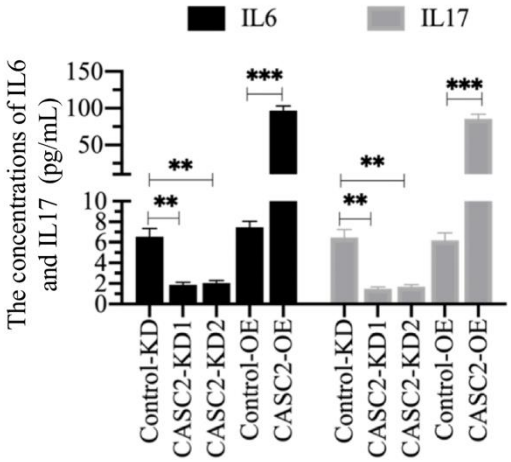
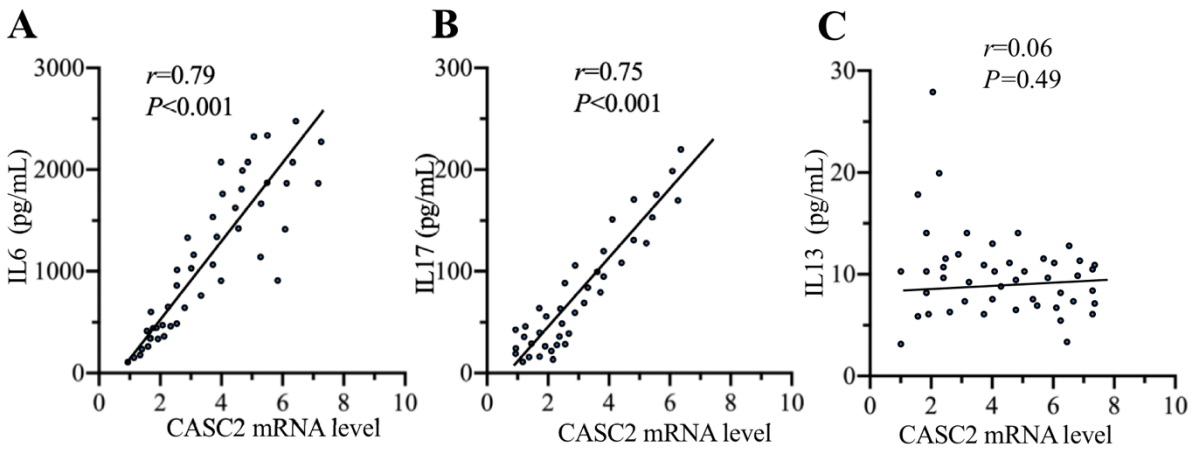


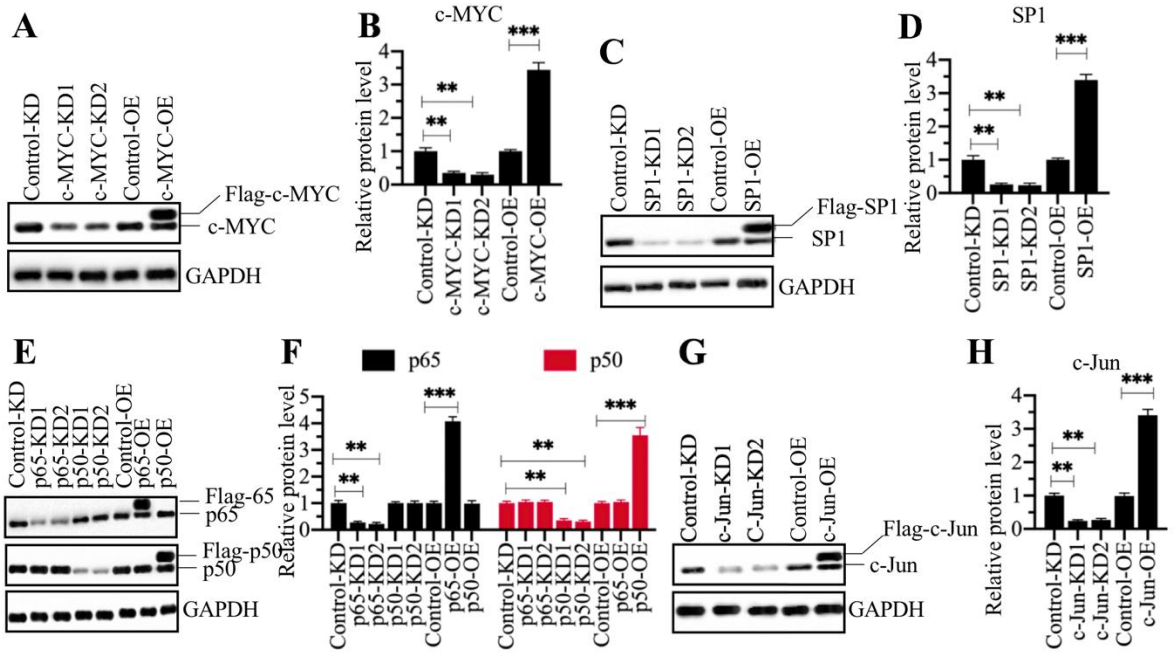

**Supplementary Figure 1. The concentrations of IL6 and IL17 in the supernatant of cell culture of CASC2-KD and CASC2-OE cells**

The Control-KD, CASC2-KD1, CASC2-KD2, Control-OE and CASC2-OE cells were cultured in DMEM medium for 24 h. Cell cultures were collected and centrifuged, and the supernatant was used to measure the concentrations of IL6 and IL17. $^{**}P < 0.001$ and $^{***}P < 0.001$.




