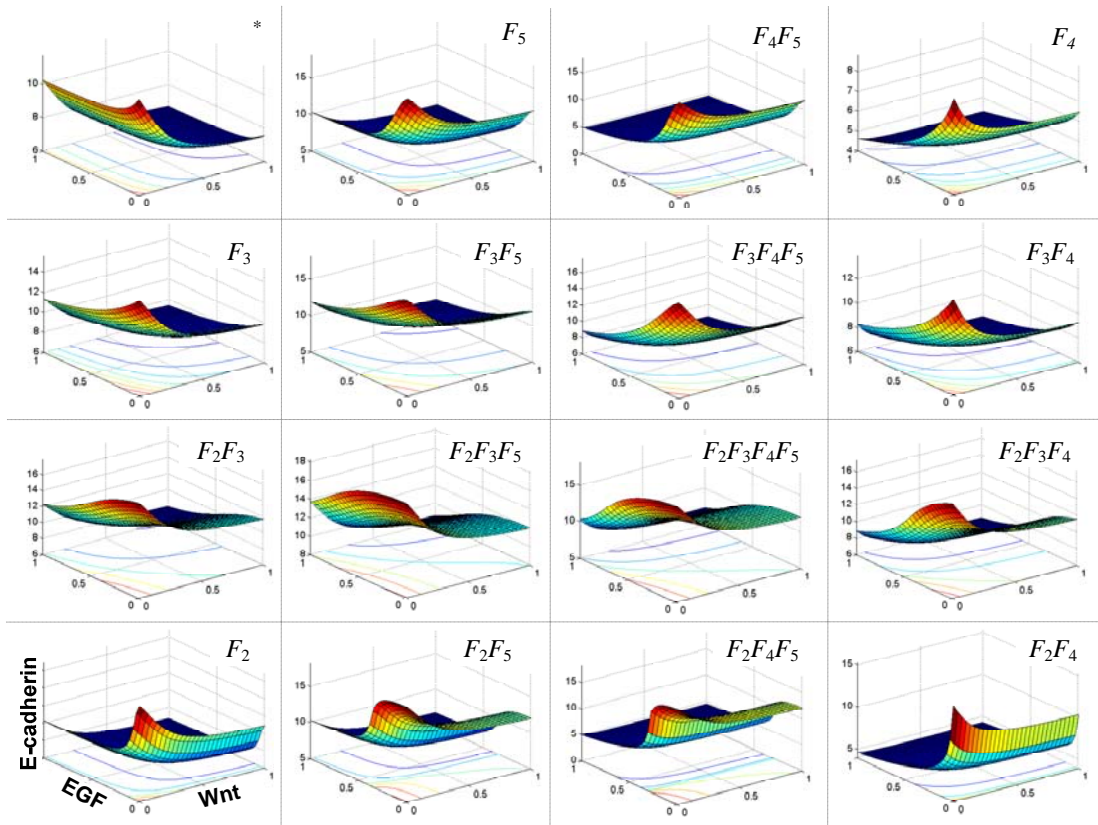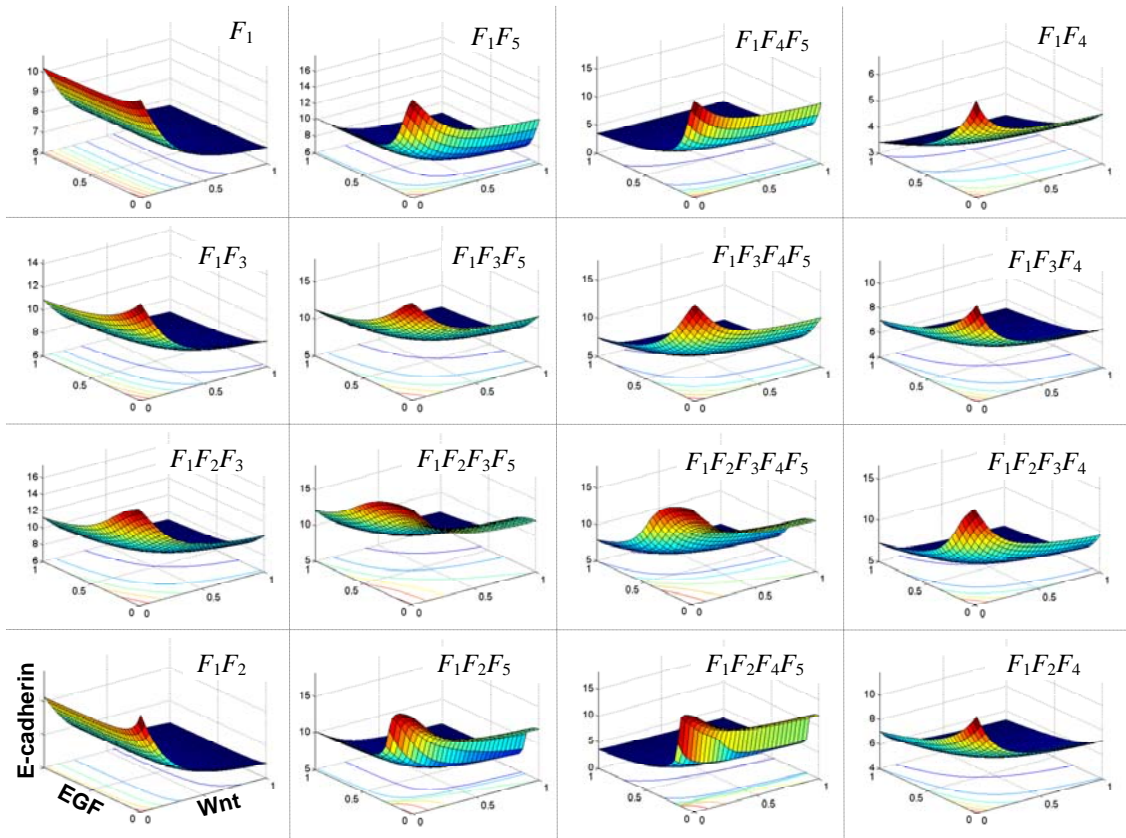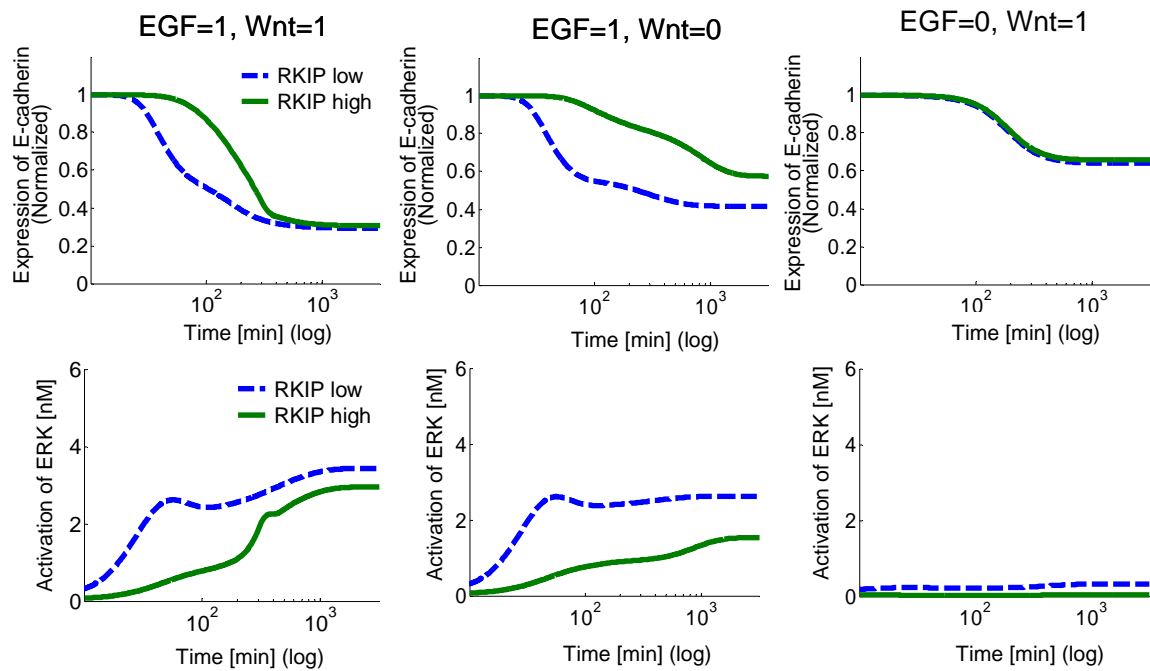# Supplementary Data C

Supplementary Figure S1A. Three-dimensional dose-response curves of E-cadherin expression for 16 network topologies obtained from different combinations of the feedback links $F_2 \sim F_5$ (only for a visualization purpose, we set the feedback link F1 disconnected in this figure) The mathematical model was stimulated by the gradual increase of EGF and Wnt up to their normalized maximum values. The symbol '*' denotes the case without any of the feedback links.

