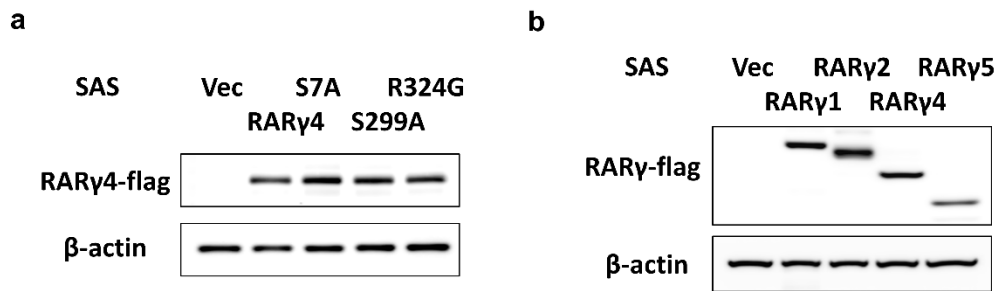
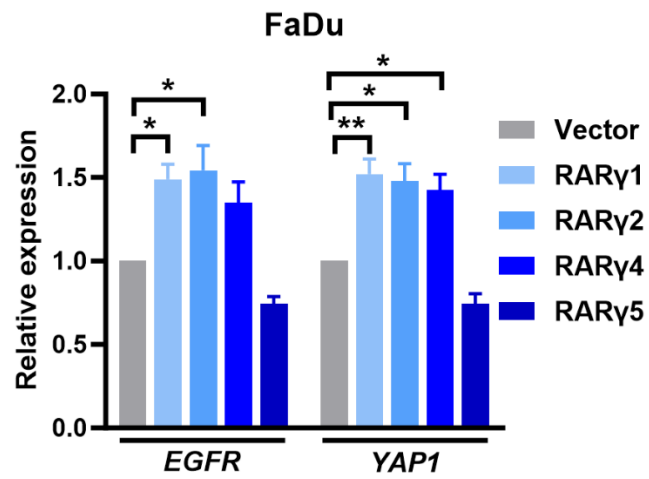


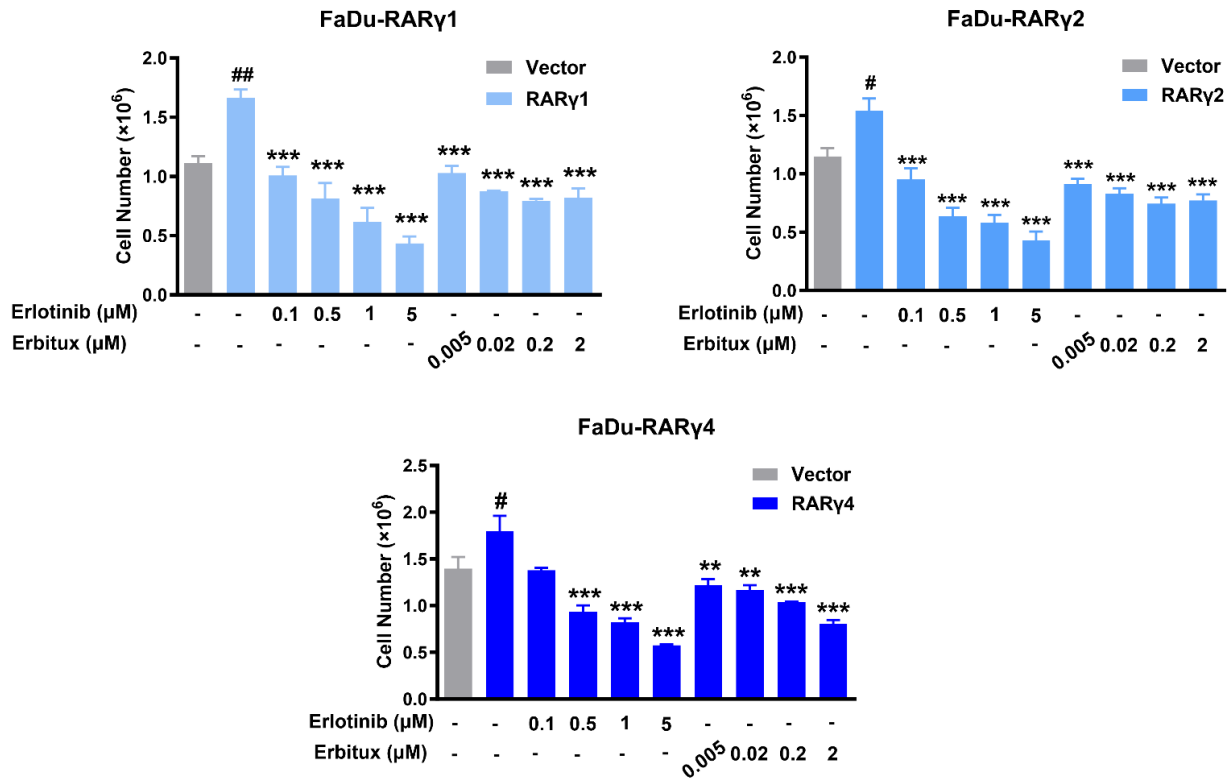
**Figure S1. Confirmation of RAR $\gamma$  isoforms expression in lentiviral transduced cells.** (a, b) Western blot results of exogenous RAR $\gamma$  were detected in FaDu and SAS cells expressing either (a) RAR $\gamma$ 4 and its mutants or (b) RAR $\gamma$ 1, 2, 4, 5 isoforms.