**Supplementary Figure 2. IL6 and IL17 were positively correlated with *CASC2* expression**

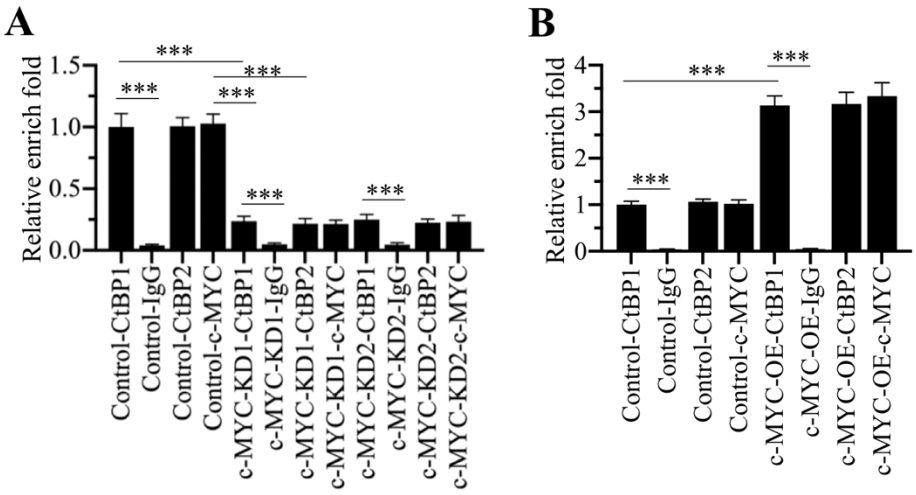
The Pearson correlation coefficient (*r*) and associated probability (*P*) were performed to determine the correlation between IL6 **(A)**, IL17 **(B)** and IL13 **(C)** using the circulating concentrations of cytokines and the relative mRNA level of *CASC2* from the same AP patients.




**Supplementary Figure 3. The protein levels of transcription factors in their corresponding knockdown and overexpression cell lines**

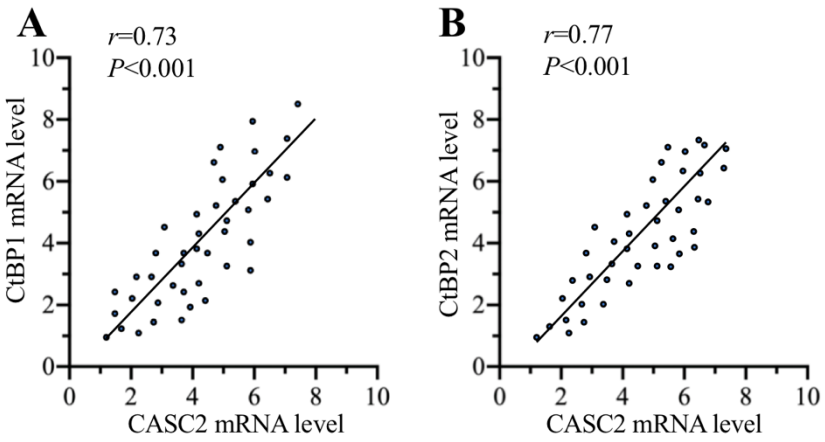
**(A)** The protein level of c-MYC. Total cell extracts from Control-KD, c-MYC-KD1, c-MYC-KD2, Control-OE, and c-MYC-OE cells were applied to immunoblots to measure c-MYC protein level. **(B)** The relative protein level of c-MYC. The protein signals in (A) were quantified using Image J and normalized to their corresponding GAPDH level. ***P*<0.01 and ****P*<0.001. **(C)** The protein level of SP1. Total cell extracts from Control-KD, SP1-KD1, SP1-KD2, Control-OE, and SP1-OE cells were applied to immunoblots to measure SP1 protein level. **(D)** The relative protein level of SP1. The protein signals in (C) were quantified using Image J and normalized to their corresponding GAPDH level. ***P*<0.01 and ****P*<0.001. **(E)** The protein levels of NF-κB subunits. Total cell extracts from Control-KD, p50-KD1, p50-KD2, p65-KD1, p65-KD2, Control-OE, p50-OE and p65-OE cells were applied to immunoblots to measure the protein levels of p50 and p65. **(F)** The relative protein levels of NF-κB subunits. The protein signals in (E) were quantified using Image J and normalized to their corresponding GAPDH level. ***P*<0.01 and ****P*<0.001. **(G)** The protein level of c-JUN. Total cell extracts from Control-KD, c-JUN-KD1, c-JUN-KD2, Control-OE, and c-JUN-OE cells were applied to immunoblots to measure c-JUN protein level. **(H)** The relative protein level of c-JUN. The

protein signals in (G) were quantified using Image J and normalized to their corresponding GAPDH level. **$P$<0.01 and ***$P$<0.001.



