Supplementary Data A

The signaling map is composed of three modules (Fig. 1): the Wnt signaling module, the ERK signaling module, and the gene regulation module.

The ERK and Wnt signaling pathway modules (green and blue boxes in Fig. 1)

The ERK signaling pathway is well described in various cell types (1-3). As shown in the upper left green box in Fig. 1, it is initiated by the growth factor induced recruitment of the SOS/Grb2 complex to the plasma membrane. The SOS/Grb2 complex (x18) catalyzes the transformation of an inactive GDP-bound form (x19) of Ras (Ras-GDP) into its active GTP-bound form (Ras-GTP) (x20) (process v28). Ras-GTP binds the Raf-1 kinase (x21) with high affinity, which induces the recruitment of Raf-1 from the cytosol to the cell membrane and activates it (process v30). Activated Raf-1 (x22) phosphorylates and activates MEK (x23) (process v32), a kinase that in turn phosphorylates and activates ERK (x25) (process v34). Activated ERK (x26) can translocate to the nucleus and regulate gene expression by the phosphorylation of transcription factors including Snail (x30) and Slug (x31) (processes v42&44). The ERK signaling pathway includes a negative feedback loop (NFL) formed by dissociation of the SOS/Grb2 complex through ERK mediated phosphorylation (process v24), and multiple positive feedback loops (PFLs) formed by regulations of RKIP (x27) and GSK3β (x5) through active ERK. As shown in the upper right blue box in Fig. 1, the canonical Wnt signaling pathway is initiated by Wnt binding to Frizzled (process v1). The activation of Disheveled (x2) by Frizzled inhibits phosphorylation of the adenomatous polyposis coli (APC) protein (x8) and Axin (x13) by GSK3β. This disassembles the destruction core complex (x4) composed of APC, Axin, and GSK3β (process v3). This destruction complex plays a role in ubiquitination and degradation of β-catenin (process v10), and its inhibition leads to the accumulation of β-catenin in the nucleus (process v16). The Wnt signaling pathway module also includes one NFL formed by expression of Axin (process v23) by the β-catenin/TCF complex (x15).

Gene transcriptional regulation module (orange box in Fig. 1)

Snail and Slug belong to the family of zinc finger-containing transcriptional repressors and their expression is regulated by multiple levels of protein interaction and post-translational modifications (4-7). Recent experimental results showed that Snail is regulated by GSK3β

mediated phosphorylation on two distinct motifs (8). As shown in the lower orange box in Fig. 1, phosphorylation of the first motif directs Snail ubiquitination and proteolytic degradation (process v43), and the phosphorylation of the second motif directs nuclear export of Snail and thereby inhibition of its transcriptional regulation (process v19&38). Recently, Peiro *et al.* (9) showed that Snail induced by active ERK inhibits its own expression (process v42) through binding to an E-box in its promoter and repressing its activity. On the other hand, Sakai *et al.* reported that Slug activates its own promoter (process v47) (10). Based on the diagrammatic interaction map, we developed a mathematical model composed of the ERK and Wnt signaling pathway modules and the gene transcriptional regulation module. For details on the mathematical modeling, see Materials and methods and Supplementary Data A.

Mathematical modeling and model reduction

By integrating available information about protein interactions and regulations in the ERK and Wnt signaling pathways, we constructed first a diagrammatic interaction map (Fig. 1), which provided the basis for the further development of a mathematical model. We then used the law of mass action, Michaelis-Menten equations, and Hill equations depending on the reaction characteristics to obtain the ordinary differential equation (ODE) model (see below for details). This model includes the ERK and Wnt signaling pathway modules and the gene regulation module as described in the Results section. Specifically, the activation and deactivation of signaling proteins in the ERK pathway module are described by first order rate equations; protein interactions in the Wnt pathway module are described by molecular association/dissociation or stoichiometric conversions; the gene transcriptional regulation module is described by Hill equations. The mathematical model was then reduced by utilizing biological constraints such as mass conservation and rapid equilibrium condition, by which kinetic parameters were converted into measureable ones.

