Zhang *et al.* "Coordination Between Cell Cycle Progression and Cell Fate Decision by the p53 and E2F1 Pathways in Response to DNA Damage"

SUPPLEMENTAL DATA

Supplemental Method S1. Algorithm for stochastic simulation of the generation and repair of double-strand breaks (DSBs)

Ionizing radiation (IR) can produce a large variety of DNA lesions, including single- and double-strand breaks (DSBs) and base excision. DSBs are most dangerous, and one DSB can kill a cell if it is located at a key gene. Thus, DSB is generally considered the typical form of IR-induced DNA damage. In mammalian cells, there are two major repair mechanisms for DSB repair: homologous recombination (HR) and nonhomologous end joining (NHEJ) [1, 2]. HR mainly contributes to DSB repair at S phase, whereas NHEJ is the predominant pathway for DSB repair in mammalian cells, especially active at G1 phase [3]. Given G1 arrest in stressed cells, NHEJ is taken as the main pathway of DSB repair.

Although it is believed that p53 plays a role in NHEJ, the detailed effect of p53 on NHEJ is still controversial. Thus, the effect of p53 on NHEJ is not considered in our model. Owing to stochasticity in DNA repair process, we use Monte Carlo method to simulate the DNA repair dynamics. In simulations, given the IR dose of y Gy, the initial number of DSBs in each cell is generated from a Poisson distribution with a mean of $35y$ [4], and the total number of repair proteins is assumed to be 20 per cell. We consider three states in the repair process: DSB, DSB-protein complex (DSBC) and fixed DNA. The number of DSBs in each of the states is represented by n_{D}, n_{C} and n_{F}, respectively (Figure S1). We use subscripts '1' and '2' to distinguish fast kinetics from slow kinetics [5]. The Monte Carlo algorithm for the dynamics of DSBs is based on the transition probabilities between two neighboring states as follows:

$$
\begin{aligned}
\mathrm{P}_{\mathrm{D}_1\to\mathrm{C}_1} &= \mathrm{n}_{\mathrm{RP}}[\mathrm{k}_{\mathrm{fb1}}+\mathrm{k}_{\mathrm{cross}}(\mathrm{D}_1+\mathrm{D}_2)]\Delta\mathrm{t}\\
\mathrm{P}_{\mathrm{D}_2\to\mathrm{C}_2} &= \mathrm{n}_{\mathrm{RP}}[\mathrm{k}_{\mathrm{fb2}}+\mathrm{k}_{\mathrm{cross}}(\mathrm{D}_1+\mathrm{D}_2)]\Delta\mathrm{t}\\
\mathrm{P}_{\mathrm{C}_1\to\mathrm{D}_1} &= \mathrm{k}_{\mathrm{rb1}}\Delta\mathrm{t}\\
\mathrm{P}_{\mathrm{C}_2\to\mathrm{D}_2} &= \mathrm{k}_{\mathrm{rb2}}\Delta\mathrm{t}\\
\mathrm{P}_{\mathrm{C}_1\to\mathrm{F}_1} &= \mathrm{k}_{\mathrm{fix1}}\Delta\mathrm{t}\\
\mathrm{P}_{\mathrm{C}_2\to\mathrm{F}_2} &= \mathrm{k}_{\mathrm{fix2}}\Delta\mathrm{t}.
\end{aligned}
$$

In the above, all the ratios of the rates for the fast kinetics to those for the slow kinetics are chosen to be close to 10, which is based on the experimental data that the ratios are abour 6$\sim$40 [5]. It is

also assumed that the binding of repair proteins to DSBs is much faster than other processes such as dissociation of repair proteins and the repair process. That is, the number of DSBCs is 20 when DSBs are more than repair proteins, whereas this number equals the number of DSBs when DSBs are fewer than repair proteins.

The Monte Carlo algorithm for the dynamics of DSB repair at the IR dose of y Gy is presented in the following:

1. Generation of DSBs. Set $t = 0$. The initial number of total DSBs $n_{\rm D}(0)$ is generated from a Poisson distribution with a mean value of 35y. The initial values for simple and complex DSB repair are taken as $n_{\rm D1}(0) = 0.7n_{\rm D}(0)$ and $n_{\rm D2}(0) = 0.3n_{\rm D}(0)$, respectively, while the numbers of DSBs in other states are set to zero, namely $n_{\rm C1}(0) = n_{\rm C2}(0) = n_{\rm F1}(0) = n_{\rm F2}(0) = 0$. The total number of repair proteins $n_{\rm RPT}$ is set to 20, and the number of free repair proteins is $n_{\rm RP}(0) = 20$.

2. Increase time from t to $t = t + \triangle t$.

3. Update the states for each of the damages sites controlled by fast repair. For each damage locus i (with $1 \le i \le n_{\rm D1}(0)$), a random number r is generated from a uniform distribution between 0 and 1. If the damage at locus i is in state 1, a transition to state 2 occurs if $0 \le r < P_{\rm D1\to C1}$, while it stays in state 1 if $P_{\rm D1\to C1} \le r \le 1$. If the damage is in state 2, a transition to state 1 occurs if $0 \le r < P_{\rm C1\to D1}$, or a transition to state 3 occurs if $P_{\rm C1\to D1} \le r < P_{\rm C1\to D1} + P_{\rm C1\to F1}$. If the damage is in state 3, it always stays in state 3 (i.e., state 3 is absorbing). Set $n_{\rm RP} = n_{\rm RP} + 1$ if transition from state 2 to 1 or from state 2 to 3 occurs ; set $n_{\rm RP} = n_{\rm RP} - 1$ if transition from state 1 to 2 occurs; otherwise $n_{\rm RP}$ remains the same. After the last damage site has been updated, set the numbers of fast repaired breaks at time t in states 1, 2, and 3 to be $n_{\rm D1}$, $n_{\rm C1}$ and $n_{\rm F1}$, respectively.