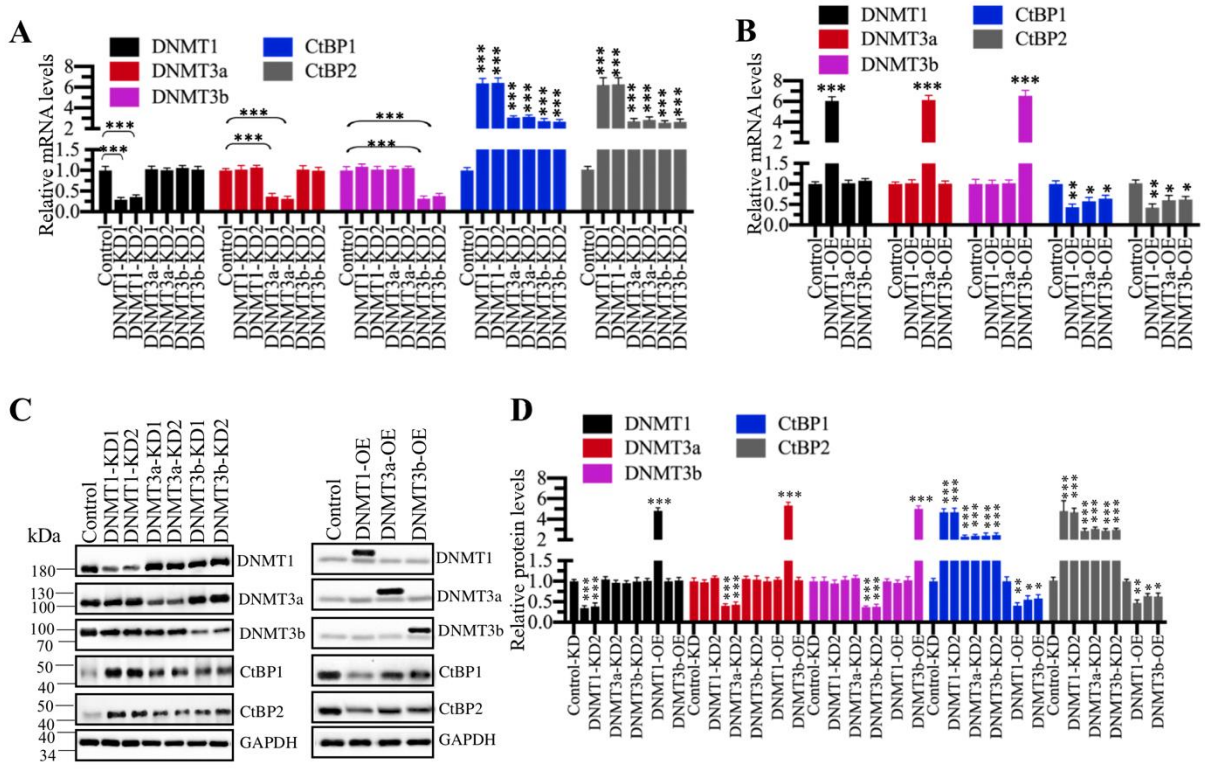

**Supplementary Figure 4. The CPM complex specifically bond to the promoter of *CASC2***

**(A)** Knockdown of *c-MYC* decreased the occupancies of CFM components in the promoter of *CASC2*. The Control-KD, c-MYC-KD1 and c-MYC-KD2 cells were subjected to ChIP assays using IgG, anti-CtBP1, anti-CtBP2 and anti-c-MYC antibodies, respectively. **$P$ < 0.01 and ***$P$ < 0.001. **(B)** Overexpression of *c-MYC* increased the occupancies of CFM components in the promoter of *CASC2*. The Control-OE and c-MYC-OE cells were subjected to ChIP assays using IgG, anti-CtBP1, anti-CtBP2 and anti-c-MYC antibodies, respectively. ***$P$ < 0.001.



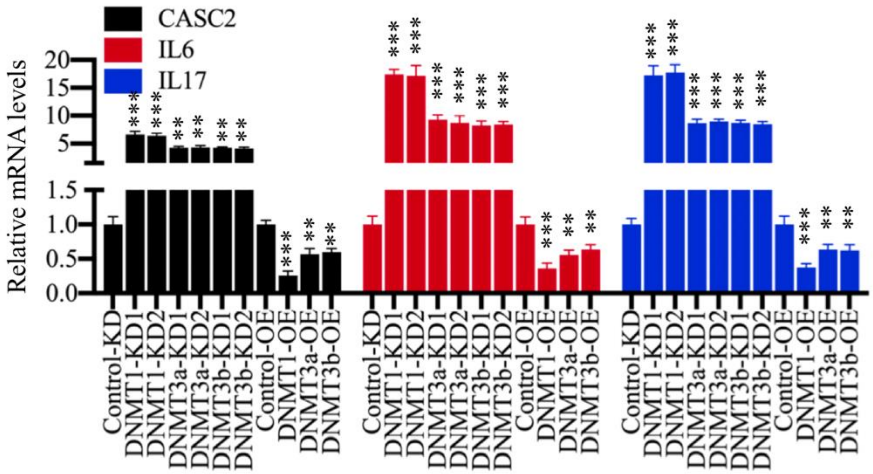

**Supplementary Figure 5. CtBP1 and CtBP2 were positively correlated with *CASC2* expression**

The Pearson correlation coefficient (*r*) and associated probability (*P*) were performed to determine the correlation between CtBP1 **(A)** and CtBP2 **(B)** using their relative mRNA levels in the same AP patients.



