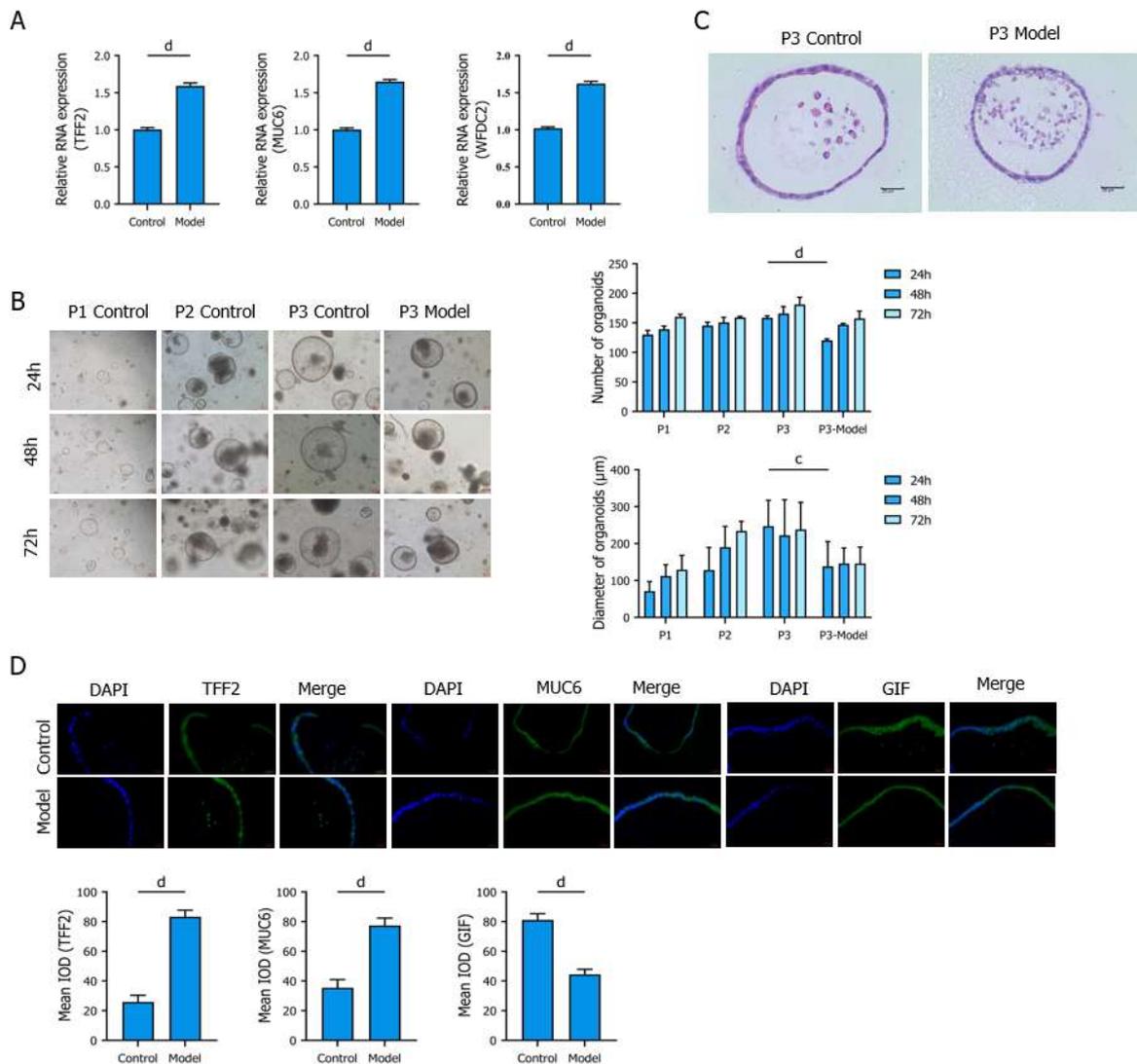