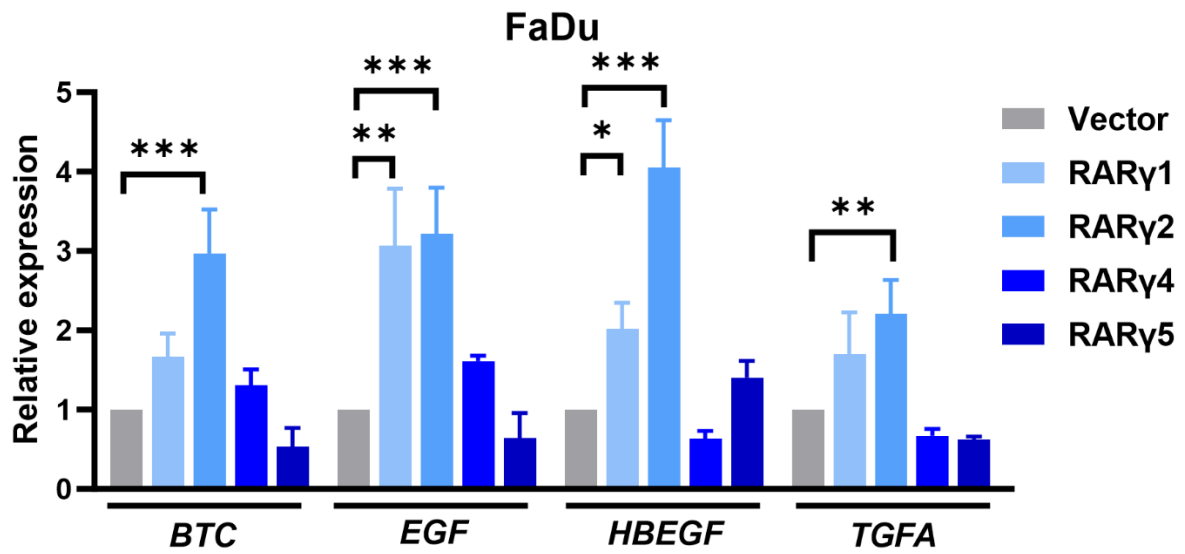
**Figure S2. Transcriptional levels of *EGFR* and *YAP1* were up-regulated by RAR $\gamma$ 1, 2, 4, but not RAR $\gamma$ 5 in FaDu cells. Expression of *EGFR* and *YAP1* were detected in FaDu cells expressing RAR $\gamma$ 1, 2, 4, 5 (\*,  $p < 0.05$ ; \*\*,  $p < 0.01$ ).**