4. Update the states for each of the damages sites controlled by slow repair. For each damage locus i (with $1 \le i \le n_{\rm D2}(0)$), a random number r is produced from a uniform distribution between 0 and 1. If the damage at locus i is in state 1, a transition to state 2 occurs if $0 \le r < P_{\rm D2\to C2}$, while it stays in state 1 if $P_{\rm D2\to C2} \le r \le 1$. If the damage is in state 2, a transition to state 1 occurs if $0 \le r \le P_{\rm C2\to D2}$, or a transition to state 3 occurs if $P_{\rm C2\to D2} \le r < P_{\rm C2\to D2} + P_{\rm C2\to F2}$. If the damage is in state 3, it always stays in state 3 (i.e., state 3 is absorbing). Set $n_{\rm RP} = n_{\rm RP} + 1$ if transition from state 2 to 1 or from state 2 to 3 occurs; set $n_{\rm RP} = n_{\rm RP} - 1$ if transition from state 1 to 2 occurs; otherwise $n_{\rm RP}$ remains the same. After the last damage site has been updated, set the numbers of slow repaired breaks at time t in states 1, 2, and 3 to be $n_{\rm D2}$, $n_{\rm C2}$ and $n_{\rm F2}$, respectively.

5. Let $n_{\rm D}(t) = n_{\rm D1}(t) + n_{\rm D2}(t)$, $n_{\rm C}(t) = n_{\rm C1}(t) + n_{\rm C2}(t)$, and $n_{\rm F}(t) = n_{\rm F1}(t) + n_{\rm F2}(t)$.

6. Repeat steps 2-5 until all of the DSBs are effectively repaired, i.e., $n_{\mathrm{D}} \leq 2$.

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[1] Sengupta, S., and Harris, C. C. (2005) Nat Rev Mol Cell Biol 6, 44-55.

[2] Gatz, S. A., and Wiesmuller, L. (2006) Cell Death Differ 13, 1003-1016.

[3] Burma, S., Chen, B. P. C., and Chen, D. J. (2006) DNA Repair 5, 1042-1048.

[4] Ma, L., Wagner, J., Rice, J., Hu, W., Levine, A., and Stolovitzky, G. (2005) Proc Natl Acad Sci USA 102, 14266 - 14271.

[5] Stewart, R. D. (2001) Radiation Research 156, 365-378.

[6] Wee, K. B., and Aguda, B. D. (2006) Biophys. J. 91, 857-865.

[7] Lev Bar-Or, R., Maya, R., Segel, L. A., Alon, U., Levine, A. J., and Oren, M. (2000) Proceedings of the National Academy of Sciences 97, 11250-11255.

[8] Yao, G., Lee, T. J., Mori, S., Nevins, J. R., and You, L. (2008) Nat Cell Biol 10, 476-482

[9] Zhang, T. L., Brazhnik, P., and Tyson, J. J. (2007) Cell Cycle 6, 85-94

[10] Geva-Zatorsky, N., Rosenfeld, N., Itzkovitz, S., Milo, R., Sigal, A., Dekel, E., Yarnitzky, T., Liron, Y., Polak, P., Lahav, G., and Alon, U. (2006) Mol Syst Biol 2, 2006 0033

Supplemental Method S2

$$\frac{d[ATM_d]}{dt} = 0.5 * k_{dim} * [ATM]^2 - k_{undim} * [ATM_d] \quad (1)$$

$$\frac{d[ATM^*]}{dt} = a_{1s} * n_c/(n_c + j_{nc}) * [ATM^*] * [ATM]/([ATM] + j_{1s}) - a_{2s} * (1 + [Wip1]) * [ATM^*]/([ATM^*] + j_{2s}) \quad (2)$$

$$[ATM] = ATM_{tot} - 2 * [ATM_d] - [ATM^*] \quad (3)$$

$$k_{dmdm2nuc} = k_{dmdm2} + k_{dmdm2nuc0} * [ATM^*]/([ATM^*] + j_{atm}) \quad (4)$$

$$k_{dHIPK2} = k_{dHIPK21} * [ATM^*]/([ATM^*] + j_{atm}) \quad (5)$$

$$k_{ac} = k_{ac0} * [ATM^*]/([ATM^*] + j_{atm}) \quad (6)$$

$$\frac{d[p53^*]}{dt} = k_{ac} * [p53] - k_{de} * [p53^*] - k_{dp53s} * [Mdm2_n] * [p53^*]/(j_{1p53n} + [p53^*]) \quad (7)$$

$$\frac{d[p53]}{dt} = k_{p53} - k_{dp53n} * [p53] - k_{dp53} * [Mdm2_n] * [p53]/(j_{1p53n} + [p53]) - k_{ac} * [p53] + k_{de} * [p53^*] \quad (8)$$

$$\frac{d[Mdm2_c]}{dt} = k_{mdm2} + k_{1mdm2} * [p53^*]^4/(j_{p53}^4 + [p53^*]^4) - k_{dmdm2} * [Mdm2_c] + k_{1mdm2s} * [Mdm2_{cp}]/(j_{1mdm2s} + [Mdm2_{cp}]) - k_{mdm2s} * [Mdm2_c] * [Akt_p]/(j_{mdm2s} + [Mdm2_c]) \quad (9)$$

$$\frac{d[Mdm2_{cp}]}{dt} = k_{mdm2s} * [Mdm2_c] * [Akt_p]/(j_{mdm2s} + [Mdm2_c]) - k_{1mdm2s} * [Mdm2_{cp}] /(j_{1mdm2s} + [Mdm2_{cp}]) - k_i * [Mdm2_{cp}] + k_o * [Mdm2_n] - k_{dmdm2} * [Mdm2_{cp}] \quad (10)$$