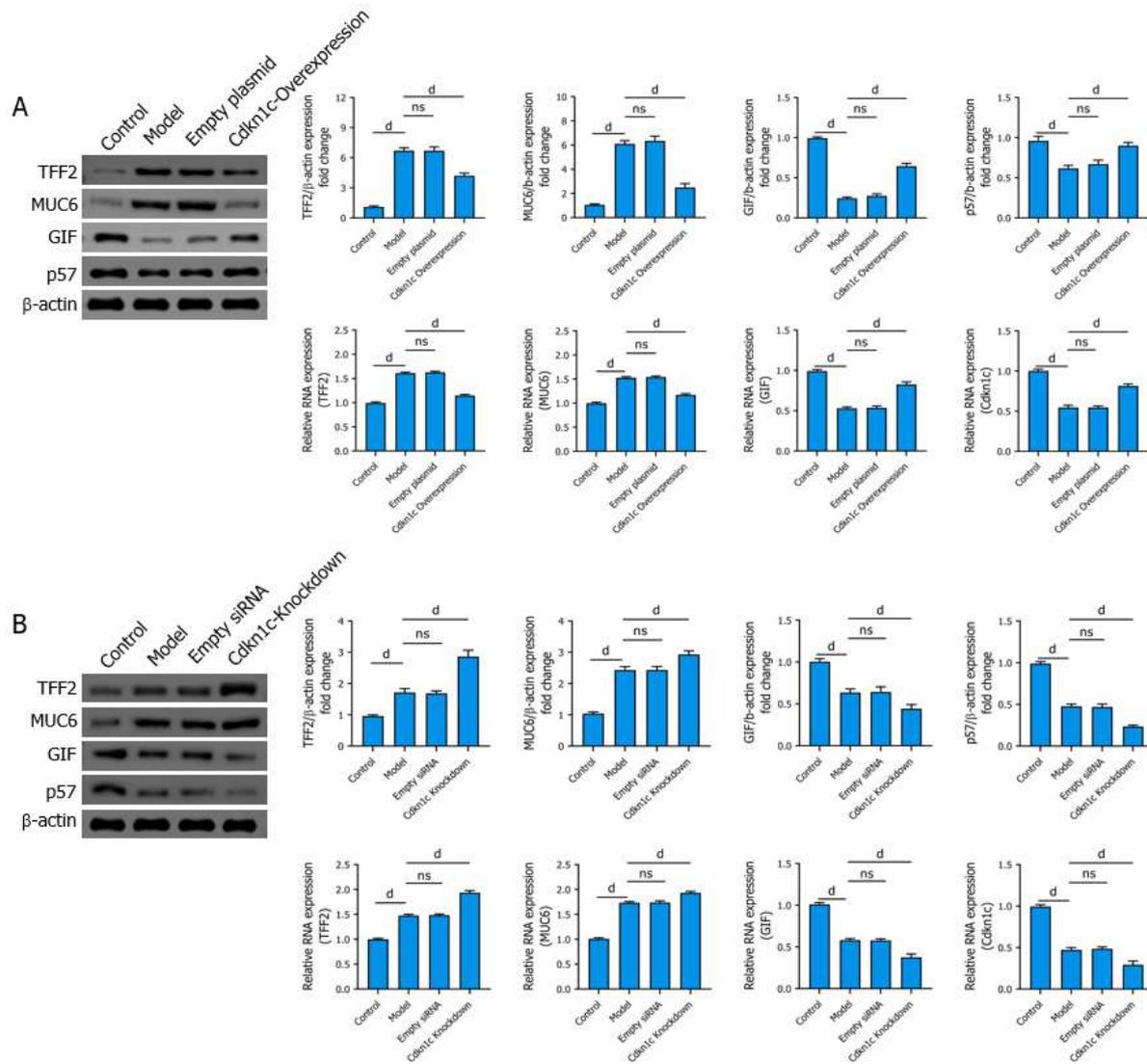


