS; this depends on PML-PS38 (Renner et al 2010).
75. cytosolic p50-p65· importin α-1-β-1· IKKε-S-P → nuclear p50-p65-P	1	Released p50-p65 Upon binding to importin α-1 and importin β-1, p50-p65 becomes transported into the nucleus (Hayden and Gosh 2008, Xu et al 2008). IKKε-S-P mediates phosphorylation of p65 at serine 468, p65 additionally becomes phosphorylated at S536 (Renner et al 2010, Tapia et al 2007); both phosphorylations are known to activate the transactivation

		by p65 (Perkins 2006).
76. Chk2-P · PML → PML-PS117	1	Chk2-P phosphorylates PML at serine 117 (Yang et al 2002).
77. DNA DSBs late → PP2A-Bx	3	In the late DNA damage response (at time scale value 3) , PP2A-Bx becomes active again (Feng et al 2009, Leung-Pineda et al 2006). Since PP2A-Bx is not regulated by specific proteins in the model, it plays no role within the model, whether ATR and Chk1 are regulated by PP2A with the same B subunit ('Bx') or not.
78. !p53-P-PS46 → Bcl-3	1	p53-P (at least phosphorylated at serin 15) mediates destabilization of Bcl-3 (Rocha et al 2003); as this is probably a pro-apoptotic event, additional phosphorylation at serine 46 (the pro-apoptotic form of p53 in the model, see logical function 95) might be essential; due to the lack of direkt evidence supporting an anti-apoptotic role of Bcl-3 in response to SSBs or DSBs, Bcl-3 is not linked to apoptosis in the model.
79. !Bcl-3 → HDAC1	1	In the absence of Bcl-3, HDAC1 binds to chromatin-bound p52 dimers (Rocha et al 2003).
80. Bcl-3 · !HDAC1 → Bcl-3-p52-p52	1	Bcl-3 competes with HDAC1 for binding to the NF-κB dimer p52-p52; Bcl-3-p52-p52 binds to DNA and mediates transactivation of target genes (Rocha et al 2003).
81. p53-P · HuR · !Cdt2-DDB1 → p21	2	Early after induction of DSBs, Cdt2-DDB1 promotes polyubiquitinylation of p21, leading to its proteolysis; this process is independent of ATM (Stuart et al 2009); later (at time scale value 2), p53-P mediates expression of p21 (El-Deiry et al 1993, Han et al 2002, Vousden and Prives 2009), HuR stabilizes p21 mRNA by binding, thereby promoting G1/S cell cycle arrest (Lafarga et al 2009).
82. p53-P → Wip1	3	p53-P mediates expression of Wip1 during the late DNA damage response (Fiscella et al 1997).
83. p53-P-PS46 → HTRA2	3	Pro-apoptotic p53 (p53-P-PS46) mediates release of HTRA2 during the late DNA damage response (Bartling et al 2002, Jin et al 2003).
84. !HTRA2 → XIAP	1	HTRA2 (becoming active at time scale value 3, as described by logical function 83) binds to and mediates inactivation of XIAP (Srinivasula et al 2003, Martins et al 2002).
85. p53-P-PS46 → Diablo	3	Pro-apoptotic p53 (p53-P-PS46) mediates the increase of the level of cytosolic Smac/Diablo during the late DNA damage response (Yu et al 2007, Schuler and Green 2001, Bartling et al 2003).
86. !Diablo → cIAP1	1	Diablo (becoming active at time scale value 3, as described by logical function 85) inhibits cIAP1 (Du et al 2000, Dai et al 2008, Fandy et al 2008, Yang et al 2011b).
87. p53-P → MDM2	3	p53-P mediates expression of MDM2 during the late DNA damage response (Ard et al 2002, Phillips et al 2010, Lev-Bar et al 2000).
88. nuclear p50-p65-P → IκBα In *GINsim*, activity of IIκBα is not defined by means of a logical functions, but by defining all conditions under which IIκBα gains either activity level '0', '1'or '2', respectively.	3	The NF-κB dimer p50-p65-P mediates expression of IκBα during the late response to many stimuli, including DNA strand breaks (Mabb et al 2006, Ma et al 2009, Hayden and Gosh 2008).
89. nuclear p50-p65-P → SENP2	3	The NF-κB dimer p50-p65-P mediates expression of SENP2 during the late DNA damage response (Lee et al 2011).
90. !c-Myc → CELL-CYCLE-ARREST	2	Downregulation of c-Myc leads to intra-S-phase cell cycle arrest (Cannell et al 2010).
91. p21 → CELL-CYCLE-ARREST	2	p21 mediates G1/S phase cell cycle arrest (Han et al 2002, Lafarga et al 2009).
92. !Cdk2 → CELL-CYCLE-ARREST	2	Loss of unphosphorylated Cdk2 leads to intra-S-phase cell cycle arrest (Blomberg and Hoffmann 1999, Falck et al 2001).
93. p53-P → CELL-CYCLE-ARREST	2	Phosphorylations of p53 at serine 15 and / or serine 20 trigger cell cycle arresting functions of p53, as long as it is not additionally phosphorylated at serine 46 (Vousden and Prives 2009, Jiang et al 2010).
94. Cdc25C-P → CELL-CYCLE-ARREST	2	Phosphorylation of Cdc25C at serine 216 causes G2/M-phase cell cycle arrest (Peng et al 1997, reviewed by Boutros et al 2006).
95. p53-P-PS46 · !nuclear_p50-p65-P → ONSET-OF-APOPTOSIS	2	Phosphorylation of p53 at serine 46 is known to mediate expression of pro-apoptotic target genes (Vousden and Prives 2009, Jiang et al 2010). In most cases, NF-κB antagonizes apoptosis by transactivation of anti-apoptotic target genes in response to DSBs (Carson et al 2004, Wu and Miyamoto 2007, McCool and Miyamoto 2012).
96. E2F-1-P · !nuclear_p50-p65-P → ONSET-OF-APOPTOSIS	2	E2F-1-P promotes p53-independent (as well as p53-dependent) apoptosis (Stevens et al 2003, Dong et al 2003). In most cases, NF-κB antagonizes apoptosis by transactivation of anti-apoptotic target genes in response to DSBs (Carson et al 2004, Wu and Miyamoto 2007, McCool and Miyamoto 2012).
97. PIDD-RAIDD-caspase2 · !nuclear_p50-p65-P → ONSET-OF-APOPTOSIS	2	Caspase 2 promotes apoptosis upon its activation within the PIDD/RAIDD/caspase2 complex (Tinel and Tschopp 2004, Tinel et al 2007, Cuenin et al 2008). In most cases, NF-κB antagonizes apoptosis by transactivation of anti-apoptotic target genes in response to DSBs (Carson et al 2004, Wu and Miyamoto 2007, McCool and Miyamoto 2012).
98. PML-PS117 · !nuclear_p50-p65-P → ONSET-OF-APOPTOSIS	2	PML-PS117 mediates p53-independent apoptosis (Yang et al 2002). In most cases, NF-κB antagonizes apoptosis by transactivation of anti-apoptotic target genes in response to DSBs (Carson et al 2004, Wu and Miyamoto 2007, McCool and Miyamoto 2012).