$$\frac{d[Mdm2_n]}{dt} = k_i * [Mdm2_{cp}] - k_o * [Mdm2_n] - k_{dmdm2nuc} * [Mdm2_n] \quad (11)$$

$$\frac{d[Akt_p]}{dt} = k_{akt} * [Akt]/(j_{akt} + [Akt]) - k_{akts} * [Akt_p]/(j_{akts} + [Akt_p]) - k_{1akts} * [p53^*] * [Akt_p]/(j_{1akts} + [Akt_p]) \quad (12)$$

$$[Akt] = Akttot - [Akt_p] \quad (13)$$

$$\frac{d[p21]}{dt} = k_{sp211} + k_{sp21} * [\text{p53 arrester}]^3/(j_{sp21}^3 + [\text{p53 arrester}]^3) - k_{dp21} * [p21] \quad (14)$$

$$k_{p1} = k_{p0} * j_{p21}/(j_{p21} + [p21]) \quad (15)$$

$$k_{p2} = k_{p0} * j_{p21}/(j_{p21} + [p21]) \quad (16)$$

$$\frac{d[Myc]}{dt} = k_{m1} * I_S/(k_s + I_S) - d_m * [Myc] \quad (17)$$

$$\frac{d[E2F1]}{dt} = k_{e1} * ([Myc]/(k_m + [Myc])) * ([E2F1]/(k_e + [E2F1])) + k_b * [Myc]/(km + [Myc]) + k_{p1} * [CycD] * [RE]/(k_{CycD} + [RE]) + k_{p2} * [CycE] * [RE]/(k_{ce} + [RE]) - d_e * [E2F1] - k_{re} * [Rb] * [E2F1] \quad (18)$$

$$\frac{d[CycD]}{dt} = k_{CycD1} * [Myc]/(k_m + [Myc]) + k_{CycDs} * I_S/(k_s + I_S) - d_{CycD} * [CycD] \quad (19)$$

$$\frac{d[CycE]}{dt} = k_{ce1} * [E2F1]/(k_e + [E2F1]) - d_{ce} * [CycE] \quad (20)$$

$$\frac{d[Rb]}{dt} = k_r + k_{dp} * [RP]/(k_{rp} + [RP]) - k_{re} * [Rb] * [E2F1] - k_{p1} * [CycD] * [Rb]/(k_{CycD} + [Rb])$$
$$-k_{p2} * [CycE] * [Rb]/(k_{ce} + [Rb]) - dr * [Rb] \quad (21)$$

$$\frac{d[RP]}{dt} = k_{p1} * [CycD] * [Rb]/(k_{CycD} + [Rb]) + k_{p2} * [CycE] * [Rb]/(k_{ce} + [Rb])$$
$$+k_{p1} * [CycD] * [RE]/(k_{CycD} + [RE]) + k_{p2} * [CycE] * [RE]/(k_{ce} + [RE])$$
$$-k_{dp} * [RP]/(k_{rp} + [RP]) - d_{rp} * [RP] \quad (22)$$

$$\frac{d[RE]}{dt} = k_{re} * [Rb] * [E2F1] - k_{p1} * [CycD] * [RE]/(k_{CycD} + [RE])$$
$$-k_{p2} * [CycE] * [RE]/(k_{ce} + [RE]) - d_{re} * [RE] \quad (23)$$

$$\frac{d[HIPK2]}{dt} = k_{sHIPK2} - k_{dHIPK2} * [HIPK2] \quad (24)$$

$$\frac{d[p53\ killer]}{dt} = k_{p46} * [HIPK2] * [p53DINP1] * [p53\ arrester]/(j_{p46} + [p53\ arrester])$$
$$-k_{dp46} * [Wip1] * [p53\ killer]/(j_{dp46} + [p53\ killer]) \quad (25)$$

$$[p53\ arrester] = [p53^*] - [p53\ killer] \quad (26)$$

$$\frac{d[Wip1]}{dt} = k_{swip11} + k_{swip12} * [p53\ arrester]^3/(j^3_{swip1} + [p53\ arrester]^3) - k_{dwip1} * [Wip1] \quad (27)$$

$$\frac{d[p53DINP1]}{dt} = k_{sdinp11} + k_{sdinp12} * [p53\ arrester]^3/(j^3_{sdinp11} + [p53\ arrester]^3)$$
$$+k_{sdinp13} * [p53\ killer]^3/(j^3_{sdinp12} + [p53\ killer]^3) * [E2F1]^3/(j^3_{sdinp13} + [E2F1]^3)$$
$$-k_{ddinp1} * [p53DINP1] \quad (28)$$

$$\frac{d[Bax]}{dt} = k_{sBax1} + k_{sBax2} * [ASPP] * [p53\ killer]^3/(j^3_{sBax} + [p53\ killer]^3) - k_{dBax} * [Bax] \quad (29)$$

$$\frac{d[ASPP]}{dt} = k_{saspp1} + k_{saspp2} * [E2F1]^3/(j^3_{saspp} + [E2F1]^3) - k_{daspp} * [ASPP] \quad (30)$$

$$\frac{d[p53AIP1]}{dt} = k_{saip11} + k_{saip12} * [ASPP] * [p53\ killer]^3/(j^3_{saip1} + [p53\ killer]^3) - k_{daip1} * [p53AIP1] \quad (31)$$

$$\frac{d[CytoC]}{dt} = (k_{CytoC0} + (k_{CytoC1} * [Bax] + k_{CytoC2} * [p53aip1]) * [Casp3]^2/([Casp3]^2 + j^2_{casp3}))$$
$$*(CytoC_{tot} - [CytoC]) - k_{deCytoC} * [CytoC] \quad (32)$$

