

1 **Supplemental Experimental Procedures**

2 **Table S1. Genotyping primers used in this study**

| Genotype                                    | Strand | Sequence (5'→3')               |
|---|--------|--------------------------------|
| Mouse $\beta$ - <i>TrCP2</i> <sup>F/Δ</sup> | F      | GCGCGTTGCTTTTGAGGGTTCTTGCCC    |
| Mouse $\beta$ - <i>TrCP2</i> <sup>F/Δ</sup> | R1     | GCCGGCAGCAGCTGTTCTTGCCATGAG    |
| Mouse $\beta$ - <i>TrCP2</i> <sup>F/Δ</sup> | R2     | TGGGA ACTGAACCGAGATCC          |
| Mouse $\beta$ - <i>TrCP2</i> <sup>+/-</sup> | F      | CCTTCTATCGCCTTCTTGACGAG        |
| Mouse $\beta$ - <i>TrCP2</i> <sup>+/-</sup> | R      | GCAGCCTCTTCCCTTCTGAAATG        |
| Mouse <i>Cdkn2a</i> <sup>+/-</sup>          | F1     | TCAACTACGGTGCAGATTTCG          |
| Mouse <i>Cdkn2a</i> <sup>+/-</sup>          | F2     | AGGATCTCCTGTCATCTCACCTTGCTCCTG |
| Mouse <i>Cdkn2a</i> <sup>+/-</sup>          | R1     | TCGCACGATGTCTTGATGTC           |
| Mouse <i>Cdkn2a</i> <sup>+/-</sup>          | R2     | AAGAACTCGTCAAGAAGGCGATAGAAGGCG |

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4 **Table S2. RT-qPCR primers used in this study**

| Gene                          | Strand | Sequence (5'→3')         |
|-------------------------------|--------|--------------------------|
| Mouse $\beta$ -TrCP2 (ORF)    | F      | CAGCGGGACTTTATCACTGC     |
| Mouse $\beta$ -TrCP2 (ORF)    | R      | GCACCATCCTCTCAATCAGC     |
| Mouse $\beta$ -TrCP2 (3' UTR) | F      | GAGTTCTGCACAGTCGGACA     |
| Mouse $\beta$ -TrCP2 (3' UTR) | R      | GGTACCCAAGTCCCCTGCTA     |
| Mouse $\beta$ -TrCP1          | F      | ACCACGGTGACACTCCGGCT     |
| Mouse $\beta$ -TrCP1          | R      | ACTCCCACGGGTCACTGCGT     |
| Mouse p19 <sup>Arf</sup>      | F      | CATGTTGTTGAGGCTAGAGAGG   |
| Mouse p19 <sup>Arf</sup>      | R      | TGAGCAGAAGAGCTGCTACG     |
| Mouse Arbp                    | F      | GGACCCGAGAAGACCTCCTT     |
| Mouse Arbp                    | R      | GCACATCACTCAGAATTTCAATGG |

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6 **Table S3. RT-PCR primers used in this study**

| Gene                           | Strand | Sequence (5'→3')         |
|--------------------------------|--------|--------------------------|
| Mouse $\beta$ -TrCP1 (Isoform) | F      | GATTATGGACCCGGCAGAGG     |
| Mouse $\beta$ -TrCP1 (Isoform) | R      | GGGCACAATCATGCTGGAAG     |
| Mouse $\beta$ -TrCP2 (Isoform) | F      | ATGGAGCCCGACTCGGTGATTG   |
| Mouse $\beta$ -TrCP2 (Isoform) | R      | GCCCGTTAGCACTTTCAAACAT   |
| Mouse $\beta$ -TrCP1 (Total)   | F      | CAGCGGGACTTTATCACTGC     |
| Mouse $\beta$ -TrCP1 (Total)   | R      | GCACCATCCTCTCAATCAGC     |
| Mouse $\beta$ -TrCP2 (Total)   | F      | ACCACGGTGACACTCCGGCT     |
| Mouse $\beta$ -TrCP2 (Total)   | R      | ACTCCCACGGGTCACTGCGT     |
| Mouse p16 <sup>Ink4a</sup>     | F      | CCGAACTCTTTCGGTCGTAC     |
| Mouse p16 <sup>Ink4a</sup>     | R      | GAGAAGGTAGTGGGGTCCTC     |
| Mouse p19 <sup>Arf</sup>       | F      | CATGTTGTTGAGGCTAGAGAGG   |
| Mouse p19 <sup>Arf</sup>       | R      | TGAGCAGAAGAGCTGCTACG     |
| Mouse Arbp                     | F      | GGACCCGAGAAGACCTCCTT     |
| Mouse Arbp                     | R      | GCACATCACTCAGAATTTCAATGG |
| Mouse Tbp                      | F      | CGGTAGCGGTGGCGGGTATC     |
| Mouse Tbp                      | R      | TTCCAGGAGTCATGGCGCCCT    |