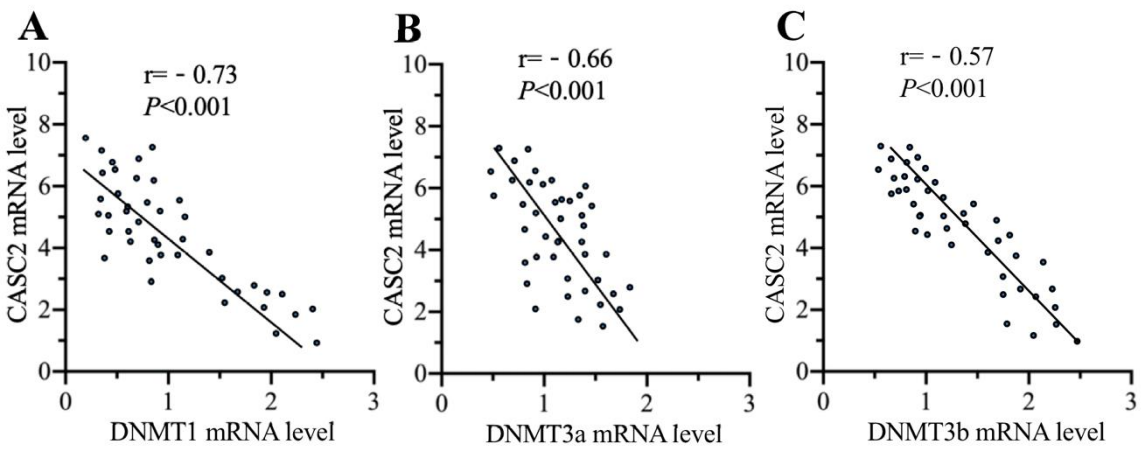

**Supplementary Figure 6. Knockdown or overexpression of *DNMTs* changed the expression of *CtBPs***

**(A)** Knockdown of *DNMTs* increased the expression *of CtBPs*. The Control-KD, DNMT1-KD1, DNMT1-KD2, DNMT3a-KD1, DNMT3a-KD2, DNMT3b-KD1 and DNMT3b-KD2 cells were subjected to RNA isolation, followed by qRT-PCR analyses to measure the mRNA levels of *DNMT1*, *DNMT3a*, *DNMT3b*, *CtBP1* and *CtBP2*. ***$P < 0.001$. **(B)** Overexpression of *DNMTs* decreased the expression *of CtBPs*. The Control-OE, DNMT1-OE, DNMT3a-OE and DNMT3b-OE cells were subjected to RNA isolation, followed by qRT-PCR analyses to measure the mRNA levels of *DNMT1*, *DNMT3a*, *DNMT3b*, *CtBP1* and *CtBP2*. ***$P < 0.001$. **(C)** The effects of knockdown or overexpression of *DNMTs* on CtBP protein levels. The DNMT-KD and DNMT-OE cells used in (A) and (B) were subjected to immunoblots to examine protein levels of DNMT1, DNMT3a, DNMT3b, CtBP1 and CtBP2. GAPDH was used as a loading control. **(D)** The relative protein levels of CtBPs in DNMT-KD and DNMT-OE cells. The protein signal intensity in (C) was quantified and normalized to GAPDH. *$P < 0.05$, **$P < 0.01$ and ***$P < 0.001$.