Modeling of the Wnt signaling module

Using the law of mass action, we can describe the mathematical model of the Wnt signaling module (Fig. 1) as follows (this will be further simplified by considering some biological constraints).

$$\frac{dX_1}{dt} = -v_1 + v_2 \qquad \text{(S.1)}$$

$$\frac{dX_2}{dt} = v_1 - v_2 \tag{S.2}$$

$$\frac{dX_3}{dt} = v_4 - v_5 - v_8 + v_{10} \tag{S.3}$$

$$\frac{dX_4}{dt} = -v_3 - v_4 + v_5 + v_6 \tag{S.4}$$

$$\frac{dX_5}{dt} = v_3 - v_6 - v_{21} + v_{22} \tag{S.5}$$

$$\frac{dX_6}{dt} = v_{21} - v_{22} \tag{S.6}$$

$$\frac{dX_7}{dt} = v_3 - v_6 + v_7 \tag{S.7}$$

$$\frac{dX_8}{dt} = -v_7 - v_{17} \tag{S.8}$$

$$\frac{dX_9}{dt} = v_8 - v_9 \tag{S.9}$$

$$\frac{dX_{10}}{dt} = v_9 - v_{10} \tag{S.10}$$

$$\frac{dX_{11}}{dt} = v_{10} - v_{11} \tag{S.11}$$

$$\frac{dX_{12}}{dt} = -v_8 + v_{12} - v_{13} - v_{16} - v_{17} \tag{S.12}$$

$$\frac{dX_{13}}{dt} = -v_7 + v_{14} - v_{15} + v_{23} \tag{S.13}$$

$$\frac{dX_{14}}{dt} = -v_{16} \tag{S.14}$$

$$\frac{dX_{15}}{dt} = v_{16} \tag{S.15}$$

$$\frac{dX_{16}}{dt} = v_{17} \tag{S.16}$$

$$\frac{dX_{17}}{dt} = -v_{18} + v_{19} + v_{20} \tag{S.17}$$

where $v_i (1 \le i \le 23)$ represent the processes shown in Fig. 1 and Table S1.

Model reduction

Using mass conservation, we can reduce the ODE system (S.1)~(S.17) as described in the following Step 1.

Step 1. Mass conservation.

Proteins Dsh, TCF, GSK3β, APC, β-catenin, Axin, and E-cadherin comprise $X_i (1 \le i \le 17)$ in which the concentrations of β-catenin* (X_{11}), β-catenin (X_{12}), Axin (X_{13}), and E-cadherin (X_{17}) are assumed to change by regulation of various signaling proteins. However, the total concentrations of Dsh, TCF, GSK3β and APC would remain constant throughout the time course of oncogenic stimuli (EGF and Wnt) since they are stable proteins (11). Thus the mass conservation equations for $X_i (1 \le i \le 17, i \ne 11,12,13,17)$ can be constructed as follows:

$$X_1 + X_2 = Dsh^0 \tag{S.18}$$

$$X_{14} + X_{15} = TCF^0 \tag{S.19}$$

$$X_3 + X_4 + X_5 + X_6 + X_9 + X_{10} = GSK3\beta^0 \tag{S.20}$$

$$X_3 + X_4 + X_7 + X_8 + X_9 + X_{10} + X_{16} = APC^0 \tag{S.21}$$

The superscript "0" denotes the total concentration of each protein. From Eqs. (S.18)-(S.19), we have the following algebraic equations:

$$X_1 = Dsh^0 - X_2 \tag{S.22}$$

$$X_{14} = TCF^0 - X_{15} \tag{S.23}$$

Since the total concentration of Axin is negligible compared to APC , β-catenin, $GSK3\beta$ and $GSK3\beta^*$(phosphorylated GSK3β) (11), the state variables X_5 and X_8 in (S.20) and (S.21) can be represented as functions of X_6 and X_{16}, respectively:

$$X_5 = GSK3\beta^0 - X_6 \tag{S.24}$$

$$X_8 = APC^0 - X_{16} \tag{S.25}$$

Thus, the state variables $X_i (i = 1,5,8,14)$ can be obtained from (S.22), (S.23), (S.24), and (S.25) and the ODEs (S.1), (S.5), (S.8), and (S.14) can be eliminated from the ODEs.

Some of the remaining ODEs can be further reduced by considering the rapid equilibrium condition of fast processes as described in the following Step 2 through Step 4.

Step 2. The rapid equilibrium condition of fast processes.