$$\frac{d[Apaf-1]}{dt} = k_{sapaf11} + k_{sapaf12} * [E2F1]^3$$
$$/(j^3_{sapaf12} + [E2F1]^3) + k_{sapaf13} * [ASPP] * [p53\ killer]^3/(j^3_{sapaf13} + [p53\ killer]^3)$$
$$-kdapaf1 * [Apaf-1] \quad (33)$$

$$\frac{d[Apops]}{dt} = k_{Apops} * (([CytoC] - 7 * [Apops]) * ([Apaf-1] - [7 * Apops]))^7$$
$$-k_{deApops} * [Apops] \quad (34)$$

$$\frac{d[Procasp9]}{dt} = k_{scasp91} + k_{scasp92} * [E2F1]^3/(j^3_{scasp9} + [E2F1]^3) - k_{dcasp9} * [Procasp9] \quad (35)$$

$$\frac{d[Casp9]}{dt} = k_{casp9} * [Apops] * ([Procasp9] - [Casp9]) - k_{decasp9} * [Casp3] \quad (36)$$

$$\frac{d[Procasp3]}{dt} = k_{scasp31} + k_{scasp32} * [E2F1]^3/(j^3_{scasp3} + [E2F1]^3) - k_{dcasp3} * [Procasp3] \quad (37)$$

$$\frac{d[Casp3]}{dt} = k_{casp3} * ([Procasp3] - [Casp3]) * [Casp9]^2/([Casp9]^2 + j^2_{casp9}) - k_{decasp3} * [Casp3] \quad (38)$$

Supplemental Table S1: Variables of the model

Variable	Description	Initial values
$[ATM_d]$	Concentration of ATM dimer	2.17
[ATM]	Concentration of inactive ATM monomer	2.73
$[ATM^*]$	Concentration of active ATM monomer	0.10
[p53]	Concentration of inactive p53	0.00
$[p53^*]$	Concentration of active p53	0.13
$[Mdm2_c]$	Concentration of cytoplasmic Mdm2	0.11
$[Mdm2_{cp}]$	Concentration of phosphorylated cytoplasmic Mdm2	0.44
$[Mdm2_n]$	Concentration of nuclear Mdm2	0.26
[M]	Concentration of Myc	0.00
[E]	Concentration of E2F1	0.05
[CycD]	Concentration of Cyclin D	0.00
[CycE]	Concentration of Cyclin E	0.03
[Rb]	Concentration of Rb	0.00
[Rp]	Concentration of phosphorylated Rb	0.00
[RE]	Concentration of Rb/E2F1 complex	1.00
[HIPK2]	Concentration of HIPK2	0.00
[p53 arrester]	Concentration of primarily phosphorylated p53	0.00
[p53 killer]	Concentration of further phosphorylated p53 at Ser46	0.00
[Wip1]	Concentration of wild-type p53 induced protein 1	0.00
[p53DINP1]	Concentration of p53-dependent damage-inducible protein 1	0.00
[Bax]	Concentration of Bax	0.01
[ASPP]	Concentration of apoptosis stimulating proteins of p53	0.00
[p53AIP1]	Concentration of p53-regulated Apoptosis-Inducing protein 1	0.01
[CytoC]	concentration of cytochrome c	0.00001
$[Apaf-1]$	Concentration of Apaf-1	0.00
[Apops]	Concentration of Apoptosome	0.00
[Procasp9]	Concentration of inactive caspase 9	0.00
[Casp9]	Concentration of active caspase 9	0.00
[Procasp3]	Concentration of inactive caspase 3	0.00
[Casp3]	Concentration of active caspase 3	0.00

Supplemental Table S2: Parameters for the whole model

Rate Constant	Description	Value	Reference
n_{RPT}	Number of repair proteins	20	[4]
k_{fb1}	Association rate of repair proteins in fast kinetics	1.3	[4]
k_{fb2}	Association rate of repair proteins in slow kinetics	0.13	[4]
k_{rb1}	Dissociation rate of repair proteins in fast kinetics	0.3	[4]
k_{rb2}	Dissociation rate of repair proteins in slow kinetics	0.03	[4]
k_{fix1}	DSB ligation rate in fast kinetics	0.02	[4]
k_{fix2}	DSB ligation rate in slow kinetics	0.002	[4]
k_{cross}	DSB binary mismatch rate	0.007	[4]
k_{dim}	ATM dimerization rate	7	[4]
k_{undim}	ATM undimerization rate	0.7	[4]
$a_{1\mathrm{s}}$	ATM activation rate	1.3	[4]
$a_{2\mathrm{s}}$	ATM inactivation rate	0.53	[4]
$j_{1\mathrm{s}}$	Michaelis constant of ATM activation	1	[4]
$j_{2\mathrm{s}}$	Michaelis constant of ATM* inactivation	2.5	[4]
$j_{\mathrm{n_C}}$	Threshold number of DSBC for ATM activation	5	[4]
j_{wip1}	Michaelis constant of Wip1 for ATM activation	1	Estimated
ATM_{tot}	the total concentration of all forms of ATM	5	[4]
j_{ATM}	Michaelis constant of ATM* as a kinase	1	[4]
k_{mdm2}	Basal production rate of Mdm2	0.0013	[4]
k_{mdm21}	p53-dependent production rate of Mdm2	0.04	[4]
j_{p53}	Michaelis constant of p53-induced Mdm2 production	1.2	Estimated
$k_{1\mathrm{mdm2s}}$	Dephosphorylation rate of cytoplasmic Mdm2	0.2	[6]
$j_{1\mathrm{mdm2s}}$	Michaelis constant of Mdm2 dephosphorylation	0.1	[6]
k_{mdm2s}	Akt-dependent phosphorylation rate of cytoplasmic Mdm2	5.3	[6]
j_{mdm2s}	Michaelis constant of Akt-dependent Mdm2 dephosphorylation	0.3	[6]
k_{akt}	Phosphorylation rate of Akt	0.133	[6]
j_{akt}	Michaelis constant of Akt phosphorylation	0.1	[6]
k_{akts}	Basal dephosphorylation rate of Akt	0.1	[6]
j_{akts}	Michaelis constant of basal Akt dephosphorylation	0.2	[6]
$k_{1\mathrm{akts}}$	p53-dependent dephosphorylation rate of Akt	0.1	[6]
$j_{1\mathrm{akts}}$	Michaelis constant of p53-dependent Akt dephosphorylation	0.2	[6]
k_{p53}	Production rate of p53	0.065	[4, 6]
k_{dp53n}	Basal degradation rate of p53	0.03	[4, 6]
k_{dp53}	Mdm2-dependent degradation rate of p53	0.45	Estimated
$j_{1\mathrm{p53n}}$	Michaelis constant of Mdm2-dependent p53 degradation	0.1	Estimated
k_{dmdm2}	Degradation rate of $\mathrm{Mdm2}_c$	0.002	[6]
k_{i}	Nuclear import rate of $\mathrm{Mdm2}_c$	0.04	Estimated
k_{o}	Nuclear export rate of $\mathrm{Mdm2}_n$	0.06	Estimated