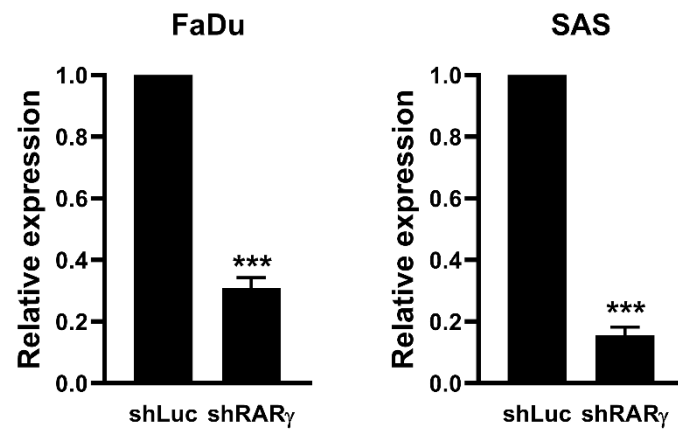
**Figure S3. Inhibition of EGFR signaling suppressed RAR $\gamma$ 1, 2, 4-mediated growth-promotion in FaDu cells.** FaDu cells expressing RAR $\gamma$ 1, 2, 4 were subjected to treatment with EGFR inhibitors (Erlotinib or Erbitux) at the specified concentrations. Cell numbers were determined for each group on day 7. (#, vector vs RAR $\gamma$ 1, 2. \*, RAR $\gamma$ 1, 2, 4 vs EGFR inhibitor treated group. #, p < 0.05; ## or \*\*, p < 0.01; \*\*\*, p < 0.001.)



**Figure S4. EGFR ligands BTC and EGF might contribute to RAR $\gamma$ -mediated EGFR activation.** Expression of EGFR ligands *BTC*, *EGF*, *HB-EGF*, and *TGFA* were detected in FaDu cells expressing RAR $\gamma$ 1, 2, 4, 5 (\*,  $p < 0.05$ ; \*\*,  $p < 0.01$ ; \*\*\*,  $p < 0.001$ ).



**Figure S5. Knockdown efficiency of shRAR $\gamma$  in FaDu and SAS cells.** Detection of RAR $\gamma$  expression in FaDu and SAS cells transduced with lentiviral vectors expressing shRNA specific to RAR $\gamma$ 1, 2, 4.



**Table S1. Changes of kinase phosphorylation levels in SAS cells expressing either RAR $\gamma$ 4 or RAR $\gamma$ 4-R324G (compared to vector control)**