Let us consider the association/dissociation of APC and Axin (v_7), β-catenin and destruction complex (v_8), TCF and β-catenin (v_{16}), and APC and β-catenin (v_{17}) in rapid

equilibrium status. At this rapid equilibrium condition, we can have the following approximations of those fast processes:

$$v_7 = v_8 = v_{16} = v_{17} \approx 0 \tag{S.26}$$

Note that the association of $GSK3\beta$ and the APC/Axin complex (v_6) can be considered as a slow process since Dsh-mediated $GSK3\beta$ release from the destruction complex (v_3) is assumed to be slow (see Fig. 1). From these approximations (S.26), we can derive the following four algebraic equations:

$$X_7 = \frac{X_8 X_{13}}{K_{813}} + \varepsilon_7 \tag{S.27}$$

$$X_9 = \frac{X_3 X_{12}}{K_{312}} + \varepsilon_9 \tag{S.28}$$

$$X_{15} = \frac{X_{12} X_{14}}{K_{1214}} + \varepsilon_{15} \tag{S.29}$$

$$X_{16} = \frac{X_8 X_{12}}{K_{812}} + \varepsilon_{16} \tag{S.30}$$

where ε_i ($i = 7,9,15,16$) denote error terms and $K_\xi = k_{d\xi} / k_{a\xi}$ $(\xi = 813, 312, 1214, 812)$ indicate the binding affinities as shown in Table S2.

Step 3. Elimination of the fast processes $v_i (i = 7,8,16,17)$ in the ODEs.

Step 3-1. Representation of the fast processes by using (S.7), (S.9), (S.15) and (S.16). Substituting four algebraic equations (S.27)~(S.30) into (S.7), (S.9), (S.15) and (S.16), respectively, and rearranging the results for $v_i (i = 7,8,16,17)$, we obtain

$$v_7 = \frac{dX_7}{dt} - v_3 + v_6 = \frac{d}{dt}\left(\frac{X_8 X_{13}}{K_{813}} + \varepsilon_7\right) - v_3 + v_6$$

$$v_8 = \frac{dX_9}{dt} + v_9 = \frac{d}{dt}\left(\frac{X_3 X_{12}}{K_{312}} + \varepsilon_9\right) + v_9$$

$$v_{16} = \frac{dX_{15}}{dt} = \frac{d}{dt}\left(\frac{X_{12} X_{14}}{K_{1214}} + \varepsilon_{15}\right)$$

$$v_{17} = \frac{dX_{16}}{dt} = \frac{d}{dt}\left(\frac{X_8 X_{12}}{K_{812}} + \varepsilon_{16}\right)$$

Step 3-2. Elimination of $v_i (i = 7,8,16,17)$ in the ODEs .

Substituting $v_i (i = 7,8,16,17)$ obtained from Step 3-1 into the ODEs other than (S.7), (S.9), (S.15) and (S.16), we obtain the following equations:

$$\frac{dX_3}{dt} = v_4 - v_5 - v_8 + v_{10} = v_4 - v_5 - \left\{ \frac{d}{dt}\left(\frac{X_3 X_{12}}{K_{312}} + \varepsilon_9 \right) + v_9 \right\} + v_{10} \tag{S.31}$$

$$\begin{aligned} \frac{dX_{12}}{dt} &= -v_8 + v_{12} - v_{13} - v_{16} - v_{17} - v_{18} \\ &= -\left\{ \frac{d}{dt}\left(\frac{X_3 X_{12}}{K_{312}} + \varepsilon_9 \right) + v_9 \right\} + v_{12} - v_{13} - \frac{d}{dt}\left(\frac{X_{12} X_{14}}{K_{1214}} + \varepsilon_{15} \right) - \frac{d}{dt}\left(\frac{X_8 X_{12}}{K_{812}} + \varepsilon_{16} \right) - v_{18} \end{aligned} \tag{S.32}$$

$$\frac{dX_{13}}{dt} = -v_7 + v_{14} - v_{15} + v_{24} = -\left\{ \frac{d}{dt}\left(\frac{X_8 X_{13}}{K_{813}} + \varepsilon_7 \right) - v_3 + v_6 \right\} + v_{14} - v_{15} + v_{24} \tag{S.33}$$

Step 4. Construction of algebraic equations and an ODE system to find state variables other than $X_i (i = 1,5,8,14)$.