Symbols: '·' logical AND, '!' logical NOT

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Supplementary Table 2

Regulatory component	Logical steady states				
	A	B	C	D	E
APOPTOSIS, ONSET OF	no logical steady state	no logical steady state	no logical steady state	0	1
ATM-P				2	0
ATM-P-RIP1-NEMO-P				0	1
ATM-P-RIP1-NEMO-Ub-TRAF6-Ub-ELKS-Ub				0	0
ATM-P-RIP1-NEMO-Ub-TRAF6-Ub-ELKS-Ub-TAB				0	0
BARD1-BRCA1				1	0
Bcl-3				1	1
Bcl-3-p52-p52				1	1
bleomycin				0	0
Ca^{2+}				1	1
c-Abl-P				1	0
camptothecin				0	0
Cdc25A				0	1
Cdc25C-P				1	0
Cdc7				1	1
Cdt2-DDB1				0	0
Cdk2				0	1
CELL-CYCLE-ARREST				1	1
Chk1-P				0	0
Chk2-P				1	0
cIAP1				1	1
claspin-P				1	1
c-Myc				1	1
cytosolic_ATM-P-RIP1-NEMO-Ub				0	0
cytosolic_c-Rel				1	1
cytosolic_p50-p50				0	0
cytosolic_p50-p65				0	0
daunomycin				0	0
Diablo				0	0
DNA_DSBs_early				1	1
DNA_DSBs_late				1	1
DNA_SSBs				0	0
doxorubicin				0	0
E2F-1-P				1	0
ERK-P				0	0
FHIT				1	1
FKBP51				1	1
HDAC1				0	0
HIPK2				1	0
Hsp90				1	1
HTRA2				0	0
HU				0	0
HuR				0	0
IκBα				1	1
IKK_complex-P				1	1
IKKε				1	1
IKKε-P				1	1
IKKε-S-P				1	1
importin_α-1_β-1				1	1
IR				1	1
Ku				1	1
LUBAC				0	0
MDM2				0	1
MDMX				0	0
MEK-P				0	0
miR-34c				0	0
MK2-P				0	0
MRN				1	1
MRN-P				1	0
NEMO				1	1
nuclear_ATM-P-RIP1-NEMO-Ub				0	0
nuclear_c-Rel				1	1

