Supplementary materials:

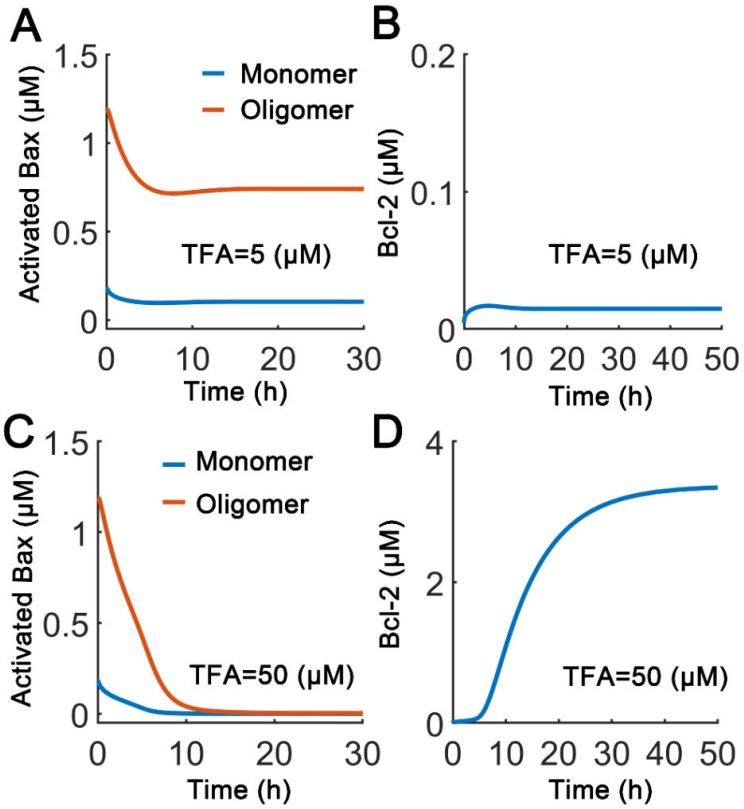

Fig. S1 Temporal responses with sub- or super-threshold TFA treatment. (A) Levels of active Bax monomer and Oligomer (MAC) with 5 μmol/L TFA treatment. The pro-apoptotic Bax forms were maintained at relatively high levels when cells were treated with sub-threshold TFA. (B) Bcl-2 levels with 5 μmol/L TFA treatment. (C) Active Bax forms (monomers and MAC) in cells treated with 50 μmol/L TFA. (D) Bcl-2 levels with 50 μmol/L TFA treatment. Super-threshold TFA treatment will lead to substantially upregulated Bcl-2 and nearly depleted active Bax forms.