Assuming error terms $\varepsilon_i = 0$ $(i = 7,9,15,16)$, the four state variables $X_i (i = 7,9,15,16)$ can be represented as functions of other variables:

$$X_7 = \frac{X_8 X_{13}}{K_{813}}. \tag{S.34}$$

$$X_9 = \frac{X_3 X_{12}}{K_{312}}. \tag{S.35}$$

$$X_{15} = \frac{X_{12} X_{14}}{K_{1214}}. \tag{S.36}$$

$$X_{16} = \frac{X_8 X_{12}}{K_{812}}. \tag{S.37}$$

Thus, (S.7), (S.9), (S.15), and (S.16) can be eliminated from the ODEs and can be replaced by the algebraic equations (S.34)~(S.37), respectively.

Therefore, the remaining nine state variables $X_i (i = 2,3,4,6,10,11,12,13,17)$ can be obtained by solving the ODE system (S.2), (S.31), (S.4), (S.6), (S.10), (S.11), (S.32), (S.33), and (S.17) with $\varepsilon_i = 0$ $(i = 7,9,15,16)$: the system is linear with respect to $\frac{dX_i}{dt} (i = 2,3,4,6,10,11,12,13,17)$.

Modeling of the ERK signaling module:

$$\frac{dX_{18}}{dt} = v_{24} - v_{25} \tag{S.38}$$

$$\frac{dX_{19}}{dt} = v_{26} - v_{27} \tag{S.39}$$

$$\frac{dX_{20}}{dt} = v_{28} - v_{29} \tag{S.40}$$

$$\frac{dX_{21}}{dt} = -v_{30} + v_{31} \tag{S.41}$$

$$\frac{dX_{22}}{dt} = v_{30} - v_{31} \tag{S.42}$$

$$\frac{dX_{23}}{dt} = -v_{32} + v_{33} \tag{S.43}$$

$$\frac{dX_{24}}{dt} = v_{32} - v_{33} \tag{S.44}$$

$$\frac{dX_{25}}{dt} = -v_{34} + v_{35} \tag{S.45}$$

$$\frac{dX_{26}}{dt} = v_{34} - v_{35} \tag{S.46}$$

$$\frac{dX_{27}}{dt} = v_{38} - v_{39} \tag{S.47}$$

$$\frac{dX_{28}}{dt} = v_{36} - v_{37} \tag{S.48}$$

$$\frac{dX_{29}}{dt} = v_{40} - v_{41} \tag{S.49}$$

Modeling of gene regulation module:

$$\frac{dX_{30}}{dt} = v_{42} - v_{43} \tag{S.50}$$

$$\frac{dX_{31}}{dt} = v_{44} + v_{45} - v_{46} + v_{47} \tag{S.51}$$

Supplemental Table S1. Each reaction process in the mathematical model.

No	Description	Equation
1	Activation of Dsh by Wnt	$v_1 = k_{a1w} X_1 [Wnt]$
2	Deactivation of Dsh	$v_2 = k_{d1w} X_2$
3	Dsh-mediated GSK3β release from the destruction complex (i.e., APC/Axin/GSK3β)	$v_3 = k_{c24} X_2 X_4$
4	Phosphorylation of the destruction complex	$v_4 = k_{c43} X_4$
5	Dephosphorylation of the destruction complex	$v_5 = k_{c34} X_3$
6	Association between GSK3β and the APC/Axin complex	$v_6 = k_{a57} X_5 X_7 - k_{d57} X_4$
7	Association between APC and Axin	$v_7 = k_{a813} X_8 X_{13} - k_{d813} X_7$
8	Association between β-catenin and the destruction complex	$v_8 = k_{a312} X_3 X_{12} - k_{d312} X_9$
9	Phosphroylation of β-catenin through the destruction complex	$v_9 = k_{c910} X_9$
10	Release of phosphorylated β-catenin from the destruction complex	$v_{10} = k_{c10} X_{10}$
11	Ubiquitination and degradation of phosphorylated β-catenin	$v_{11} = k_{u11} X_{11}$
12	Synthesis of β-catenin	v_{12} =constant
13	Basal degradation of β-catenin	$v_{13} = k_{u12} X_{12}$
14	Synthesis of Axin	v_{14} =constant
15	Basal degradation of Axin	$v_{15} = k_{u13} X_{13}$
16	Association between β-catenin and TCF	$v_{16} = k_{a1214} X_{12} X_{14} - k_{d1214} X_{15}$
17	Association between β-catenin and APC	$v_{17} = k_{a812} X_8 X_{12} - k_{d812} X_{16}$
18	Basal degradation of E-cadherin	$v_{18} = k_{u17} X_{17}$
19	Repression of the E-cadherin transcription by Sanil and inhibition of Snail by GSK3β	$v_{19} = \dfrac{V_{19}}{1 + \left(\dfrac{\dfrac{X_{30}}{1 + \left(\dfrac{X_5}{k_{i530}} \right)^2}}{k_{i3017}} \right)}$

