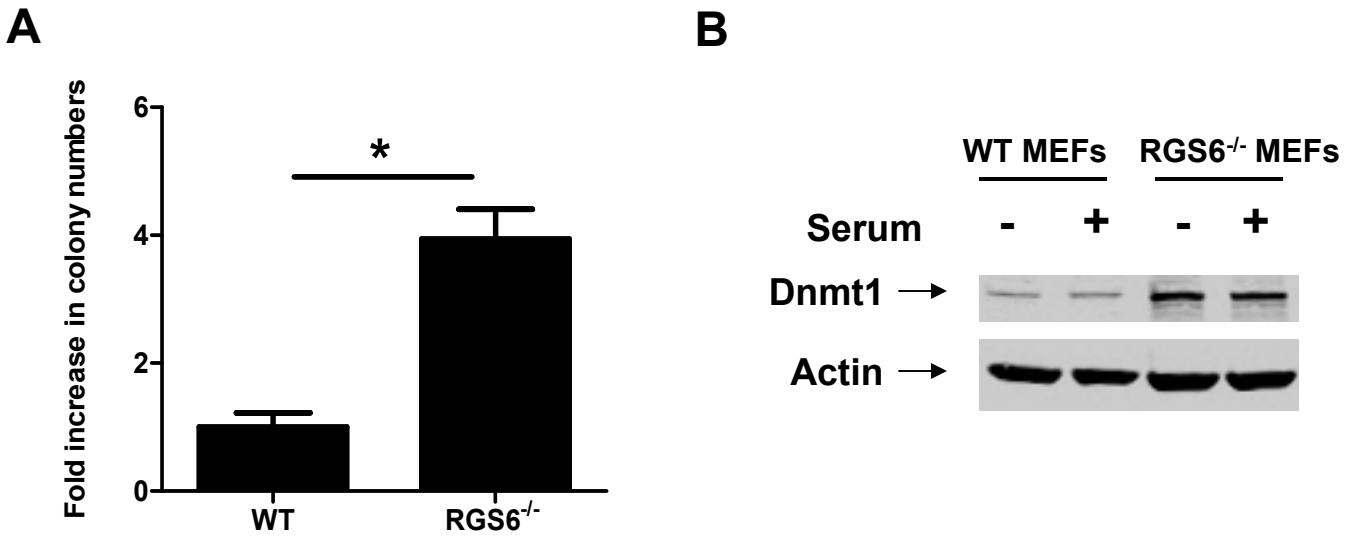
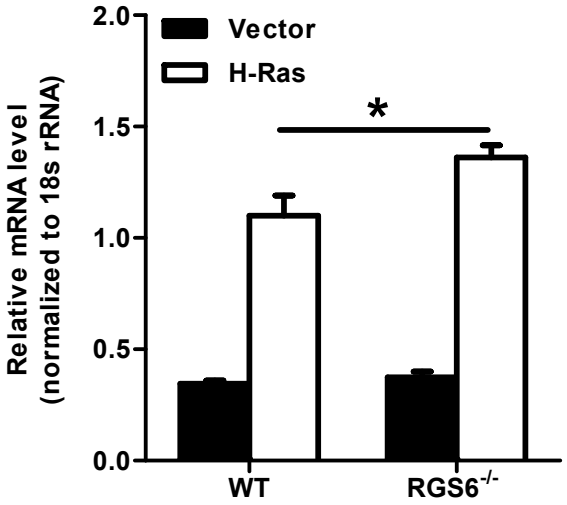
Supplementary Figure 1