Supplemental Table S2-Continued

k_{ac0}	ATM-dependent activation rate constant of p53	0.15	Estimated
k_{de}	Inactivation rate of p53*	0.07	Estimated
k_{dp53s}	Degradation rate of p53*	0.0065	Estimated
k_{d2n0}	Basal degradation rate of Mdm2$_n$	0.035	[6]
Akt_{tot}	Total of Akt	1	[6, 7]
k_{sp211}	Basal induction rate of p21	0.007	Estimated
k_{sp212}	p53 arrester inducible production rate of p21	0.07	Estimated
j_{sp21}	Michaelis constant of p53 arrester inducible $p21$ production	0.6	Estimated
j_{p21}	Michaelis constant of p21 inhibited cyclin phosphorylation	0.6	Estimated
k_{dp211}	Degradation rate of $p21$	0.055	Estimated
k_{e1}	Rate constant of E2F1 production by a synergy between Myc and E2F	0.007	[8]
k_{b}	Rate constant of basal E2F1 production by Myc	1/30000	[8]
k_{m1}	Rate constant of Myc production by Myc	1/90	[8]
k_{cd1}	Rate constant of CycD production by Myc	1/3000	[8]
k_{cds}	Rate constant of CycD production by serum	0.005	[8]
k_{r}	Basal production rate of Rb	0.002	[8]
k_{re}	Associate rate of Rb and E2F1	2	[8]
k_{s}	Threshold of serum in E2F1 and CycD induction	2	[8]
k_{ce}	Production rate of CycE	7/1800	[8]
d_{m}	Degradation rate of Myc	7/1800	[8]
d_{e}	Degradation rate of E2F1	1/360	[8]
d_{cd}	Degradation rate of CycD	1/60	[8]
d_{ce}	Degradation rate of CycE	1/60	[8]
d_{r}	Degradation rate of Rb	1/1500	[8]
d_{rp}	Degradation rate of phosphorylated Rb	1/1500	[8]
d_{re}	Degradation rate of Rb/E2F1 complex	1/3000	[8]
k_{p0}	Phosphorylation rate constant of Rb	0.2	[8]
k_{dp}	Dephosphorylation rate of Rb	0.04	[8]
k_{m}	Michaelis constant of Myc in transactivation	0.15	[8]
k_{e}	Michaelis constant of E2F1 in transactivation	0.15	[8]
k_{cd}	Michaelis constant of Rb in CycD-dependent phosphorylation	0.92	[8]
k_{ce}	Michaelis constant of Rb in CycE-dependent phosphorylation	0.92	[8]
I_{S}	Intensity of growth factor in normal cases	0.15	[8]
k_{sWip11}	Basal induction rate of Wip1	0.007	Estimated
k_{sWip12}	p53 arrester inducible production rate of Wip1	0.15	Estimated
j_{sWip1}	Michaelis constant of p53 dependent Wip1 production	0.8	Estimated
k_{dWip1}	Degradation rate of Wip1	0.0006	Estimated
k_{sDINP11}	Basal induction rate of p53DINP1	0.0006	[9]
k_{sDINP12}	p53 arrester inducible production rate of p53DINP1	0.014	[9]
k_{sDINP13}	p53 killer and E2F1 inducible production rate of p53DINP1	0.08	[9]