20	Repression of the E-cadherin transcription by Slug	$v_{20} = \frac{V_{20}}{1 + \left(\frac{X_{31}}{k_{i3117}} \right)^{1.2}}$
21	Phosphorylation of GSK3β	$v_{21} = k_{c526} X_5 X_{26}$
22	Dephosphorylation of GSK3β	$v_{22} = k_{r65} X_6$
23	Transcription of Axin by the β-catenin/TCF complex	$v_{23} = \frac{k_{ct1513} X_{15}}{k_{mt1513} + X_{15}}$
24	Activation of the SOS/Grb2 complex and its inhibition by the active ERK	$v_{24} = \frac{\left(k_{c18e}[EGF] + EGF_0 \right) + k_{c1829} X_{29}}{1 + \left(\frac{X_{26}}{k_{i2618}} \right)}$
25	Deactivation of the SOS/Grb2 complex	$v_{25} = k_{r18} X_{18}$
26	Synthesis of Ras	v_{26} =constant
27	Degradation of Ras and inhibition by β-catenin through LPDM	$v_{27} = \frac{k_{u19} X_{t1}}{1 + \left(\frac{X_{15}}{k_{i1519}} \right)^2}$
28	Activation of Ras by the active SOS/Grb2 complex	$v_{28} = k_{c1819} X_{t1} X_{18}$
29	Deactivation of Ras	$v_{29} = v_{\max 20} X_{20}$
30	Activation of Raf-1 by the active Ras	$v_{30} = k_{c2021} X_{20} X_{t2}$
31	Deactivation of Raf-1	$v_{31} = v_{\max 22} X_{22}$
32	Activation of MEK by active Raf-1 and inhibition by the phoshorylated RKIP	$v_{32} = \frac{k_{c2223} X_{22} X_{t3}}{1 + \left(\frac{X_{t5} - X_{28}}{k_{i2327}} \right)^2}$
33	Deactivation of MEK	$v_{33} = v_{\max 24} X_{24}$
34	Activation of ERK	$v_{34} = k_{c2425} X_{t4} X_{25}$
35	Deactivation of ERK	$v_{35} = v_{\max 26} X_{26}$
36	Phosphorylation of RKIP	$v_{36} = k_{c2627} \left(X_{t5} - X_{28} \right) X_{26}$
37	Dephosphorylation of RKIP	$v_{37} = v_{\max 28} X_{28}$
38	Repression of RKIP transcription by Snail and inhibition of Snail by GSK3β	$v_{38} = \frac{V_{38}}{1 + \left(\frac{\frac{X_{30}}{1 + \left(\frac{X_5}{k_{i530}} \right)^2}}{k_{i3027}} \right)^{1.5}}$

39	Basal degradation of RKIP	$v_{39} = k_{u27} X_{t5}$
40	Inhibition of the PKCδ activation by GSK3β	$v_{40} = \dfrac{V_{40}}{1 + \left(\dfrac{X_5}{k_{i529}}\right)^{2.5}}$
41	Deactivation of PKCδ	$v_{41} = k_{r29} X_{29}$
42	Transcription of Snail by active ERK	$v_{42} = \dfrac{k_{ct2630}}{\left(\left(\dfrac{k_{mt2630}}{X_{26}}\right)^{2.5} + 1\right)\left(\left(\dfrac{X_{30}}{k_{i30}}\right)^{2} + 1\right)}$
43	Degradation of Snail by GSK3β phosphorylation	$v_{43} = \dfrac{k_{u530} X_{30}}{\left(\dfrac{k_{mu530}}{X_5}\right)^{2} + 1}$
44	Transcription of Slug by active ERK	$v_{44} = \dfrac{k_{ct2631}}{\left(\dfrac{k_{mt2631}}{X_{26}}\right)^{3.5} + 1}$
45	Transcription of Slug by the β-catenin/TCF complex	$v_{45} = \dfrac{k_{ct1531}}{\left(\dfrac{k_{mt1531}}{X_{15}}\right)^{7} + 1}$
46	Basal degradation of Slug	$v_{46} = k_{u31} X_{31}$
47	Auto-activation of Slug	$v_{47} = \dfrac{k_{c30}}{\left(\dfrac{k_{m30}}{X_{31}}\right)^{3} + 1}$

Supplementary Table S2. Model parameters. Most of the reaction parameters used in the mathematical model were obtained or modified from the previous models (11-12) and those not available from the literature were estimated through iterative simulations such that they are qualitatively well in accord with the experimental evidences. In particular, the parameter estimates were carefully chosen such that they produce robust output profiles and meet the physical constraints found in other similar molecular reactions.

