Text S1. ODEs system of the preliminary pathway model

To describe the biochemical reactions and connectivity of signaling molecules in this study, we adopted a deterministic ordinary differential equations (ODEs) model using the law of mass action, which are used to describe the time evolution of concentrations of various molecules and molecular complexes of interest. Here we describe the details for the ODEs system except for the TNFα receptor sub-system which has been described in Materials and Methods of main text. The equations along with the explanations are given as follows.

ASK1: Equation (1) describes the change on the concentration of ASK1 due to TRAF2C-mediated phosphorylation of ASK1 by (with rate k_1) and pp38/pAKT-mediated dephosphorylation of pASK1 by (with rates k_2 and k_3 respectively).

$$\frac{d[ASK1]}{dt} = -k_1 * [ASK1][TRAF2C] + k_2 * [pASK1][pp38] + k_3 * [pASK1][pAKT]; \quad (1)$$

pASK1: Equation (2) describes the change on the concentration of pASK1 due to TRAF2C-mediated phosphorylation of ASK1 by (with rate k_1) and pp38/pAKT-mediated dephosphorylation of pASK1 by (with rates k_2 and k_3 respectively).

$$\frac{d[pASK1]}{dt} = k_1 * [ASK1][TRAF2C] - k_2 * [pASK1][pp38] - k_3 * [pASK1][pAKT]; \quad (2)$$

MKK3/6: Equation (3) describes the change on the concentration of MKK3/6 due to pASK1-mediated phosphorylation of MKK3/6 (with rate k_4) and auto-dephosphorylation of pMKK3/6 (with rate k_5).

$$\frac{d[MKK3/6]}{dt} = -k_4 * [MKK3/6][pASK1] + k_5 * [pMKK3/6]; \quad (3)$$

pMKK3/6: Equation (4) describes the change on the concentration of pMKK3/6 due to pASK1-mediated phosphorylation of MKK3/6 (with rate k_4) and auto-dephosphorylation of pMKK3/6 (with rate k_5).

$$\frac{d[pMKK3/6]}{dt} = k_4 * [MKK3/6][pASK1] - k_5 * [pMKK3/6]; \quad (4)$$

p38: Equation (5) describes the change on the concentration of p38 due to pMKK3/6-mediated phosphorylation of p38 (with rate k_6) and pJNK-mediated dephosphorylation of pp38 (with rate k_7).

$$\frac{d[p38]}{dt} = -k_6 * [p38][pMKK3/6] + k_7 * [pp38][pJNK]; \quad (5)$$

pp38: Equation (6) describes the change on the concentration of pp38 due to pMKK3/6-mediated phosphorylation of p38 (with rate k_6) and pJNK-mediated dephosphorylation of pp38 (with rate k_7).

$$\frac{d[pp38]}{dt} = k_6 * [p38][pMKK3/6] - k_7 * [pp38][pJNK]; \tag{6}$$

MEKK1: Equation (7) describes the change on the concentration of MEKK1 due to TRAF2C-mediated phosphorylation of MEKK1 (with rate k_8) and auto-dephosphorylation of pMEKK1 (with rate k_9).

$$\frac{d[MEKK1]}{dt} = -k_8 * [MEKK1][TRAF2C] + k_9 * [pMEKK1]; \tag{7}$$

pMEKK1: Equation (8) describes the change on the concentration of pMEKK1 due to TRAF2C-mediated phosphorylation of MEKK1 (with rate k_8) and auto-dephosphorylation of pMEKK1 (with rate k_9).

$$\frac{d[pMEKK1]}{dt} = k_8 * [MEKK1][TRAF2C] - k_9 * [pMEKK1]; \tag{8}$$

MKK4/7: Equation (9) describes the change on the concentration of MKK4/7 due to pASK1/pMEKK1-mediated phosphorylation of MKK4/7 (with rates k_{10} and k_{11} respectively) and pAKT-mediated dephosphorylation of pMKK4/7 (with rate k_{12}).

$$\frac{d[MKK4/7]}{dt} = -k_{10} * [MKK4/7][pASK1] - k_{11} * [MKK4/7][pMEKK1] + k_{12} * [pMKK4/7][pAKT]; \tag{9}$$

pMKK4/7: Equation (10) describes the change on the concentration of pMKK4/7 due to pASK1/pMEKK1-mediated phosphorylation of MKK4/7 (with rates k_{10} and k_{11} respectively) and pAKT-mediated dephosphorylation of pMKK4/7 (with rate k_{12}).

$$\frac{d[pMKK4/7]}{dt} = k_{10} * [MKK4/7][pASK1] + k_{11} * [MKK4/7][pMEKK1] - k_{12} * [pMKK4/7][pAKT]; \tag{10}$$