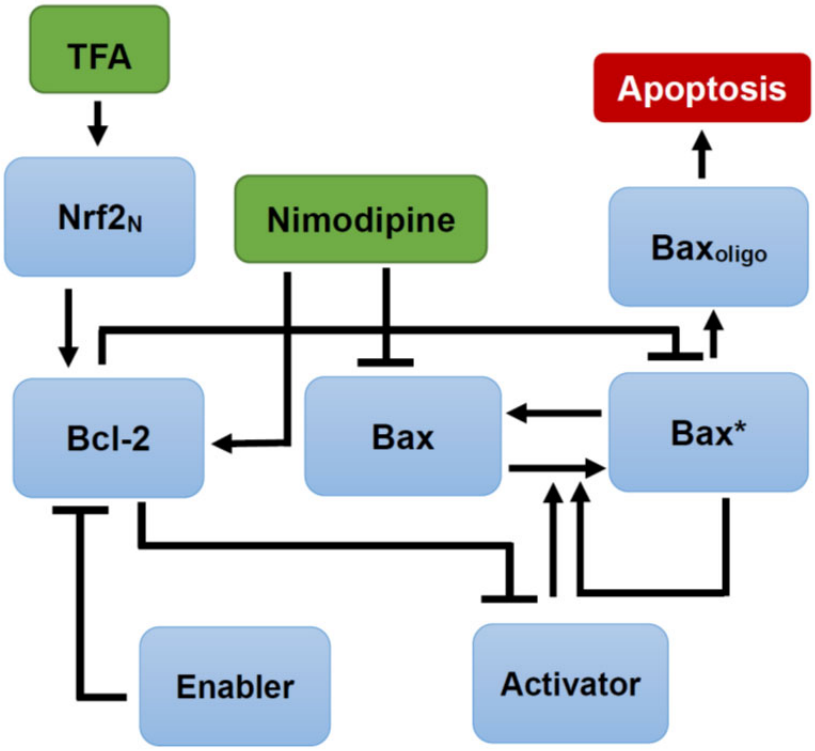

Fig. S2 Model diagrams with Nimodipine and TFA. Nimodipine can inhibit Bax expression while increase Bcl-2 expression. Arrows indicate activation/upregulation, blunt arrows denote inhibition.

Table S1 Reactions of model

Reactions	Description	$k+$	$k-$
InBax+Act->AcBax+Act	Act-mediated InBax activation	k_1	–
AcBax+Bcl2<->AcBaxBcl2	AcBax-Bcl2 dimerization and dissociation	k_2	k_3
Act+Bcl2<->ActBcl2	Act-Bcl2 dimerization and dissociation	k_4	k_5
AcBax+ActBcl2<->AcBaxBcl2+Act	Displacement between AcBax and Act	k_6	k_7
AcBax->InBax	AcBax inactivation	k_8	–
Ena+Bcl2<->EnaBcl2	Ena-Bcl2 dimerization and dissociation	k_9	k_{10}
Act+EnaBcl2<->ActBcl2+Ena	Displacement between Act and Ena	k_{12}	k_{11}
AcBax+EnaBcl2<->AcBaxBcl2+Ena	Displacement between AcBax and Ena	k_{14}	k_{13}
InBax+AcBax->MAC	Bax auto-activation and dimerization	k_{15}	
2AcBax<->MAC	AcBax dimerization and dissociation	k_{16}	k_{17}
InBax<->Φ	InBax degradation and production	u_1	p_1
AcBax->Φ	AcBax degradation	u_2	–
Act<->Φ	Act degradation and production	u_3	p_2
Bcl2<->Φ	Bcl-2 degradation and production	u_4	$p_{\text{Bcl-2}}$
ActBcl2->Φ	ActBcl2 degradation	u_5	–
AcBaxBcl2->Φ	AcBaxBcl2 degradation	u_6	–
Ena<->Φ	Ena degradation and production	u_7	p_3
EnaBcl2->Φ	EnaBcl2 degradation	u_8	–
MAC->Φ	MAC degradation	u_9	–

Abbreviations used: *InBax* (Inactive Bax/Bak), *Act* (Activator), *AcBax* (Activated Bax/Bak), *Bcl2* (Anti-apoptotics), *AcBaxBcl2* (Activated Bax/Bak-Bcl2 dimer), *ActBcl2* (Activator-Bcl2 dimer), Ena (Enabler), *EnaBcl2* (Enabler-Bcl2 dimer), *MAC* (Bax/Bak pore), *Φ* (null). Parametric expression "p" represents production, while "u" donates degradation. Parameter values were listed in Table S3.

In model with TFA treatment only, $p_{\text{Bcl-2}}=p_{\text{TFA}}\times\text{Nrf2}_{\text{nuc}}/(\text{Nrf2}_{\text{nuc}}+K_{\text{Nrf2}})$, $\text{Nrf2}_{\text{nuc}}=[k_{\text{basal}}+(1-k_{\text{basal}})\times\text{TFA}\times k_{\text{in}}/(\text{TFA}\times k_{\text{in}}+k_{\text{out}})]\times\text{Nrf2}_{\text{T}}$. Nrf2_{nuc} is the nuclear Nrf2. Nrf2_{T} is the total Nrf2 concentration.