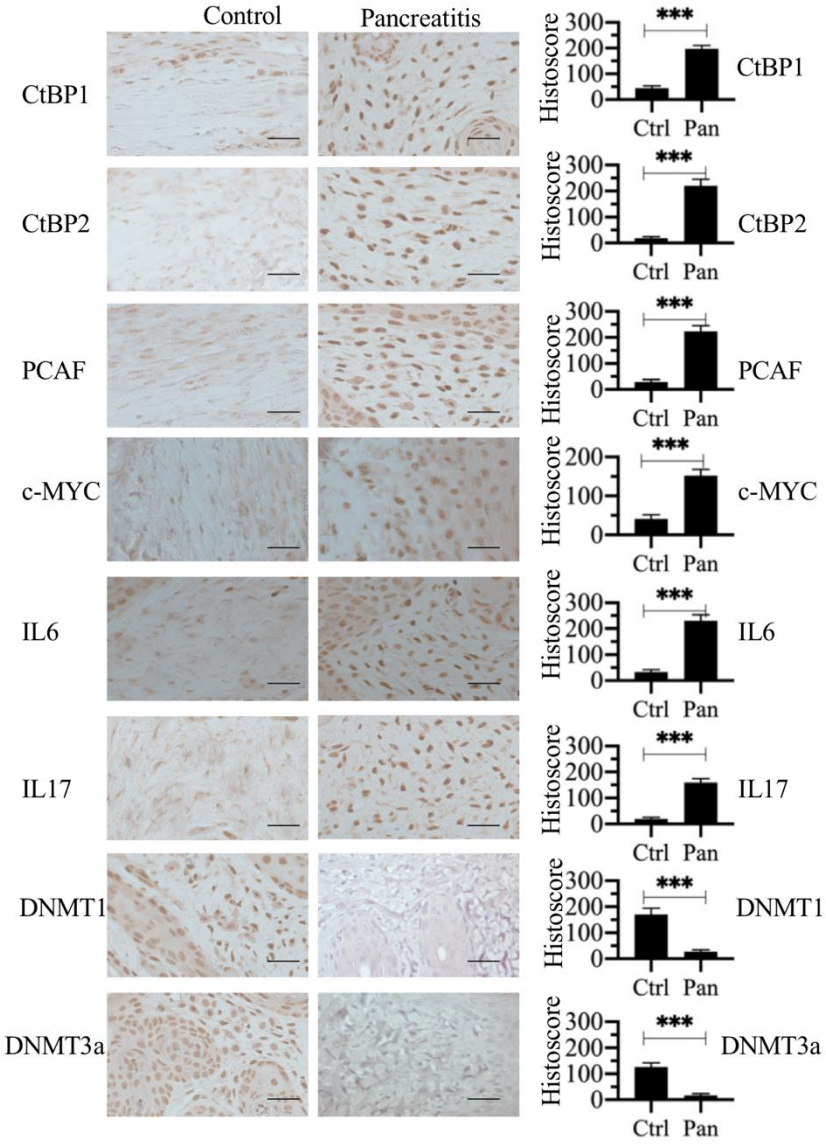

**Supplementary Figure 7. The expression of *CASC2*, *IL6* and *IL17* in DNMT-KD and DNMT-OE cells**

Total RNA from Control-KD, DNMT1-KD1, DNMT1-KD2, DNMT3a-KD1, DNMT3a-KD2, DNMT3b-KD1, DNMT3b-KD2, Control-OE, DNMT1-OE, DNMT3a-OE and DNMT3b-OE cells were subjected to qRT-PCR analyses to measure the expression of *CASC2*, *IL6* and *IL17*. $^{**}P < 0.01$ and $^{***}P < 0.001$.



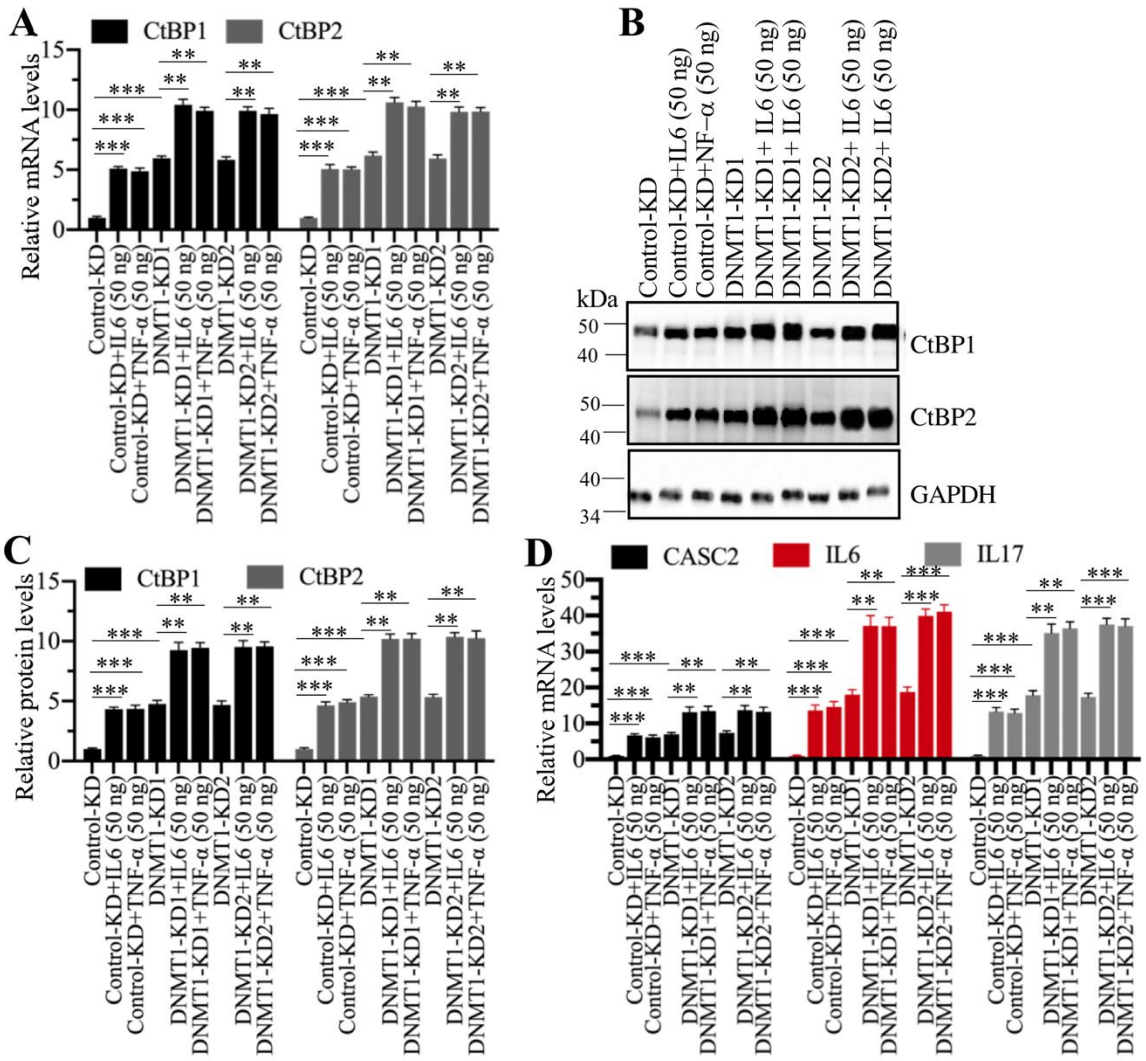

**Supplementary Figure 8. The expression of *DNMTs* was negatively correlated with *CASC2* expression**

The Pearson correlation coefficient (*r*) and associated probability (*P*) were performed to determine the correlation between DNMT1 **(A)**, DNMT3a **(B)** and DNMT3b **(C)** using their relative mRNA levels in the same AP patients.




