A Hidden Oncogenic Positive Feedback Loop Caused by Crosstalk Between Wnt and ERK Pathways

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Supplementary Information

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Table S1. The summary of state variables and their steady states for a normal system (W=0).

State variables	Symbols	Concentrations (nM)
Dsh_i	X1	100
Dsh_a	X2	0
APC*/Axin*/GSK-3β	X3	0.0153
APC/Axin/GSK-3β	X4	0.0076
GSK3β	X5	49.1372
APC/Axin	X6	0.0015
APC	X7	96.6019
β-catenin/APC*/Axin*/GSK-3β	X8	0.002
β-catenin*/APC*/Axin*/GSK-3β	X9	0.002
β-catenin*	X10	0.9881
β-catenin	X11	42.7224
Axin	X12	0.0008
TCF	X13	6.1879
β-catenin/TCF	X14	8.8121
β-catenin/APC	X15	3.4392
Ras_i	X16	200.0000
Ras_a	X17	0
Raf-1	X18	112.5585
Raf-1*	X19	6.4860
MEK	X20	296.1137
MEK*	X21	3.8863
ERK	X22	297.8897
ERK*	X23	2.1103
Raf1/RKIP	X24	180.9595
RKIP	X25	418.1788
RKIP*	X26	0.8619
unknown molecule X	X27	10.2630
GSK-3β*	X28	0.85544

(Notations: i: inactivated state, a: activated state, /: complex, *: phosphorylated state)

The conserved molecular concentrations (nM) (X_T: The total molecular concentration of X):

$Dsh_T = 100$,

$APC_T = 100$,

$TCF_T = 15$,

$GSK\text{-}3\beta_T = 50$,

$Ras_T = 200$,

$Raf\text{-}1_T = 300$,

$MEK_T = 300$,

$ERK_T = 300$,

$RKIP_T = 600$.

Table S2. The mathematical model of the Wnt/ERK signaling pathways.

$V1 = k_1 * X1 * W$
$V2 = k_2 * X2$
$V3 = k_3 * X2 * X4$
$V4 = k_4 * X4$
$V5 = k_5 * X3$
$V6 = k_{+6} * X5 * X6 - k_{-6} * X4$
$V7 = k_{+7} * X7 * X12 - k_{-7} * X6$
$V8 = k_{+8} * X3 * X11 - k_{-8} * X8$
$V9 = k_9 * X8$
$V10 = k_{10} * X9$
$V11 = k_{11} * X10$
$V12 = V12$
$V13 = k_{13} * X11$
$V14 = k_{14} + k_{21} * (X11 + X14)$ %We assume that the availabile β-catenin (X11+X14) induces Axin.
$V15 = k_{15} * X12$
$V16 = k_{+16} * X11 * X13 - k_{-16} * X14$
$V17 = k_{+17} * X7 * X11 - k_{-17} * X15$
$V18 = (V_{max1} * X16 * W / (Km_1 + X16)) * (K_i / (K_i + X23))$
$V19 = V_{max2} * X17 / (Km_2 + X17)$
$V20 = kcat_1 * X17 * X18 / (Km_3 + X18)$
$V21 = V_{max3} * X19 / (Km_4 + X19)$