Supplemental Table S2-Continued

j_{sDINP11}	Michaelis constant of p53 arrester dependent p53DINP1 production	0.8	[9]
j_{DINP12}	Michaelis constant of p53 killer dependent p53DINP1 production		[9]
j_{DINP13}	Michaelis constant of E2F1 dependent p53DINP1 production		[9]
k_{dDINP1}	Degradation rate of p53DINP1	0.007	[9]
k_{sHIPK2}	Production rate of HIPK2	0.07	Estimated
k_{sHIPK2}	Degradation rate constant of HIPK2	0.07	Estimated
k_{sASPP1}	Basal induction rate of ASPP	0.0007	Estimated
k_{sASPP2}	E2F1-inducible production rate of ASPP	0.3	Estimated
j_{sASPP1}	Michaelis constant of p53 dependent ASPP production	0.4	Estimated
k_{dASPP}	Degradation rate of ASPP	0.007	Estimated
k_{p46}	Rate constant of p53 arrester phosphorylation	0.07	Estimated
k_{dp46}	Rate constant of p53 killer dephosphorylation	0.14	Estimated
j_{p46}	Michaelis constant of p53 arrester phosphorylation	0.4	Estimated
j_{dp46}	Michaelis constant of p53 killer dephosphorylation	0.2	Estimated
k_{sAIP11}	Basal induction rate of p53AIP1	0.0007	Estimated
k_{sAIP12}	p53 killer inducible production rate of p53AIP1	0.3	Estimated
j_{sAIP1}	Michaelis constant of p53 dependent p53AIP1 production	0.4	Estimated
k_{dAIP1}	Degradation rate of p53AIP1	0.007	Estimated
k_{sbax1}	Basal production rate of Bax	0.007	Estimated
k_{sbax2}	p53 killer inducible production rate of Bax	0.3	Estimated
j_{sbax}	Michaelis constant of p53 dependent Bax production	0.4	Estimated
k_{dbax}	Degradation rate of Bax	0.07	Estimated
k_{cytc0}	Basal release rate of mitochondrial cytochrome c	0.00007	Estimated
k_{cytc1}	Bax dependent release rate of mitochondrial cytochrome c	4	Estimated
k_{cytc2}	p53AIP1 dependent release rate of mitochondrial cytochrome c	4.5	Estimated
j_{casp3}	Michaelis constant of caspase 3-dependent cytochrome c release	3	Estimated
k_{decytc}	Mitochondrial influx rate of cytochrome c	0.007	Estimated
$CytoC_{\mathrm{tot}}$	Total of cytochrome c	5	Estimated
k_{sapaf11}	Basal production rate of Apaf $-$ 1	0.00007	Estimated
k_{sapaf12}	E2F1-inducible production rate of Apaf $-$ 1	0.4	Estimated
j_{sapaf12}	Michaelis constant of E2F1 dependent Apaf $-$ 1 production	0.5	Estimated
k_{sapaf13}	p53 killer inducible production rate of $Apaf-1$	0.035	Estimated
j_{sapaf13}	Michaelis constant of p53 killer dependent $Apaf-1$ production	0.5	Estimated
k_{dapaf1}	Degradation rate of Apaf $-$ 1	0.07	Estimated
k_{Apops}	Activation rate of Apoptosome	0.1	Estimated
k_{deApops}	Inactivation rate of Apoptosome	0.01	Estimated
k_{scasp91}	Basal induction rate of caspase 9	0.00007	Estimated
k_{scasp92}	E2F1-inducible production rate of caspase 9	0.35	Estimated
j_{scasp9}	Michaelis constant of E2F1-induced caspase 9 production	0.5	Estimated
k_{dcasp9}	Degradation rate of procaspase 9	0.07	Estimated

Supplemental Table S2-Continued

k_{casp9}	Activation rate of caspase 9	0.07	Estimated
k_{decasp9}	Inactivation rate of caspase 9	0.007	Estimated
k_{scasp31}	Basal induction rate of caspase 3	0.00007	Estimated
k_{scasp32}	E2F1-induced production rate of caspase 3	0.7	Estimated
k_{dcasp3}	Degradation rate of caspase 3	0.00007	Estimated
j_{scasp3}	Michaelis constant of E2F1-induced caspase 3 production	0.5	Estimated
k_{casp3}	Activation rate of caspase 3	0.07	Estimated
j_{casp9}	Michaelis constant of caspase 9 dependent caspase 3 activation	2	Estimated
k_{decasp3}	Inactivation rate of caspase 3	0.01	Estimated

Supplemental Figures

Figure legends

Supplemental Figure S1: Schematic illustration of DSB generation and repair module. We consider the DSB repair dynamics as a three-state process:DSB("D"), DSB-protein complex ("C") and fixed DNA ("F"). Here two parallel repair pathways with fast and slow repair dynamics are considered. Subscripts "1" and "2" are used to distinguish the fast and slow kinetic, respectively.

Supplemental Figure S2: Illustration of the ATM sensor. ATM mainly exists as a dimer in unstressed cells. Upon DNA damage, ATM dimer dissociates into active monomers by intermolecular autophosphorylation. There exists a positive feedback loop, in which ATM monomers activates themselves, and the process is also stimulated by DSBCs. Moreover, there exists a negative feedback loop, in which p53 deactivates active ATM via Wip1. Therefore, ATM may undergoes recurrent cycles of activation and inactivation regulated by the two feedback loops until DNA damage is efficiently repaired within a realtively short time.

Supplemental Figure S3: Schematic diagram of the conversion between p53 arrester and p53 killer. Two forms of active p53 are distinguished according to different phosphorylatory states and their functions. p53 arrester induces expression of p21, Wip1 and p53DINP1; p53 killer cooperate with E2F1 to induce p53DINP1. As a partner of the kinase HIPK2, p53DINP1 promotes further phosphorylation at Ser46. By contrast, Wip1 inhibits the accumulation of p53 killer by dephosphorylation p53 killer or inhibiting HIPK2 through ATM. In addition, p21 may indirectly prevent the activation of p53 killer by inhibiting E2F1.

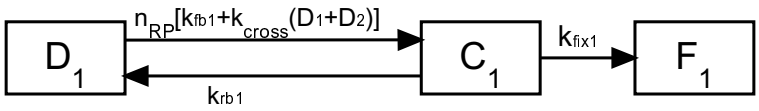
Supplemental Figure S4: Schematic diagram of cell cycle control by p53 and E2F1. In unstressed cells, growth factor induced cyclin D (CycD) forms complex with Cdk4,6. CycD-Cdk4,6 in turn promotes the release of E2F1 from the inhibitor Rb by phosphorylation. Activated E2F1 further induces expression of its own gene and *CycE* gene. CycE forms complex with Cdk2 to activate E2F1 by phosphorylating Rb. Thus, there exists two positive feedback loops. Moreover, growth factor induced Myc can also activate E2F1by inducing CycD and E2F1. In stressed cells, p53-induced p21 represses the activity of Cdk4,6 or Cdk2 and blocks E2F1 activation. Thus, growth factor promotes the G1/S transition through Rb-E2F1 pathway,while p53 inhibits E2F1 activation and arrested the cell cycle at G1 phase.