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8 **Table S4. Antibodies used in this study**

| Antigen               | Provider       | Catalog number |
|-----------------------|----------------|----------------|
| $\beta$ -Catenin      | BD             | 610153         |
| CDC25A                | Santa Cruz     | sc-7157        |
| CDC25B                | Santa Cruz     | sc-326         |
| c-Jun                 | Santa Cruz     | sc-1694        |
| c-Myc                 | Santa Cruz     | sc-764         |
| Cyclin D1             | Santa Cruz     | sc-753         |
| Dnmt1                 | Imgenex        | IMG-261A       |
| Emi1                  | Santa Cruz     | sc-50928       |
| I $\kappa$ B $\alpha$ | Santa Cruz     | sc-371         |
| I $\kappa$ B $\beta$  | Santa Cruz     | sc-946         |
| Mcl-1                 | Rockland       | 600-401-394S   |
| Mdm2                  | Santa Cruz     | sc-965         |
| PLK4                  | Proteintech    | 12952-1-AP     |
| p63                   | Neomarker      | MS-1081-P0     |
| Snail                 | Cell Signaling | 3895           |
| Smad3                 | Cell Signaling | 9523           |
| Smad4                 | Cell Signaling | 9515           |

|                                    |                |             |
|------------------------------------|----------------|-------------|
| Uhrf1                              | Santa Cruz     | sc-98817    |
| Wee1                               | Santa Cruz     | sc-9037     |
| Hsp90                              | BD             | 610418      |
| p19 <sup>Arf</sup> (for IB)        | Abcam          | Ab80        |
| p19 <sup>Arf</sup> (for IB and IP) | Santa Cruz     | sc-32748    |
| p53                                | Santa Cruz     | sc-126      |
| p21 <sup>Cip1</sup>                | BD             | 556430      |
| p15 <sup>Ink4b</sup>               | Cell Signaling | 4822        |
| p16 <sup>Ink4a</sup>               | Santa Cruz     | sc-1207     |
| p27 <sup>Kip1</sup>                | BD             | 610241      |
| $\alpha$ -Tubulin                  | Sigma          | T-5168      |
| HA (3F10)–HRP (for IB)             | Roche          | 11667475001 |
| FLAG (M2)–HRP (for IB)             | Abcam          | ab49763     |
| FLAG (M2)                          | SIGMA          | F1804       |
| pS6K1                              | Cell Signaling | 9234        |
| S6K1                               | Cell Signaling | 9202        |
| pAKT                               | Cell Signaling | 9271        |
| AKT                                | Cell Signaling | 9272        |
| 4E-BP1                             | Cell Signaling | 9644        |

|           |                   |         |
|-----------|-------------------|---------|
| pERK1/2   | Cell Signaling    | 9101    |
| ERK1/2    | Cell Signaling    | 9102    |
| pp38      | Cell Signaling    | 9211    |
| p38       | Cell Signaling    | 9212    |
| CUL1      | Life Technologies | 32-2400 |
| RXRXXpS/T | Cell Signaling    | 10001   |
| Ubiquitin | DAKO              | Z0458   |

9 IB, immunoblot analysis; IP, immunoprecipitation; HRP, horseradish peroxidase.

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