**Supplementary Figure 9. The IHC staining results of CPM components and DNMTs in pancreatic tissues**

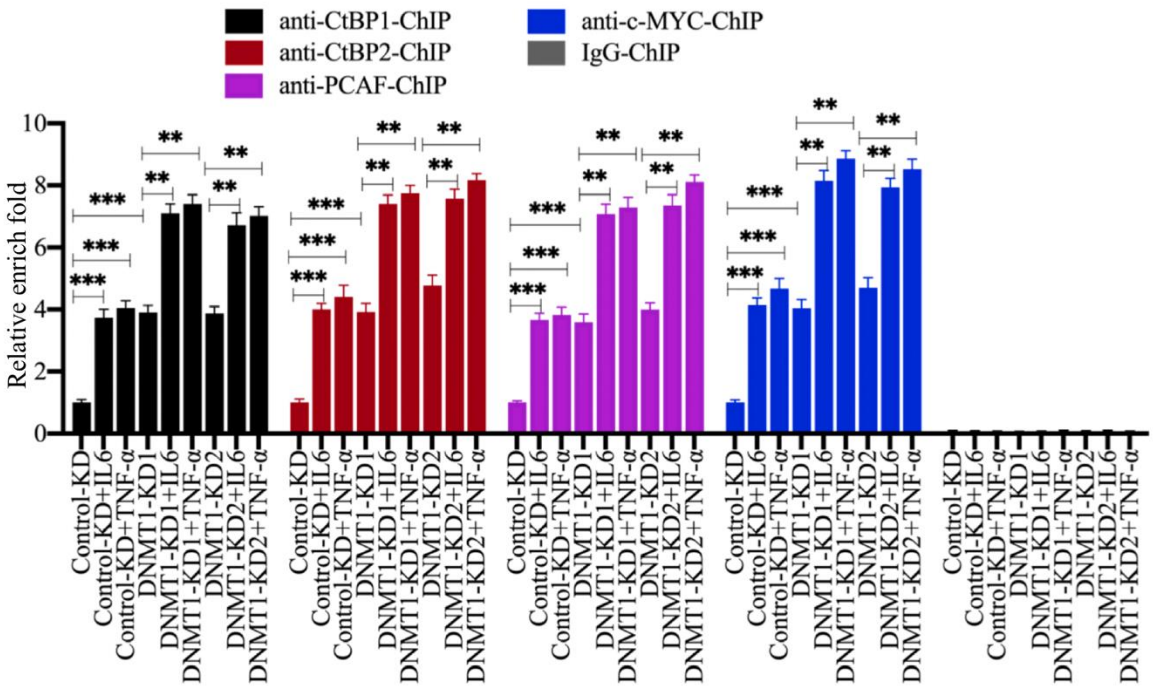
Three-paired pancreatic tissues from controls (stage 0 pancreatic cancer patients) and AP patients were subjected to IHC staining assays using anti-CtBP1, anti-CtBP2, anti-PCAF, anti-c-MYC, anti-IL6, anti-IL17, anti-DNMT1 and anti-DNMT3a, respectively. The representative pictures from the same control and AP patient were shown. Bars=100 μm. Histoscore was calculated by a semi-quantitative assessment of both the intensity of staining and the percentage of positive cells. ***$P < 0.001$.




**Supplementary Figure 10. Inflammation and DNA methylation coactivated the expression of *CtBPs***

**(A)** Combined effects of *DNMT1* knockdown and IL6 (or TNF-α) treatment on *CtBP* mRNA levels. The Control-KD and DNMT1-KD cells were treated with or without 50 ng/mL IL6 or TNF-α. The resulting cells were used for RNA isolation, followed by qRT-PCR analyses to determine the mRNA levels of *CtBP1* and *CtBP2*. ***$P$<0.001. **(B)** Combined effects of *DNMT1* knockdown and IL6 (or TNF-α) treatment on CtBP protein levels. Cells used in (A) were subjected to immunoblots to examine protein levels of CtBP1 and CtBP2. GAPDH was probed as a loading control. **(C)** The relative protein levels of CtBPs. The protein bands in (B)

were quantified and normalized to GAPDH. ***$P < 0.001$. **(D)** Combined effects of *DNMT1* knockdown and IL6 (or TNF-α) treatment on the expression of *CASC2*, *IL6* and *IL17*. RNA samples used in (A) were subjected to examine mRNA levels of *CASC2*, *IL6* and *IL17* by qRT-PCR analyses. ***$P < 0.001$.