Supplemental Figure S5: Schematic diagram of apoptosis induction by p53 and E2F1. p53 killer-ASPP complex induces synthesis of Bax and p53AIP1, which promotes the release of cytochrome c (CytoC) from mitochondrial. On the other hand, p53 killer and E2F1 cooperates to induce Apaf-1, which associates with CytoC to form apoptosome. At the same time, E2F1 upregulates the levels of Procasp9 and Procasp3. Apoptosome activated Casp9, which in turn activates Casp3. Thus, apoptosis ensues.

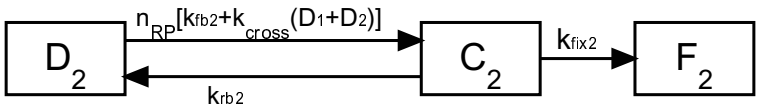
Supplemental Figure S6: A comparison of our theoretical results of p53 pulses with the experimentally measured p53 pulses. For convenience, the amplitudes of the pulses are normalized, and the times courses are limited to the first four pulses. The experimental dada are collected from Geva-Zatorsky *et al.* 2006, Molecular Systems Biology [10].

Supplemental Figure S7: Time courses of [p53 arrester], [p21] and [E2F1] at (A) D_{IR}=2 Gy;(B) D_{IR}=3 Gy; (C) D_{IR}=4 Gy. With increasing D_{IR}, more pulse of p53 arrester and p21 are produced, and E2F1 is activated after the pulses of p21 disappears. Thus, cells undergo longer cell cycle arrest when DNA damage is more serious.