nuclear_p50-p50				1	0
nuclear_p50-p65-P				1	0
p21				0	0
p38-P				0	0
p53-P				0	1
p53-P-PS46				0	0
p90-P				0	0
PARP1-PAR				1	1
PIDD				1	1
PIDD-RAIDD-caspase2				1	1
PIDD-RIP1-NEMO-PIASy				1	1
PIDD-RIP1-NEMO-S				0	1
PML				1	1
PML-PS117				1	0
PML-PS38				1	1
PP1				0	1
PP1-CUEDC2				1	1
PP2A-B55				0	1
PP2A-Bx				1	1
PP5				1	1
RPA-P-ATR-ATRIP-P				0	0
SENP2				1	0
SN38				0	0
TAK1-P				0	0
Timeless-Tipin				1	1
TopBP1				1	1
topoisomeraseI				1	1
topoisomeraseII				1	1
TOPORS				1	1
Ubc13				1	1
VP16				0	0
Wip1				0	1
XIAP				1	1

Supplementary Table 3 Excluded targets from search (see Table 2)

Excluded targets	Reasons
ATRIP	no enzymatic activity (UniProtKB)
Ca^{2+}	has too many functions not captured by the model (Bootman et al 2009)
c-Abl	has too many functions not captured by the model (UniProtKB)
Cdc7	required for proliferation (UniProtKB)
cIAP1	has too many functions not captured by the model (UniProtKB)
claspin-P	no enzymatic activity (UniProtKB)
ELKS	no enzymatic activity (UniProtKB)
FHIT	substrate analog inhibitors of FHIT may actually promote its function in the DNA damage response (Varnum et al 2001, Saldivar et al 2010)
importin_α1_β1	has too many functions not captured by the model (UniProtKB)
miR-34c	microRNA, has thus no enzymatic activity
NEMO	no enzymatic activity (UniProtKB)
p38α	has too many functions not captured by the model (UniProtKB)
PIASy	has too many functions not captured by the model (UniProtKB)
PML	has too many functions not related to DNA damage response (UniProtKB)
RIP1	role of RP1 in the model independent of its kinase activity (Biton and Ashkenazi 2011)
RPA	required for proliferation (UniProtKB)
TAB proteins	no enzymatic activity (UniProtKB)
Timeless-Tipin	required for proliferation (UniProtKB)
TopBP1	required for proliferation (Mäkiniemi et al 2001)
TOPORS	promotes proliferation (UniProtKB)
Ubc13	required for proliferation (UniProtKB)

References Supplementary Table 3

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Supplementary Table 4 Excluded targets from search (see Table 4)

Excluded activations	Reasons
ATM-P	tumor suppressor (Tumor Gene Family of Databases)
BARD1-BRCA1-P	BRCA1 is a tumor suppressor (Tumor Gene Family of Databases)
Chk2-P	tumor suppressor (Sherr et al 2004)
E2F1-P	tumor suppressor (Tumor Gene Family of Databases)
FHIT	tumor suppressor (Tumor Gene Family of Databases)
p53-P	tumor suppressor (Tumor Gene Family of Databases)

Excluded inactivations	Reasons
c-Abl-P	proto-oncogene (Tumor Gene Family of Databases)
Cdc7	overexpression associated with tumor growth (UniProtKB)
Chk1-P	necessary for proliferation (Petermann et al 2010)
c-Myc	proto-oncogene (Tumor Gene Family of Databases)
c-Rel	proto-oncogene (Tumor Gene Family of Databases)
MDM2	proto-oncogene (Tumor Gene Family of Databases)
PML	proto-oncogene (Tumor Gene Family of Databases)
PP1	necessary for proliferation (UniProtKB)
RPA-P-ATR-ATRIP-P	ATR and RPA are necessary for proliferation (Nam and Cortez 2011, UniProtKB)
Timeless-Tipin	necessary for proliferation (UniProtKB)
TopBP1	necessary for proliferation (UniProtKB)
topoisomerase I	proto-oncogene (UniProtKB)

References Supplementary Table 4

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