**Supplementary Figure 11. Knockdown of *DNMTs* and IL6/TNF-α treatment increased the occupancies of CPM components on the promoter of *CASC2***

The Control-KD, DNMT1-KD1 and DNMT1-KD2 cells were treated with or without 50 ng/mL IL6 and TNF-α, respectively. The treated cells were applied to ChIP assays with anti-CtBP1, anti-CtBP2, anti-PCAF, anti-c-MYC, and IgG (negative control), respectively. The purified DNA was used for qRT-PCR analyses to measure the occupancies of CPM components on the promoter of *CASC2*. $^{**}P < 0.01$ and $^{***}P < 0.001$.

**Supplementary Table-1. The basic information of pancreatic cancer patients (Control, n=48) and acute pancreatitis patients (AP, n=48)**

| Parameters | Control | AP |
|---|---|---|
| Mean age | 59.3±6.3 | 53.4±4.5 |
| Gender | 30M/18F | 33M/15F |
| Cancer stage | 0 | NA |

F: female; M: male

**Supplementary Table-2. Primers used for qRT-PCR analyzes**

| Gene | Forward Primers | Reverse primers |
|---|---|---|
| CtBP1 | 5’- AGGCGGATAGAGACCACGCCA -3’ | 5’-CTCTGCAGTGCCAGGGCCACC-3’ |
| CtBP2 | 5’-TGGAGAAGTTCAAGGCCCTGA-3’ | 5’-GGCAGATGGTAGAGTCCGCT-3’ |
| DNMT1 | 5’- AGCAAAGTGAAAGTCATCTACA-3’ | 5’-GGACTCGAATCTCGCGTAG-3’ |
| DNMT3a | 5’-TGAGCGCACAAGAGAGCGGCT-3’ | 5’-GCACACTCCAGAAAGCAGTT-3’ |
| DNMT3b | 5’-GACTCGAAGACGCACAGCTG-3’ | 5’-GTTGGCAACATCTGAAGCCA-3’ |
| SP1 | 5’-GTGAGTCTTCCAAGAATCGCAC-3’ | 5’-CGGTCTGGAACTGTGGGATTA-3’ |
| c-MYC | 5’-CAGCAGCAGCAGCAGAGCGAGC-3’ | 5’-AAGGGTGTGACCGCAACGTAG-3’ |
| IL6 | 5’- ACCTAGAGTACCTCCAGAACAG-3’ | 5’- AGATGAGTTGTCATGTCCTGCA-3’ |
| IL17 | 5’-CTGCTACTGCTGCTGAGCCTGG-3’ | 5’-TGAGGACCTTTTGGGATTGG-3’ |
| p65 | 5’-AGTGCGGGACCCATCAGGCA-3’ | 5’- TCATCCCCACCGAGGCAGCT-3’ |
| p50 | 5’-AGCTAATCCGCCAAGCAGCT-3’ | 5’-TTTCAAGTTGGATGCATTGG-3’ |
| c-Jun | 5’-GCCTTCGTTAACTGTGTAT-3’ | 5’- AACACTGGGCAGGATACCC-3’ |
| CDH1 | 5’- CACCACTGGGCTGGACCGAG-3’ | 5’-TGGGATTGAAGATCGGAGGA-3’ |
| SOX4 | 5’-GGAGAAGAAGGTGAAGCGCGT-3’ | 5’-CTGGGCGCGTCGGGCGAGCA-3’ |
| ALT1 | 5’-CGCCTTCTCCTTTTCGCAATG-3’ | 5’-TGTGCAGTTTCAGCAAAGCTC-3’ |
| ADPGK-AS1 | 5’-GCCGATGTCGACACAAGCG-3’ | 5’-AGCAAATGTGTTCCCATCCCT-3’ |
| lincIRX5 | 5’-TCCTGGCTCTCCATGGAGAAG-3’ | 5’-CCTTCATAGTTGATGACCACCTC-3’ |
| CASC2 | 5′-GCTGATCAGAGCACATTGGA-3′ | 5′-ATAAAGGTGGCCACAACTGC-3′ |
| LincROR | 5′-CTCCAGCCTAGATGACAGA-3′ | 5′-CACAGCAGCACTATTCCTAT-3′ |
| MRUL | 5′-ACCCACAGACAACTGTGGACCC-3″ | 5′-GCCGCCCCTATTGTTGCCCA-3′ |
| β-Actin | 5’- AGAGCTACGAGCTGCCTGAC-3’ | 5’- AGCACTGTGTTGGCGTACAG -3’ |