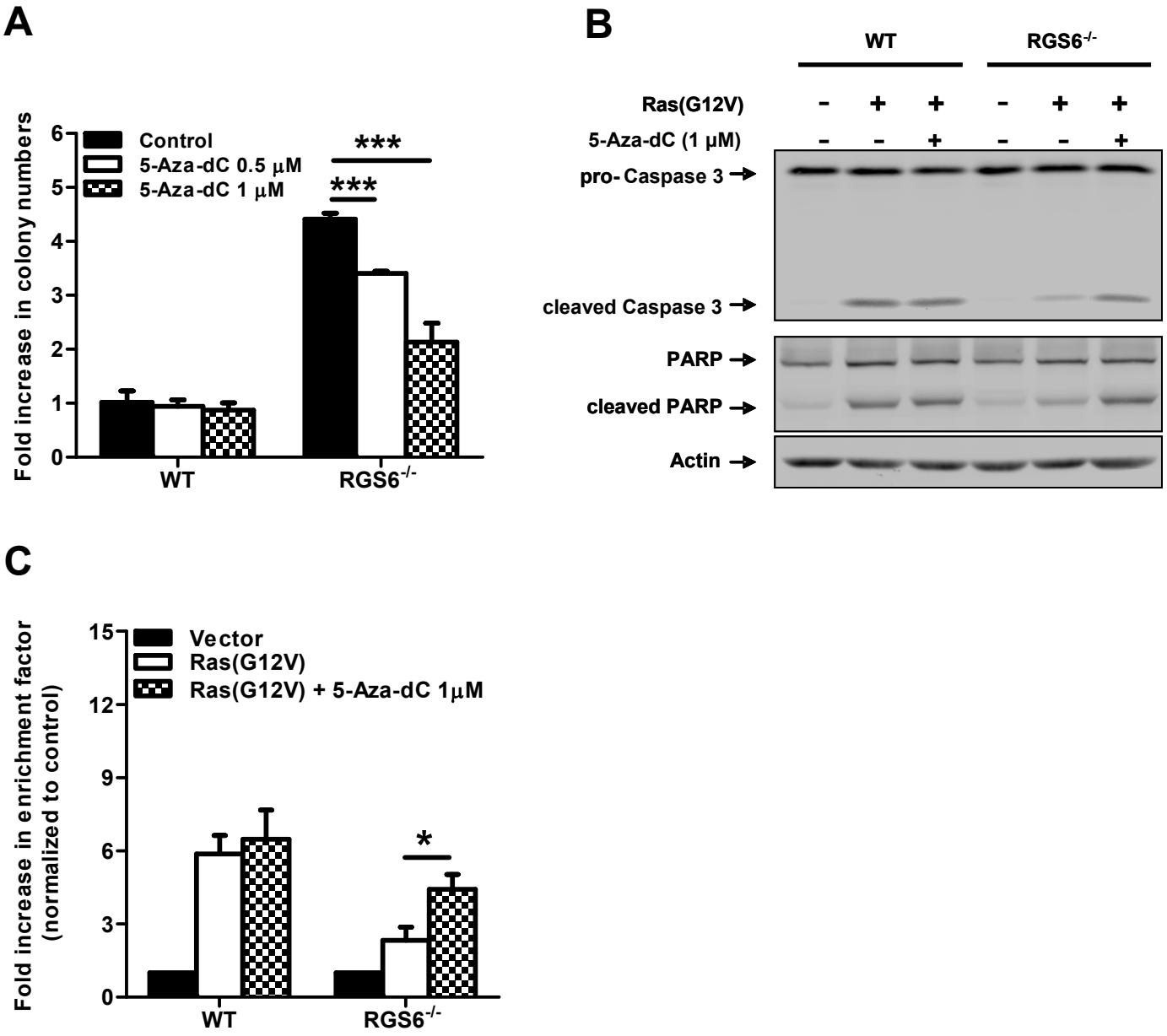
Supplementary Figure 1. RGS6 blocks Ras-induced oncogenic cellular transformation and suppresses DNMT1 expression in a second pair of MEF cell lines. MEFs expressing control vectors or H-Ras(G12V)/p53(R175H) were prepared as described in Fig.1. (**A**) H-Ras(G12V)-induced colonies formed in soft agar by WT or RGS6$^{-/-}$ MEFs from three independent experiments were quantified. Numbers of colonies formed by WT MEFs are set as 1. *, $p<0.001$ (student's t-test). Data are presented as mean ± S.E.M. (**B**) Dnmt1 expression levels are increased in RGS6$^{-/-}$ MEFs compared to control cells in the absence of Ras(G12V) infection. Serum starvation did not impact Dnmt1 expression in cells of either genotype. Immunoblotting was performed as described in Fig. 1.

Supplementary Figure 2



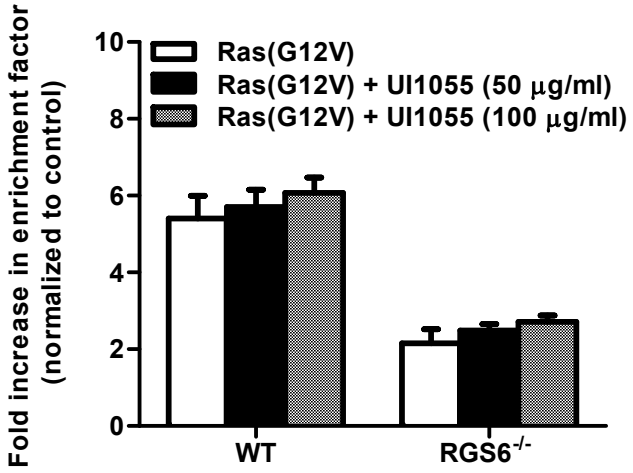
Supplementary Figure 2. RGS6$^{-/-}$ MEFs exhibit no difference in basal Dnmt1 mRNA levels (n = 3) and a small increase in Ras-induced Dnmt1 mRNA expression compared to WT MEFs. mRNA was isolated from MEFs expressing control vectors or H-Ras(G12V)/p53 (R175H) prepared as described in Fig.1. Two weeks after antibiotics selection, total mRNA, first strand cDNA synthesis and RT-PCR were performed as outlined in the legend of Fig. 2C. 18S rRNA level was used as internal control to normalize mRNA levels. Primers used for RT-PCR are depicted in Table S1. Two-way ANOVA revealed a significant effect of infection condition ($F_{1,8}$ = 7.07; p=0.0289) and genotype ($F_{1,8}$ = 254.44; p<0.0001). *, p<0.05 (bonferroni multiple comparisons). Data are presented as mean ± S.E.M.