JNK: Equation (11) describes the change on the concentration of JNK due to pMKK4/7-mediated phosphorylation of JNK (with rate k_{13}) and pp38-mediated dephosphorylation of pJNK (with rate k_{14}).

$$\frac{d[JNK]}{dt} = -k_{13} * [JNK][pMKK4/7] + k_{14} * [pJNK][pp38]; \tag{11}$$

pJNK: Equation (12) describes the change on the concentration of pJNK due to pMKK4/7-mediated phosphorylation of JNK (with rate k_{13}) and pp38-mediated dephosphorylation of pJNK (with rate k_{14}).

$$\frac{d[pJNK]}{dt} = k_{13} * [JNK][pMKK4/7] - k_{14} * [pJNK][pp38]; \tag{12}$$

c_Jun: Equation (13) describes the change on the concentration of c_Jun due to pp38/pJNK-mediated phosphorylation of c_Jun (with rates k_{15} and k_{16} respectively) and auto-dephosphorylation of pc_Jun (with rate k_{17}).

$$\frac{d[c\_Jun]}{dt} = -k_{15} * [c\_Jun][pp38] - k_{16} * [c\_Jun][pJNK] + k_{17} * [pc\_Jun]; \quad (13)$$

pc_Jun: Equation (14) describes the change on the concentration of pc_Jun due to pp38/pJNK-mediated phosphorylation of c_Jun (with rates k_{15} and k_{16} respectively) and auto-dephosphorylation of pc_Jun (with rate k_{17}).

$$\frac{d[pc\_Jun]}{dt} = k_{15} * [c\_Jun][pp38] + k_{16} * [c\_Jun][pJNK] - k_{17} * [pc\_Jun]; \quad (14)$$

AKT: Equation (15) describes the change on the concentration of AKT due to auto-phosphorylation of AKT (with rate k_{18}) and pp53-mediated dephosphorylation of pAKT (with rate k_{19}).

$$\frac{d[AKT]}{dt} = -k_{18} * [AKT] + k_{19} * [pAKT][pp53]; \quad (15)$$

pAKT: Equation (16) describes the change on the concentration of pAKT due to auto-phosphorylation of AKT (with rate k_{18}) and pp53-mediated dephosphorylation of pAKT (with rate k_{19}).

$$\frac{d[pAKT]}{dt} = k_{18} * [AKT] - k_{19} * [pAKT][pp53]; \quad (16)$$

p53: Equation (17) describes the change on the concentration of p53 due to pp38/pJNK-mediated phosphorylation of p53 (with rates k_{20} and k_{21} respectively) and pAKT-mediated dephosphorylation of pp53 (with rate k_{22}).

$$\frac{d[p53]}{dt} = -k_{20} * [p53][pp38] - k_{21} * [p53][pJNK] + k_{22} * [pp53][pAKT]; \quad (17)$$

pp53: Equation (18) describes the change on the concentration of pp53 due to pp38/pJNK-mediated phosphorylation of p53 (with rates k_{20} and k_{21} respectively) and pAKT-mediated dephosphorylation of pp53 (with rate k_{22}).

$$\frac{d[pp53]}{dt} = k_{20} * [p53][pp38] + k_{21} * [p53][pJNK] - k_{22} * [pp53][pAKT]; \quad (18)$$

BCL_XL: Equation (19) describes the change on the concentration of BCL_XL due to pp38/pJNK-mediated phosphorylation of BCL_XL (with rates k_{23} and k_{24} respectively) and auto-dephosphorylation of pBCL_XL (with rate k_{25}).

$$\frac{d[BCL\_XL]}{dt} = -k_{23} * [pp38][BCL\_XL] - k_{24} * [pJNK][BCL\_XL] + k_{25} * [pBCL\_XL]; \quad (19)$$

pBCL_XL: Equation (20) describes the change on the concentration of pBCL_XL due to pp38/pJNK-mediated phosphorylation of BCL_XL (with rates k_{23} and k_{24} respectively), auto-dephosphorylation of pBCL_XL (with rate k_{25}) and auto-degradation of pBCL_XL (with rate k_{26}).

$$\frac{d[pBCL\_XL]}{dt} = k_{23} * [pp38][BCL\_XL] + k_{24} * [pJNK][BCL\_XL] - k_{25} * [pBCL\_XL] - k_{26} * [pBCL\_XL]; \qquad (20)$$

dBCL_XL: Equation (21) describes the change on the concentration of dBCL_XL (degraded BCL_XL) due to the auto-dephosphorylation of pBCL_XL (with rate k_{26}).

$$\frac{d[dBCL\_XL]}{dt} = k_{26} * [pBCL\_XL]; \qquad (21)$$