$V22 = kcat_2 * X19 * X20 / (Km_5 + X20)$

$V23 = V_{max4} * X21 / (Km_6 + X21)$

$V24 = kcat_3 * X21 * X22 / (Km_7 + X22)$

$V25 = V_{max5} * X23 / (Km_8 + X23)$

$V26 = kcat_4 * X23 * X24 / (Km_9 + X24)$

$V27 = k_{18} * X18 * X25 – k_{19} * X24$

$V28 = V_{max6} * X26 / (Km_{10} + X26)$

$V29 = kcat_5 * X14^n / (Km_{11}^n + X14^n)$

$V30 = k_{20} * X27$

$V31 = kcat_6 * X27 * X18 / (Km_{12} + X18)$

$V32 = kcat_7 * X23 * X5 / (Km_{13} + X5)$

$V33 = V_{max7} * X28 / (Km_{14} + X28)$

$dX1/dt = -V1 + V2$

$dX2/dt = V1 - V2$

$dX3/dt = V4 - V5 - V8 + V10$

$dX4/dt = -V3 - V4 + V5 + V6$

$dX5/dt = V3 - V6 - V32 + V33$

$dX6/dt = V3 - V6 + V7$

$dX7/dt = -V7 - V17$

$dX8/dt = V8 - V9$

$dX9/dt = V9 - V10$

$dX10/dt = V10 - V11$

$dX11/dt = -V8 + V12 - V13 - V16 - V17$

$dX12/dt = -V7 + V14 - V15$

$dX13/dt = -V16$

$dX14/dt = V16$

$dX15/dt = V17$

$dX16/dt = -V18 + V19$

$dX17/dt = V18 - V19$

$dX18/dt = -V20 + V21 + V26 -V27 - V31$

$dX19/dt = V20 - V21 + V31$

$dX20/dt = -V22 + V23$

$dX21/dt = V22 - V23$

$dX22/dt = -V24 + V25$

$dX23/dt = V24 - V25$

$dX24/dt = -V26 + V27$

$dX25/dt$ = -V27 + V28 $dX26/dt$ = -V28 + V26 $dX27/dt$ = V29 -V30 $dX28/dt$ = V32 - V33

Table S3. The summary of parameter values used for simulation of the Wnt/ERK signaling pathway model.

Reaction parameters	Values	Units
k_1	0.182	min^{-1}
k_2	0.0182	min^{-1}
k_3	0.05	$nM^{-1}\ min^{-1}$
k_4	0.267	min^{-1}
k_5	0.133	min^{-1}
k_{+6}/ k_{-6}	0.0909/0.909	$nM^{-1}\ min^{-1}$/ min^{-1}
k_{+7}/ k_{-7}	1/50	$nM^{-1}\ min^{-1}$/ min^{-1}
k_{+8}/ k_{-8}	1/120	$nM^{-1}\ min^{-1}$/ min^{-1}
k_9	206	min^{-1}
k_{10}	206	min^{-1}
k_{11}	0.417	min^{-1}
V12	0.423	$nM^{-1}\ min^{-1}$
K_{13}	0.000257	min^{-1}
k_{14}	0.0000822	$nM^{-1}\ min^{-1}$
k_{15}	0.167	min^{-1}
k_{+16}/ k_{-16}	1/30	$nM^{-1}\ min^{-1}$/ min^{-1}
k_{+17}/ k_{-17}	1/1200	$nM^{-1}\ min^{-1}$/ min^{-1}
V_{max1}	150	$nM\ min^{-1}$
Km_1	10	nM
k_i	9	nM
V_{max2}	15	$nM\ min^{-1}$
Km_2	8	nM
$kcat_1$	1.5	min^{-1}
Km_3	15	nM

V_{max3}	45	nM min^{-1}
Km_4	15	nM
$kcat_2$	1.5	min^{-1}
Km_5	15	nM
V_{max4}	45	nM min^{-1}
Km_6	15	nM
$kcat_3$	1.5	min^{-1}
Km_7	15	nM
V_{max5}	45	nM min^{-1}
Km_8	15	nM
$kcat_4$	1.5	min^{-1}
Km_9	9	nM
k_{18}	0.15	nM^{-1} min^{-1}
k_{19}	39	min^{-1}
V_{max6}	45	nM min^{-1}
Km_{10}	12	nM
$kcat_5$	0.6	min^{-1}
Km_{11}	15	nM
n	2	
k_{20}	0.015	min^{-1}
$kcat_6$	1.5	min^{-1}
Km_{12}	15	nM
$kcat_7$	1.5	min^{-1}
Km_{13}	15	nM
V_{max7}	45	nM min^{-1}
Km_{14}	15	nM
k_{21}	0.000001	min^{-1}