Supplementary Figure 3



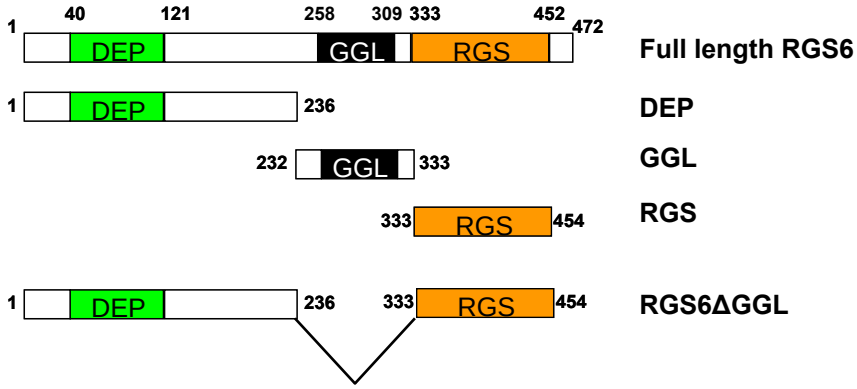
Supplementary Figure 3. (**A**) DNA methyltransferase inhibitor 5'-Aza-2'-dC (5-Aza-dC) blocked enhancement of oncogenic Ras-induced colony formation by RGS6$^{-/-}$ MEFs in a dose-dependent manner. Two-way ANOVA revealed a significant effect of genotype ($F_{1,12}$ = 706.25; p<0.0001) and drug treatment ($F_{2,12}$ = 61.79; p<0.0001). 5-Aza-dC (1μM) restored oncogenic Ras-induced apoptotic response in RGS6$^{-/-}$ MEFs including (**B**) caspase 3 and PARP cleavage and (**C**) formation of cytoplasmic histone-associated DNA fragments. For apoptosis assays, two-way ANOVA revealed a significant effect of genotype ($F_{1,12}$ = 35.40; p<0.0001) and drug treatment ($F_{2,12}$ = 70.74; p<0.0001). Methods for these figures are outlined in the legend of Figs. 2B, 2D, and 2E. *, p<0.05; ***, p<0.001 (bonferroni multiple comparisons). Unless otherwise indicated all experiments were performed in triplicate and representative results are shown. Data are presented as mean ± S.E.M.

Supplementary Figure 4



Supplementary Figure 4. UI1055, an inactive anthraquinone, did not restore Ras-induced apoptosis in RGS6$^{-/-}$ MEFs. Two-way ANOVA revealed a significant effect of genotype ($F_{1,12}$ = 323.92; p<0.0001), but no effect of drug treatment. Methods utilized in this panel are outlined in the legend of Fig. 2E. Data are presented as means ± S.E.M (n = 3).

Supplementary Figure 5



Supplementary Figure 5. Schematic outline of RGS6 truncation mutants used in Tip60 interactions studies depicted in Fig. 3F and Dnmt1 protein expression rescue experiments in RGS6$^{-/-}$ MEFs shown in Fig. 3C.

Supplementary Table 1

Target	Forward Primer	Reverse Primer
Dnmt1	5’-TGCAAGGCGTGCAAAGATATGGTG-3’	5’-TGGGTGATGGCATCTCTGACACAT-3’
Fas	5’-GAACACTGTGACCCTTGCACCAAA-3’	5’-CTCTTTGCACTTGGTGTTGCTGGT-3’
Nore1a	5’-TGTCCTCTCAGTGCCCTCCAATTT-3’	5’-TGTGGTGGGTTAGCAGGAATCGAA-3’
Rassf1a	5’-GCAAGTTCACCTGCCATTACCGTT-3’	5’-AGGTTGCTGTTGATCTGGCCATTG-3’
18s rRNA	5’-CAAAGATTAAGCCATGCATGTCTAAGTACGC-3’	5’-GGCATGTATTAGCTCTAGAATTACCACAGTTATCC-3’

Supplementary Table 1. PCR primer sequences for RT-PCR experiments depicted in Fig. 2C and Supplementary Fig. 2.