Supplementary Figure S1B. The three-dimensional dose-response curves of E-cadherin expression for 16 network topologies obtained from different combinations of the feedback links $F_2 \sim F_5$ (in the sequel of the previous figure, we set the feedback link F1 connected here).

Supplementary Figure S2. The initial level of RKIP and the different combination of constitutively activated mutations in either or both of ERK and Wnt signaling pathways play an important role in shaping the dynamics of ERK activity and determining the E-cadherin expression.
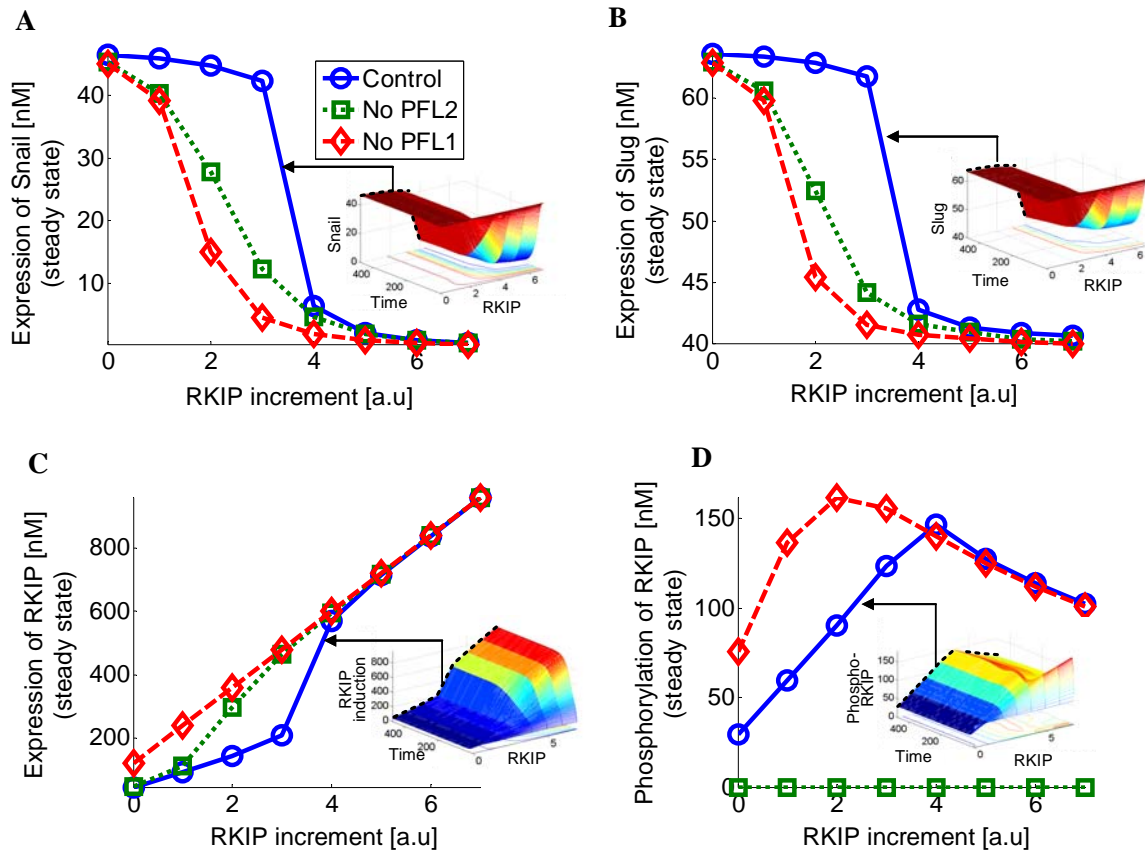
Supplementary Figure S3. RKIP determines the EMT progression by enhancing the expression of Snail and Slug and leading to the suppression of E-cadherin. RKIP causes switch-like behaviors in the suppression of Snail and Slug, which disappear when one of CPFLs mediated by RKIP is blocked. (A) Simulations for expression of Snail. (B) Expression of Slug. (C) Expression of RKIP. (D) Phosphorylation of RKIP. See Fig. 5D&E to compare with ERK activation and E-cadherin expression curves. Insets show that cellular responses exhibit quite different dynamics according to the increment of RKIP. There is no prominent change for the expression of Snail and Slug below a certain threshold of RKIP increment (3 in this case), but they become significantly decreased above this threshold.