Supplementary Figure 1 Chemical structure of pristimerin.

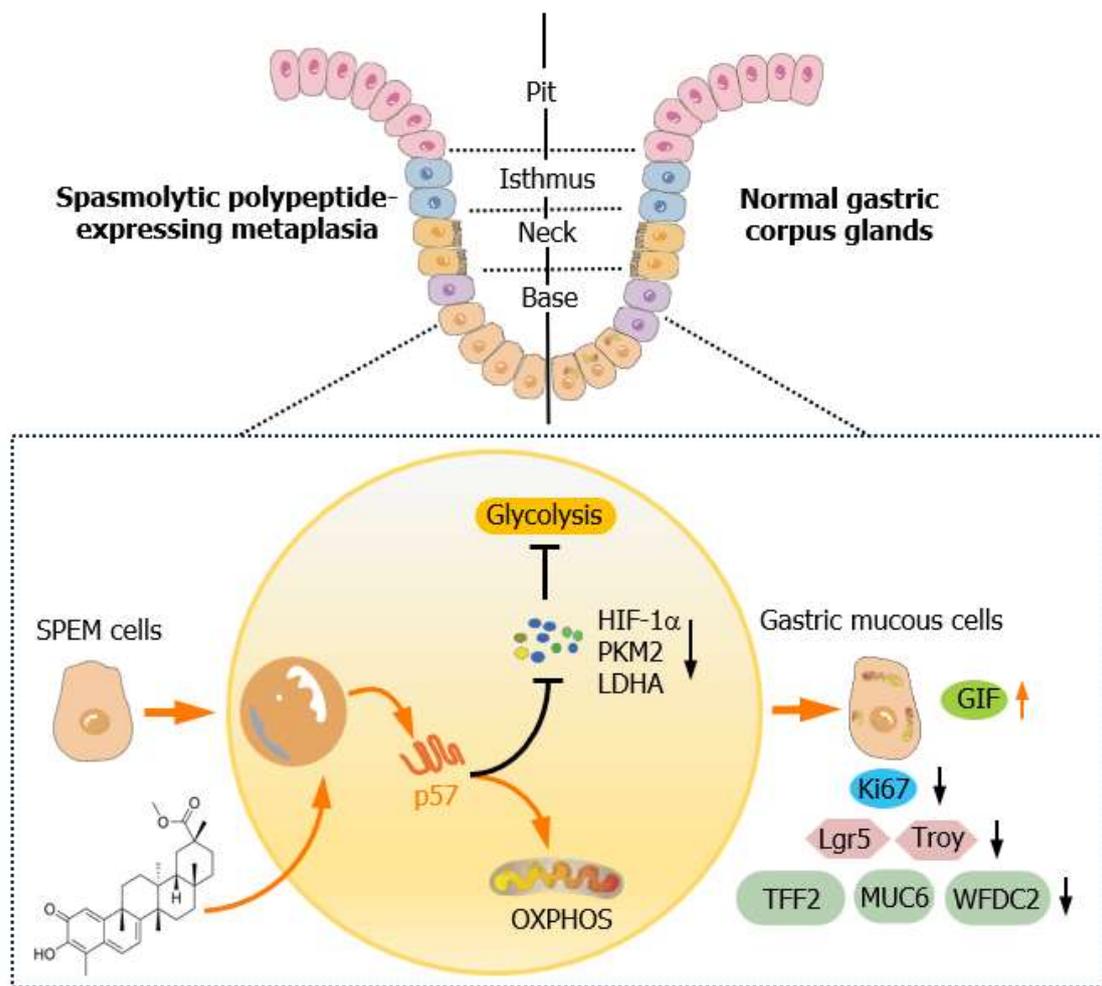


Supplementary Figure 2 Establishment and characterization of SPEM cell and gastric organoid models. A: TAM induction upregulates the expression of SPEM-specific marker genes (TFF2, MUC6, and WFDC2) in GES-1 cells. B: Comparative analysis of growth status in normal gastric organoids (P1-P3) *vs* SPEM gastric organoids (at P3), and quantitative assessments of organoid number and diameter. Scale bar, 100 µm. C: H&E staining of gastric organoids. Scale bar, 25 µm. D Immunofluorescence analysis of TFF2, MUC6, and GIF expression in gastric organoids. Scale bar, 20 µm. ^c*P* < 0.001, ^d*P* < 0.0001. Values represent the mean ± SD (*n* = 5). GIF: Gastric intrinsic factor; MUC6: Mucin 6; TFF2 Trefoil factor 2; WFDC2: Whey-acidic-protein (WAP) four-disulfide core domain protein 2.



Supplementary Figure 3 Establishment and characterization of SPEM gastric organoids with *Cdkn1c* overexpression (*Cdkn1c*-OE) and knockdown (*Cdkn1c*-KD).