<b>Target</b>	<b>RAR<math>\gamma</math>4 / Vector</b>	<b><i>p</i>-value</b>	<b>R324G / Vector</b>	<b><i>p</i>-value</b>
LCK <sup>Y394</sup>	1.4766	0.0269	1.0702	0.4483
HSP60	1.427	0.0014	1.2417	0.0036
CREB <sup>S133</sup>	1.4081	0.0264	1.0735	0.3916
HSP27 <sup>S78/S82</sup>	1.3158	0.0001	1.1046	0.0101
EGFR <sup>Y1086</sup>	1.2777	0.0088	0.8525	0.0547
GSK-3 $\beta$ <sup>S9</sup>	1.2294	0.0105	1.0337	0.0133
STAT3 <sup>S727</sup>	1.1979	0.0525	0.8835	0.1105
STAT5a/b <sup>Y694/Y699</sup>	1.1737	0.0119	1.0512	0.0581
Lyn <sup>Y397</sup>	1.1146	0.1659	1.0015	0.9940
GSK-3 $\alpha$ / $\beta$ <sup>S21/S9</sup>	1.1087	0.1603	0.9502	0.2555
Yes <sup>Y426</sup>	1.1292	0.0156	0.8203	0.0362
STAT1 <sup>Y701</sup>	1.0895	0.409	0.9639	0.0413
MSK1/2 <sup>S376/S360</sup>	1.0848	0.3568	0.8791	0.0481
WNK1 <sup>T60</sup>	1.0635	0.0191	0.9304	0.0184
PYK2 <sup>Y402</sup>	1.0556	0.0475	0.9671	0.0371
$\beta$ -catenin	1.053	0.1298	0.9838	0.6275
Akt1/2/3 <sup>S473</sup>	1.0398	0.4197	1.0043	0.9335
PRAS40 <sup>T246</sup>	1.0315	0.5524	0.9281	0.3391
eNOS <sup>S1177</sup>	1.0157	0.9042	0.6614	0.1427
STAT6 <sup>Y641</sup>	1.027	0.862	1.0129	0.8707
Src <sup>Y419</sup>	1.0169	0.4815	0.9474	0.0047
RSK1/2 <sup>S221/S227</sup>	0.9968	0.9633	0.9164	0.0552
JNK1/2/3 <sup>T183/Y185,T221/Y223</sup>	0.9744	0.6956	1.0669	0.2734
STAT2 <sup>Y689</sup>	0.9704	0.0949	0.9730	0.2242
PLC- $\gamma$ <sup>Y783</sup>	0.9613	0.4316	0.9039	0.0708
p53 <sup>S392</sup>	0.9527	0.0878	0.8955	0.1192
Akt1/2/3 <sup>T308</sup>	0.9501	0.3995	0.8014	0.0444
RSK1/2/3 <sup>S380/S386/S377</sup>	0.9373	0.1799	0.7954	0.0297
p70S6K <sup>T389</sup>	0.9282	0.3215	0.8783	0.1862
ERK1/2 <sup>T202/Y204, T185/Y187</sup>	0.9276	0.1606	0.7313	0.0133
P38 $\alpha$ <sup>T180/Y182</sup>	0.9273	0.0927	0.9536	0.1672
Fgr <sup>Y412</sup>	0.924	0.2048	0.9051	0.5508
PDGFR $\beta$ <sup>Y751</sup>	0.9098	0.2735	0.8915	0.1282
c-Jun <sup>S63</sup>	0.8952	0.1668	0.5616	0.0082

Chk-2 <sup>T68</sup>	0.8951	0.1556	0.7990	0.0618
STAT3 <sup>Y705</sup>	0.8779	0.3042	0.8922	0.3516
p53 <sup>S46</sup>	0.8675	0.0241	0.9445	0.2101
p53 <sup>S15</sup>	0.7349	0.0124	0.7067	0.0808
p70S6K <sup>T421/S424</sup>	0.6212	0.0127	0.6534	0.0859

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**Table S2. Primers used for RT-PCR and qRT-PCR**

Name	Forward primer (5' to 3')	Reverse primer (5' to 3')	T <sub>m</sub>
<b>For RT-PCR</b>			
RAR $\gamma$ 1,4,5	GCGGTTTGGGAGAAAATGTGTC	GTTCTTCTGGATGCTTCGGCG	59°C
RAR $\gamma$ 2,3	CGCCGGACTTGAATCTTTT	CTGGCAGAGCGAGGGGAAAGT	60°C
$\beta$ -actin	TCCACCTTCCAGCAGATGTG	CAACTAAGTCATAGTCCGCCTAGAA	60°C
<b>For qRT-PCR</b>			
EGFR	CAGCGCTACCTTGTCATTCA	TGCACTCAGAGAGCTCAGGA	60°C
YAP1	TCTTCAACGCCGTCATGAAC	GGTCAGTGTCCC AGGAGAAA	60°C
BTC	CCTCTTCGGAAACGTCGTAAAAG	CTTGCCACCAACCTGGAGGTAA	60°C
EGF	CCAGCTCTGCGTTCCTCTTA	GCAAACAGCAAAAATGGTTGTGG	60°C
HB-EGF	TGTATCCACGGACCAGCTGCTA	TGCTCCTCCTTGTTTGGTGTGG	60°C
TGFA	GGTCCGAAAACACTGTGAGTGG	CAAACCTCCTCTGGGCTCTT	60°C
$\beta$ -actin	TCCACCTTCCAGCAGATGTG	CAACTAAGTCATAGTCCGCCTAGAA	60°C