Supplementary Table S1. The feedback combinations that have a significant influence on three output indexes and the most commonly involved feedback combinations among those. All these were investigated by gradually increasing EGF for five fixed levels of Wnt and vice versa. The results for simultaneous increase of both EGF and Wnt stimuli are also summarized.

Input		SD	STI	EC50
EGF	**Wnt**			
Gradual increase from 0 to 1	**0**	$\overline{F_3}F_4F_5$ $\overline{F_1F_2F_3}F_4$	$F_1F_2\overline{F_3}F_5$ $F_1\overline{F_3}F_4F_5$ $F_2\overline{F_3}F_4$	$\overline{F_1F_2F_3F_4}$ $\overline{F_1F_2F_3}F_5$ $F_2F_3\overline{F_4}F_5$
	0.25	$\overline{F_3}F_4F_5$ $\overline{F_1F_2F_3}F_4$	$F_2\overline{F_3}F_5$ $F_1\overline{F_3}F_4F_5$ $\overline{F_1F_2F_3}F_4$	$\overline{F_1F_2F_3}F_4$ $\overline{F_1F_2F_3}F_5$ $F_2F_3\overline{F_4}F_5$
	0.5	$\overline{F_3}F_4F_5$	$F_2\overline{F_3}F_5$ $F_1\overline{F_3}F_4F_5$ $F_1F_2\overline{F_3}F_4$	$\overline{F_1F_2F_3}F_4$ $\overline{F_1F_2F_3}F_5$
	0.75	$\overline{F_3}F_4F_5$	$F_2\overline{F_3}F_4F_5$ $F_1\overline{F_3}F_4F_5$ $\overline{F_1F_2F_3}F_4F_5$ $F_1F_2\overline{F_3}F_5$	$\overline{F_1F_2F_3}F_4$ $\overline{F_1F_2F_3}F_5$
	1	$\overline{F_3}F_4F_5$	$F_2\overline{F_3}F_4F_5$ $F_1\overline{F_3}F_4F_5$ $\overline{F_1F_2F_3}F_4F_5$ $F_1F_2\overline{F_3}F_5$	$\overline{F_1F_2F_3}F_4$ $\overline{F_1F_2F_3}F_5$
0	**Gradual increase from 0 to 1**	$F_1F_3\overline{F_5}$ $F_1F_2\overline{F_4F_5}$	$\overline{F_1F_2}F_4\overline{F_5}$ $\overline{F_1F_3}F_4\overline{F_5}$	$\varnothing$
0.25		$F_1F_2F_3\overline{F_5}$ $F_1F_2\overline{F_3F_4}F_5$	$\varnothing$	$\overline{F_1F_2F_3}F_4$ $\overline{F_1F_3}F_4\overline{F_5}$ $\overline{F_1F_2}F_4\overline{F_5}$ $F_2F_3\overline{F_4}F_5$
0.5		$F_1F_2F_3F_5$	$\overline{F_1F_2}F_4$ $\overline{F_1}F_4\overline{F_5}$ $\overline{F_1F_2F_3}F_4$ $F_1F_2F_3F_4F_5$	$\overline{F_1F_2F_3F_4}F_5$ $F_2F_3\overline{F_4}F_5$
0.75		$F_1F_2F_3\overline{F_4}F_5$	$\overline{F_1F_2}F_3F_4F_5$ $\overline{F_1}F_2F_3F_4\overline{F_5}$	$F_1\overline{F_2}F_3F_4$ $F_1\overline{F_3}F_4\overline{F_5}$ $\overline{F_2F_3F_4}F_5$ $F_2\overline{F_3F_4}F_5$ $\overline{F_1F_2}F_3\overline{F_4}F_5$
1		$\varnothing$	$\overline{F_1F_2}F_3F_4$ $\overline{F_1}F_3F_4\overline{F_5}$	$\overline{F_1F_2F_3}F_4$ $F_2\overline{F_3}F_4$
Most commonly	**Gradual increase of EGF**	$\overline{F_3}F_4F_5$	$F_2\overline{F_3}F_5$，$F_1\overline{F_3}F_4F_5$，$F_2\overline{F_3}F_4$	$\overline{F_1F_2F_3}F_4$，$\overline{F_1F_2F_3}F_5$

involved feedback combinations	with a fixed level of Wnt			
	Gradual increase of Wnt with a fixed level of EGF	None	None	None
	Gradual increase of both EGF and Wnt	$\overline{F_3}F_4F_5$	$F_1F_2\overline{F_3}F_5$ $\overline{F_1}F_2\overline{F_3}F_4\overline{F_5}$	$\overline{F_1}F_2F_5$, $F_2F_3F_5$