A-B: Western blot analysis of TFF2, MUC6, GIF and p57 protein expression normalized to β-actin (fold change relative to control) with corresponding RT-qPCR results. ^c*P* < 0.001, ^d*P* < 0.0001, *ns*, not significant. Values represent the mean ± SD (*n* = 5). *Cdkn1c*-KD: *Cdkn1c*-knockdown SPEM organoids; *Cdkn1c*-OE: *Cdkn1c*-overexpressing SPEM gastric organoids; GIF: Gastric intrinsic factor; MUC6: Mucin 6; SPEM: Spasmolytic polypeptide-expressing metaplasia; TFF2 Trefoil factor 2



Supplementary Figure 4 Schematic diagram of the mechanism. Pristimerin ameliorates SPEM by upregulating p57 to modulate glycolytic reprogramming. GIF: Gastric intrinsic factor; HIF-1a: hypoxia-inducible factor 1a; Ki67 Marker of proliferation Kiel 67; LDHA: Lactate dehydrogenase A; Lgr5 Leucine-rich repeat-containing G-protein coupled receptor 5; MUC6: Mucin 6; OXPHOS: Oxidative Phosphorylation; PKM2: Pyruvate kinase M2; SPEM: Spasmolytic polypeptide-expressing metaplasia; TFF2 Trefoil factor 2; Troy: Tumor necrosis factor receptor superfamily member 19; WFDC2: Whey-acidic-protein (WAP) four-disulfide core domain protein 2

Supplementary Table 1 Small interfering RNA sequences targeting mouse *Cdkn1c* mRNA

Gene name	Forward 5'-3'	Reverse 5'-3'
<i>Cdkn1c</i>	5'- GCCUUCAGCUUCAGAACAA -3'	5'- UUGUUCUGAAGCUGAAGGC -3'

Supplementary Table 2 Primer sequences for reverse transcription polymerase chain reaction analysis

Gene name	Primer (5'-3')
H ⁺ /K ⁺ (mouse)	ATPase F: CCTTCCAGACAGCCTACCTCA R: GGATACAAGTCCCGCAAAGCA
GIF (mouse)	F: GAAAAGTGGATCTGTGCTACTT R: AGACAATAAGGCCCCAGGATG
Mist (mouse)	F: GCAGGACCTACATGTCCCTT R: TCCTGCTATCCCAGACTCCT
TFF2 (mouse)	F: TCCAAACCAAGAATCGGAGCAG R: ACCCACAATTCTTGCGAGCTGA
MUC6 (mouse)	F: GACGCCCATCTTACGGTCCA R: CTTCCAAAAGTTTGCCGTCCT
Ki67 (mouse)	F: GGAGAAACGCCAACCAAGAG R: GGGCCGTTTCCTTGATGATTG
<i>Cdkn1c</i> (mouse)	F: GGACGAGAATCAAGAGCAG R: GAAGAAGTCGTTCCGCATTG
HIF-1 α (mouse)	F: ACATCAAGTCAGCAACGTGGAAGG R: GCAAGCATCCTGTACTGTCTGTG
LDHA (mouse)	F: TGTCTCCAGCAAAGACTACTGT R: GACTGTACTTGACAATGTTGGGA
PKM2 (mouse)	F: TCAGAGCTCCAACGCTTGTAGAACTCACTC R: CCGCTCGAGAAATGGAAGGTGGAGGG F: TGTACCCAGGCATTGCTGAC

β -actin (mouse)	R: AACGCAGCTCAGTAACAGTCC
HIF-1 α (human)	F: GAGCCTTGGAGGGTTTCA R: GAGGAGGCAGTTGTTGGT
LDHA (human)	F: GGTGGTTGAGAGTGCTTATGA R: GCAAGGAACACTAAGGAAGAC
PKM2 (human)	F: ACTGGCATCATCTGTACCATTG R: AGCCACATTCATTCCAGACTTA
<i>Cdkn1c</i> (human)	F: ATTTAGAGCCCAAAGAGCCCC R: TGCTACATGAACGGTCCCAG
β -actin (human)	F: CTGGGACGACATGGAGAAAA R: AAGGAAGGCTGGAAGAGTGC