**T<sub>m</sub>:** annealing temperature



**Table S3. Linker primers for RAR $\gamma$ 4 and RAR $\gamma$ 5 with AsiAI and BstBI restriction enzyme sites**

<b>Name</b>	<b>Forward primer (5' to 3')</b>	<b>Reverse primer (5' to 3')</b>	<b>T<sub>m</sub></b>
RAR $\gamma$ 4	TTTTGCGATCGCCATGGTGCCAGCTCGCCCTC	CTTCACCTCTTTCTTCTTCTTGTCC	55°C
RAR $\gamma$ 5	TTTTGCGATCGCCATGGTGTACACGTGTCACCGC	CTTCACCTCTTTCTTCTTCTTGTCC	55°C

**T<sub>m</sub>**: annealing temperature

**Table S4. Primers used for site-directed mutagenesis of RAR $\gamma$ 4**

<b>Name</b>	<b>Forward primer (5' to 3')</b>	<b>Reverse primer (5' to 3')</b>	<b>T<sub>m</sub></b>
RAR $\gamma$ 4-S5A	TGCCCAGCGCGCCCTCGCCCCCT	AGGGGGCGAGGGCGCGCTGGGCA	55°C
RAR $\gamma$ 4-S7A	TGCCCAGCTCGCCCGCGCCCCCT	AGGGGGCGCGGGCGAGCTGGGCA	55°C
RAR $\gamma$ 4-S7E	TGCCCAGCTCGCCCGAGCCCCCT	AGGGGGCTCGGGCGAGCTGGGCA	55°C
RAR $\gamma$ 4-S299A	CCGGCGGCCCGCCCAGCCCTACA	TGTAGGGCTGGGCGGGCCGCCGG	55°C
RAR $\gamma$ 4-S299E	CCGGCGGCCGAGCAGCCCTACA	TGTAGGGCTGCTCGGGCCGCCGG	55°C
RAR $\gamma$ 4-R324G	GGGAGCTGAAGGGGCCATTACTC	GAGTAATGGCCCTTTCCTCCC	55°C

**T<sub>m</sub>**: annealing temperature

**Table S5. Primary antibodies used in this study**

<b>Antibodies</b>	<b>Manufacturers</b>	<b>Catalog</b>	<b>Applications</b>						
Akt	Cell Signaling Technology	2920	WB	1:2000					
pAkt <sup>S473</sup>	Cell Signaling Technology	9271	WB	1:1000					
All RAR $\gamma$ s	Santa Cruz Biotechnology	sc-398065			IF	1:100			
$\beta$ -actin	Abcam	ab6276	WB	1:10000					
EGFR	Santa Cruz Biotechnology	sc-03	WB	1:3000	IF	1:500			
pEGFR <sup>Y1068</sup>	Abcam	ab40815	WB	1:1000					
pEGFR <sup>Y1086</sup>	R&D	MAB8967	WB	1:1000					
ERK	Cell Signaling Technology	9102	WB	1:3000					
pERK <sup>T202/T204</sup>	Cell Signaling Technology	9101	WB	1:1000					
Flag	Sigma	F1804	WB	1:1000	IF	1:300	IP	1:100	
RAR $\gamma$ 1	Cell Signaling Technology	8965	WB	1:1000					
RAR $\gamma$ 1	Sigma	HPA053883			IF	1:100	IHC	1:50	
RAR $\gamma$ 2	Abcam	ab51368	WB	1:200	IF	1:100	IHC	1:50	
Rhotekin	Abnova	H00006242-M01	WB	1:2000					
pSrc <sup>Y416</sup>	Cell Signaling Technology	2101	WB	1:1000					
Vinexin	Abnova	H00010174-B01P	WB	1:1000			IP	1:100	
YAP1	Abnova	H00010413-M01	WB	1:2000	IF	1:100			