In model with both TFA and Nimodipine treatment, $p_{\text{Bcl-2}}=p_{\text{TFA}}\times\text{Nrf2}_{\text{nuc}}/(\text{Nrf2}_{\text{nuc}}+K_{\text{Nrf2}})+p_{\text{Nimo}}\times\text{Nimo}/(Ec+\text{Nimo})$, $\text{Nrf2}_{\text{nuc}}=[k_{\text{basal}}+(1-k_{\text{basal}})\times\text{TFA}\times k_{\text{in}}/(\text{TFA}\times k_{\text{in}}+k_{\text{out}})]\times\text{Nrf2}_{\text{T}}$. Meanwhile, $p_1'=p_1\times Ec/(Ec+\text{Nimo})$.

Table S2 Model equations

$$\mathrm{d}[InBax]/\mathrm{d}t = J_{InBax} - J_1 + J_5$$
$$\mathrm{d}[AcBax]/\mathrm{d}t = J_{AcBax} + J_1 - J_2 - J_4 - J_5 + J_8 - J_9 - 2\cdot J_{10}$$
$$\mathrm{d}[Bcl2]/\mathrm{d}t = J_{Bcl2} - J_2 - J_3 - J_6$$
$$\mathrm{d}[Act]/\mathrm{d}t = J_{Act} - J_3 + J_4 + J_7$$
$$\mathrm{d}[ActBcl2]/\mathrm{d}t = J_{ActBcl2} + J_3 - J_4 - J_7$$
$$\mathrm{d}[AcBaxBcl2]/\mathrm{d}t = J_{AcBaxBcl2} + J_2 + J_4 - J_8$$
$$\mathrm{d}[Ena]/\mathrm{d}t = J_{Ena} - J_6 - J_7 - J_8$$
$$\mathrm{d}[EnaBcl2]/\mathrm{d}t = J_{EnaBcl2} + J_6 + J_7 + J_8$$
$$\mathrm{d}[MAC]/\mathrm{d}t = J_{MAC} + J_9 + J_{10}$$

$$J_{InBax} = p_1 - u_1\cdot[InBax] \qquad J_1 = k_1\cdot[InBax]\cdot[Act]$$
$$J_{AcBax} = -u_2\cdot[AcBax] \qquad J_2 = k_2\cdot[AcBax]\cdot[Bcl2] - k3\cdot[AcBaxBcl2]$$
$$J_{Act} = p_2 - u_3\cdot[Act] \qquad J_3 = k_4\cdot[Act]\cdot[Bcl2] - k_5\cdot[ActBcl2]$$
$$J_{Bcl2} = p_{Bcl-2} - u_4\cdot[Bcl2] \qquad J_4 = k_6\cdot[AcBax]\cdot[ActBcl2] - k_7\cdot[AcBaxBcl2]\cdot[Act]$$
$$J_{ActBcl2} = -u_5\cdot[ActBcl2] \qquad J_5 = k_8\cdot[AcBax]$$
$$J_{AcBaxBcl2} = -u_6\cdot[AcBaxBcl2] \qquad J_6 = k_9\cdot[Ena]\cdot[Bcl2] - k_{10}\cdot[EnaBcl2]$$
$$J_{Ena} = p_3 - u_7\cdot[Ena] \qquad J_7 = k_{11}\cdot[Ena]\cdot[ActBcl2] - k_{12}\cdot[Act]\cdot[EnaBcl2]$$
$$J_{EnaBcl2} = -u_8\cdot[EnaBcl2] \qquad J_8 = k_{13}\cdot[Ena]\cdot[AcBaxBcl2] - k_{14}\cdot[AcBax]\cdot[EnaBcl2]$$
$$J_{MAC} = -u_9\cdot[MAC] \qquad J_9 = k_{15}\cdot[InBax]\cdot[AcBax]$$
$$J_{10} = k_{16}\cdot[AcBax]^2 - k_{17}\cdot[MAC]$$

In model with TFA treatment only, $J_{InBax}=p_1-u_1\cdot[InBax]$; In model with both TFA and Nimodipine (Nimo) treatment, $J_{InBax}=p_1'-u_1\cdot[InBax]$. p_1' and p_{Bcl-2} were defined as in footnote for Table S1.