Parameter	**Description**	**Value [unit]**	**Sources**
	Wnt pathway		
K_{812}	Binding affinity between β-catenin and APC	1200 [nM]	(11)
K_{813}	Binding affinity between Axin and APC	50 [nM]	(11)
K_{312}	Binding affinity between β-catenin and the	120 [nM]	(11)

	destruction complex		
K_{1214}	Binding affinity between β-catenin and TCF	50 [nM]	Modified from (11)
k_{a1w}	Rate constant for Dsh activation	0.0091 [min^{-1}]	Modified from (11)
k_{d1w}	Rate constant for Dsh deactivation	1.82e-2 [min^{-1}]	(11)
k_{c24}	Rate constant for Dsh-mediated GSK3β release from the destruction complex (disassembly of the destruction complex)	5e-2 [$nM^{-1}min^{-1}$]	(11)
k_{c43}	Rate constant for phosphorylation of the destruction complex	0.267 [min^{-1}]	(11)
k_{c34}	Rate constant for dephosphorylation of the destruction complex	0.133 [min^{-1}]	(11)
k_{a57}	Association rate constant between GSK3β and the APC/Axin complex	9.09e-2[$nM \cdot min^{-1}$]	(11)
k_{d57}	Dissociation rate constant between GSK3β and the APC/Axin complex	0.909 [min^{-1}]	(11)
k_{c910}	Rate constant for the β-catenin phosphorylation	206 [min^{-1}]	(11)
k_{c10}	Rate constant for release of the phosphorylated β-catenin release from the destruction complex	206 [min^{-1}]	(11)
k_{u11}	Degradation rate of the phosphorylated β-catenin	0.417 [min^{-1}]	(11)
v_{12}	Synthetic rate of β-catenin	0.423 [$nM \cdot min^{-1}$]	(11)
k_{u12}	Degradation rate of the non-phosphorylated β-catenin	2.57e-4 [min^{-1}]	(11)
v_{14}	Synthetic rate of Axin	8.22e-5 [$nM \cdot min^{-1}$]	(11)
k_{u13}	Degradation rate of Axin	0.167 [min^{-1}]	(11)
k_{u17}	Degradation rate of E-cadherin	0.4636[min^{-1}]	Estimated
V_{19}	Synthetic rate of Snail	4.457 [$nM \cdot min^{-1}$]	Estimated
k_{i3017}	Inhibitory concentration (IC50) of Snail to E-cadherin expression	25.605 [nM]	Estimated
k_{i530}	IC50 of GSK3β to the Snail activity	50 [nM]	Estimated
V_{20}	Synthetic rate of Slug	4.457 [$nM \cdot min^{-1}$]	Estimated
k_{i3117}	IC50 of Slug to E-cadherin expression	17.829[nM]	Estimated
k_{c526}	Rate constant for GSK3β phosphorylation by the active ERK	0.12 [$nM^{-1}min^{-1}$]	Estimated
k_{r65}	Rate constant for GSK3β dephosphorylation	0.98 [min^{-1}]	Estimated
Dsh^0	Total concentration of Dsh	100 [nM]	(11)