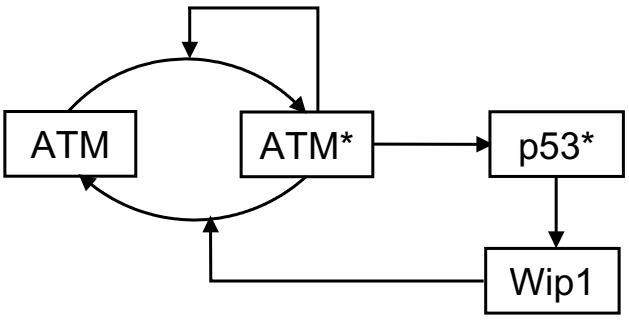
1.DNA repair for fast kinetics



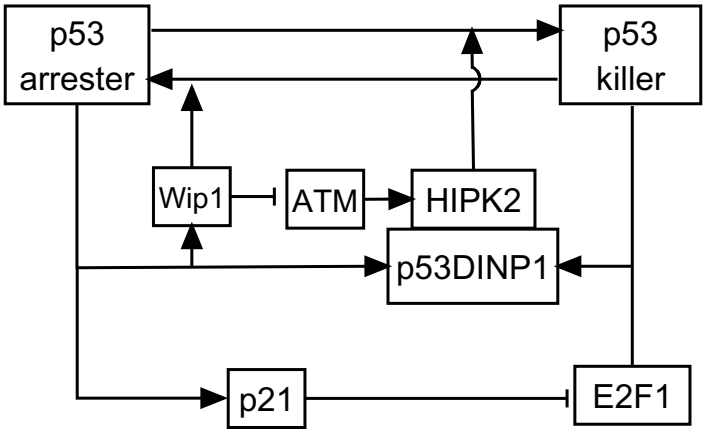
2.DNA repair for slow kinetics



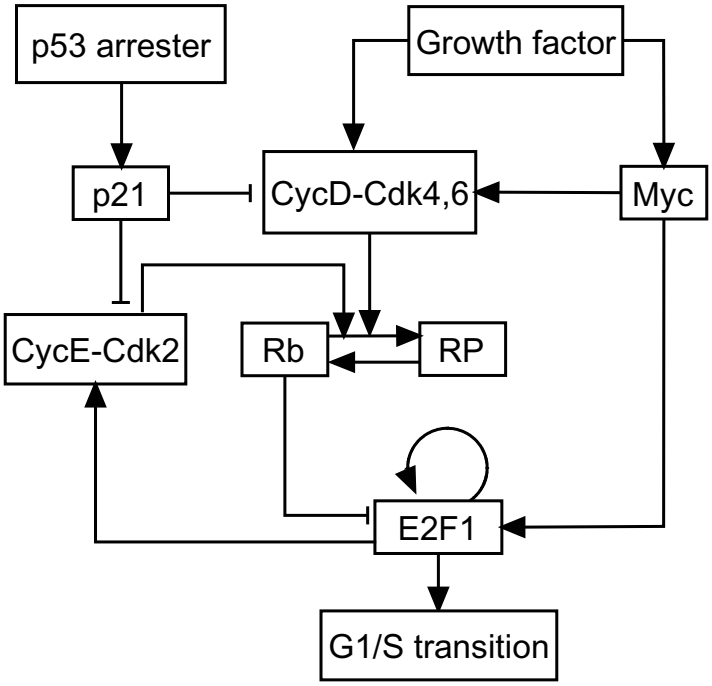
Supplemental Figure S1



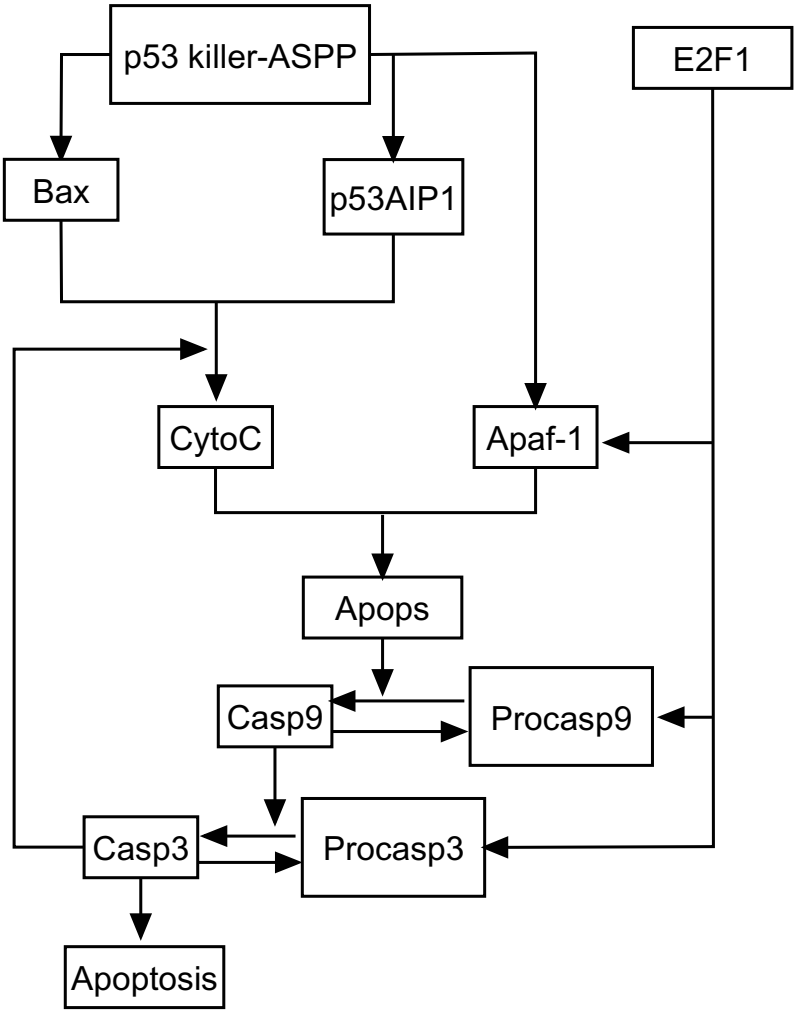
Supplemental Figure S2



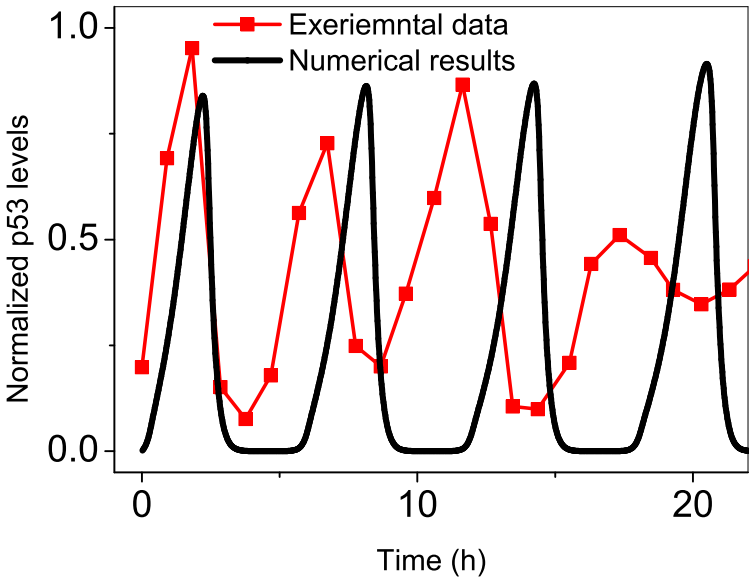
Supplemental Figure S3



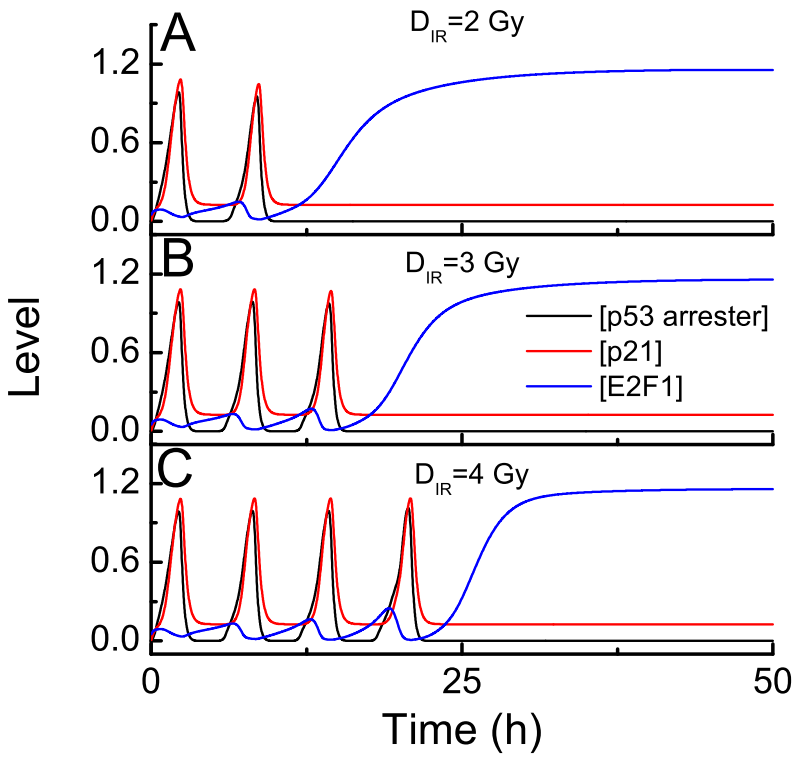
Supplemental Figure S4



Supplemental Figure S5



Supplemental Figure S6



Supplemental Figure S7