Table S3 Model parameters

Parameters	Description	Value
k_1	Act-mediated Activation of Bax	0.1
k_2	Dimerization between AcBax and Bcl2	1
k_3	Dissociation of Bax-Bcl2 dimer	0.001
k_4	Dimerization between Act and Bcl2	10
k_5	Dissociation of Act-Bcl2 dimer	0.06
k_6	AcBax displace Act from Act-Bcl2 dimer	0.5
k_7	Act displace AcBax from Bax-Bcl2 dimer	0.01
k_8	Bax/Bak inactivation	0.001
k_9	Dimerization between Ena and Bcl2	0.1
k_{10}	Dissociation of Ena-Bcl2 dimer	0.001
k_{11}	Ena displace Act from Act-Bcl2 dimer	0.5
k_{12}	Act displace Ena from Ena-Bcl2 dimer	0.05
k_{13}	Ena displace AcBax from Bax-Bcl2 dimer	10
k_{14}	AcBax displace Ena from Ena-Bcl2 dimer	0.5
k_{15}	Bax Auto-activation & dimerization	0.2
k_{16}	Homo-dimerization of AcBax	0.2
k_{17}	Dissociation of Bax homo-dimer	0.01
p_1	Production rate of InBax	0.04
p_2	Production rate of Act	0.002
$p_{\text{Bcl-2}}$	Production rate of Bcl2	/
p_3	Production rate of Ena	0.002
u_1	Degradation rate of InBax	0.03
u_2	Degradation rate of AcBax	0.002
u_3	Degradation rate of Act	0.01
u_4	Degradation rate of Bcl2	0.002
u_5	Degradation rate of Act-Bcl2 dimer	0.002
u_6	Degradation rate of Bax-Bcl2 dimer	0.01
u_7	Degradation rate of Ena	0.001
u_8	Degradation rate of Ena-Bcl2 dimer	0.005
u_9	Degradation rate of Bax oligomer	0.01
p_{TFA}	Bcl-2 production rate by TFA treatment	0.03
k_{basal}	Basal Nrf2 nuclear fraction	0.2402
k_{in}	Nrf2 nuclear import rate	0.2099
k_{out}	Nrf2 nuclear import rate	0.4992
Nrf2_{T}	Total Nrf2 concentration	1
K_{Nrf2}	Threshold concentration for Nrf2_{nuc}	1.6779
p_{Nimo}	Bcl-2 production rate by Nimodipine	0.01
Ec	Threshold concentration for Nimodipine	70
Initial conditions	**Description**	**Value**
InBax	Inactivated Bax	0.47306
AcBax	Activated Bax	0.18182
Act	Activator	0.18577
Bcl2	Bcl-2 protein	0.00420
ActBcl2	Activator-Bcl-2 complex	0.07114
ActBaxBcl2	Activated Bax and Bcl-2 complex	0.16313
Ena	Enabler	0.02516
EnaBcl2	Enabler-Bcl-2 complex	0.39497
MAC	Mitochondrial apoptosis channel	1.19066

Units: The total amounts of different species are in units of μmol/L. The first and second order rate constants are expressed in units of min^{-1} and μL/(mol·min), respectively. The production rate constants are expressed in unit of μmol/(L·min).
$p_{\text{Bcl-2}}$ differs in distinct models as defined in Table S1.
The parameters k_1–k_{17}, p_1, p_3, u_1–u_9 were assigned according to our previous work (Sun et al., 2009).
The initial conditions correspond to an OGD/R induced apoptotic state with TFA or Nimodipine=0 μmol/L.

Reference

Sun T, Chen C, Wu Y, et al., 2009. Modeling the role of p53 pulses in DNA damage- induced cell death decision. *BMC Bioinformatics*, 10:190. https://doi.org/10.1186/1471-2105-10-190