APC^0	Total concentration of APC	100 [nM]	(11)
TCF^0	Total concentration of TCF	15 [nM]	(11)
$GSK3\beta^0$	Total concentration of GSK3β	50 [nM]	(11)
	ERK pathway		
k_{c18e}	Rate constant for activation of the SOS/Grb2 complex by EGF	0.2079[min^{-1}]	Estimated
k_{c1829}	Rate constant for Ras activation by PKCδ	0.0173[min^{-1}]]	Estimated
k_{i2618}	IC50 of the active ERK to SOS/GRB2 activation	1.5[nM]	Estimated
k_{r18}	Rate constant for SOS/Grb2 deactivation	0.0231[min^{-1}]	Estimated
v_{26}	Synthetic rate constant of Ras	4.3 [nM·min^{-1}]	Estimated
k_{u19}	Basal degradation rate of Ras	0.0136[min^{-1}]	Estimated
k_{i1519}	IC50 of the β-catenin/TCF complex to inhibition of LPDM	8.5 [nM]	Estimated
k_{c1819}	Rate constant for Ras activation by the active SOS/Grb2 complex	9.8e-4[nM^{-1}min^{-1}]	Modified from (12)
$v_{\max 20}$	Rate constant for Ras deactivation	0.2822 [min^{-1}]	Modified from (12)
k_{c2021}	Rate constant for Raf-1 activation by the active Ras	6.7e-4[nM^{-1}min^{-1}]	Modified from (12)
$v_{\max 22}$	Rate constant for Raf-1 deactivation	0.143[min^{-1}]	Modified from (12)
k_{c2223}	Rate constant for MEK activation	6.7e-4[nM^{-1}min^{-1}]	Modified from (12)
k_{i2327}	IC of RKIP to MEK activation	120[nM]	Estimated
$v_{\max 24}$	Rate constant for MEK deactivation	0.2316[min^{-1}]	Modified from (12)
k_{c2425}	Rate constant for ERK activation	8.8e-4[nM^{-1}min^{-1}]	Modified from (12)
$v_{\max 26}$	Rate constant for ERK deactivation	0.3713[min^{-1}]	Modified from (12)
k_{c2627}	Rate constant for RKIP phosphorylation	78[nM^{-1}min^{-1}]	Modified from (12)
$v_{\max 28}$	Rate constant for RKIP dephosphorylation	240[min^{-1}]	Modified from (12)
V_{38}	Synthetic rate constant of RKIP	27.72[nM·min^{-1}]	Estimated
k_{i3027}	IC50 of Snail to RKIP expression	25[nM]	Estimated
k_{i530}	IC50 of GSK3β to the Snail activity	80[nM]	Estimated
k_{u27}	Degradation rate of RKIP	0.1155 [min^{-1}]	Estimated
V_{40}	Rate constant for PKCδ activation	0.0924[nM·min^{-1}]	Estimated
k_{i529}	IC50 of GSK3β to the PKCδ activity	20[nM]	Estimated

k_{r29}	Rate constant for PKCδ deactivation	0.0231 [min^{-1}]	Estimated
EGF^0	Basal activity of EGFR	0.00231[$nM\cdot min^{-1}$]	Estimated
Raf^0	Total concentration of Raf-1	120 [nM]	(12)
MEK^0	Total concentration of MEK	360 [nM]	(12)
ERK^0	Total concentration of ERK	700 [nM]	(12)
	Gene regulation		
k_{ct2630}	Transcription rate constant for Snail by the active ERK	2.0775[$nM^{-1}min^{-1}$]	Estimated
k_{mt2630}	Half maximal concentration of Snail expression	2.5[nM]	Estimated
k_{i30}	IC50 of GSK3β to Snail expression	80[nM]	Estimated
k_{u530}	Maximal degradation rate constant of Snail	0.043[min^{-1}]	Estimated
k_{mu530}	Half maximal concentration of the Snail degradation	20[nM]	Estimated
k_{ct2631}	Transcription rate constant for Slug by the active ERK	2.0775[$nM^{-1}min^{-1}$]	Estimated
k_{mt2631}	Half maximal concentration of Slug expression	2.5[nM]	Estimated
k_{ct1531}	Transcription rate constant for Slug through the β-catenin/TCF complex	2.0775[$nM^{-1}min^{-1}$]	Estimated
k_{mt1531}	Half-maximal concentration of Slug expression	7.2[nM]	Estimated
k_{u31}	Degradation rate constant of Slug	0.051[min^{-1}]	Estimated
k_{ct31}	Transcription rate constant for auto-activation	2.0775[$nM^{-1}min^{-1}$]	Estimated
k_{mt31}	Half-maximal concentration of Slug for auto-activation	80[nM]	Estimated
k_{ct1513}	Transcriptional rate constant for Axin by the β-catenin/TCF complex	1.0e-4[$nM^{-1}min^{-1}$]	Estimated
k_{mt1513}	Half-maximal concentration of the β-catenin/TCF complex	100[nM]	Estimated

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