**Supplementary Table-3. Primers used for vector constructions**

| Gene | Forward Primers | Reverse primers |
|---|---|---|
| CtBP1 | 5'-CGGGATCCATGGGCAGCTCGCACTTGCTCA3' | 5'-CGGAATTCCTACAACTGGTCACTGGCGTGGT3' |
| CtBP2 | 5'-CGGGATCCATGGCCCTTGTGGATAAGCACAA-3' | 5'-CGGAATTCCTATTGCTCGTTGGGGTGCTCTCGA-3' |
| PCAF | 5'-CGGGATCCATGTCCGAGGCTGGCGGGGCC-3' | 5'-CGGAATTCTCACTTGTCAATTAATCCAGC-3' |
| DNMT1 | 5'-CGGGATCCATGCCGGCGCGTACCGCCCCA-3' | 5'-CGGAATTCCTAGTCCTTAGCAGCTTCCTC-3' |
| DNMT3a | 5'-CGGGATCCATGCCCGCCATGCCCTCCAGCG-3' | 5'-CGGAATTCTTACACACACGCAAAATACTCCTTC-3' |
| DNMT3b | 5'-CGGGATCCATGAAGGGAGACACCAGGCATCT-3' | 5'-CGGAATTC CTATTCACATGCAAAGTAGTCC-3' |
| SP1 | 5'-CGGGATCCATGAGCACCAAGATCACTCCATG-3' | 5'-CGGAATTCTCAGAAGCCATTGCCACTGATA-3' |
| c-MYC | 5'-CGGGATCCATGCCCCTCAACGTTAGCTTCA-3' | 5'-CGGAATTCTTACGCACAAGAGTTCCGTAGC-3' |
| p65 | 5'-CGGGATCCATGGACGAACTGTTCCCCCTC-3' | 5'-CGGAATTCTGCTGAGTCAGATCAGCTCCTAA-3' |
| p50 | 5'-CGGGATCCATGGCAGAAGATGATCCATATT-3' | 5'-CGGAATTCCTAAATTTTGCCTTCTAGAGGTC-3' |
| c-JUN | 5'-CGGGATCCATGACTGCAAAGATGGAAACGAC-3' | 5'-CGGAATTCTCAAAATGTTTGCAACTGCTGC-3' |

**Supplementary Table-4. Primers used for qMSP assays.**

| Gene | Forward Primers | Reverse primers |
|---|---|---|
| CpG1-CtBP1 | 5'-TTGGTTGAGGGTTTAGTATTGTTAG-3' | 5'-AATAATTACATAATTTCAAAAACCAC-3' |
| CpG2-CtBP1 | 5'-AGTTTTTGGGTGAGTAGGTTTAGTG-3' | 5'-AAATTCAAAACTAAAAAACCCCTTC-3' |
| CpG1-CtBP2 | 5'-TATTTGTAGTATAGAGGGTTTTTTTT-3' | 5'- AACTCCAACTTCCTCCTAATACC-3' |
| CpG2-CtBP2 | 5'- TTTTAAATGGTTTTGAATTAATGAAGG-3' | 5'- TCTCAAATCAAAAAACAAAACAATC-3' |

**Supplementary Table-5. The aberrantly expressed lncRNAs in AP tissues**

| Ensembl Gene ID | lncRNA name | Average fold change | P Value | Expression |
|---|---|---|---|---|
| ENSG00000231607 | ALT1 | -13.4 | 0.0024 | Down |
| ENSG00000260105 | ACO4 | -11.1 | 0.00043 | Down |
| ENSG00000233026 | AC026166.2-001 | -10.2 | 0.00041 | Down |
| ENSG00000227033 | AC105461.1 | -9.3 | 0.00033 | Down |
| ENSG00000233858 | AC026904.1 | -8.5 | 0.00065 | Down |
| ENSG00000267296 | CEBPA-AS1 | -6.7 | 0.00099 | Down |
| ENSG00000260898 | ADPGK-AS1 | -5.9 | 0.00021 | Down |
| ENSG00000281406 | BLACAT1 | -5.2 | 0.00046 | Down |
| ENSG00000280977 | lincIRX5 | -4.5 | 0.0013 | Down |
| ENSG00000177640 | CASC2 | 14.8 | 0.00024 | Up |
| ENSG00000213453 | FTH1P3 | 13.7 | 0.00022 | Up |
| ENSG00000234741 | GAS5 | 11.3 | 0.00076 | Up |
| ENSG00000228630 | HOTAIR | 10.4 | 0.0083 | Up |
| ENSG00000275874 | LINC00162 | 9.4 | 0.0024 | Up |
| ENSG00000224259 | LINC01133 | 8.6 | 0.00016 | Up |
| ENSG00000172965 | AWPPH | 7.8 | 0.00054 | Up |
| ENSG00000281183 | lncRNA-LET | 7.6 | 0.00025 | Up |
| ENSG00000258609 | linc-RoR | 6.7 | 0.00065 | Up |
| ENSG00000246582 | LOC389641 | 5.4 | 0.00041 | Up |
| ENSG00000225783 | Gomafu | 5.3 | 0.00066 | Up |
| ENSG00000135164 | MRUL | 4.5 | 0.00084 | Up |

**Supplementary Table-6. The aberrantly expressed genes dependent on *CASC2***

| Gene | CASC2-KD1 | CASC2-KD2 | CASC2-KD3 | CASC2-OE1 | CASC2-OE2 | CASC2-OE3 |
|---|---|---|---|---|---|---|
| *IL6* | -12.1 | -9.3 | -9.1 | 12.1 | 13.5 | 14.1 |
| *IL17* | -10.4 | -11.1 | -8.6 | 11.1 | 10.4 | 12.1 |
| *S100A8* | -9.3 | -8.5 | -7.2 | 9.4 | 10.1 | 11.2 |
| *S100A9* | -8.8 | -8.2 | -7.1 | 8.5 | 7.7 | 9.3 |
| *RUNX1* | -6.5 | -5.4 | -6.6 | 5.7 | 4.6 | 6.3 |
| *IDO1* | -5.9 | -4.5 | -5.4 | 5.1 | 5.5 | 5.7 |
| *NCF2* | -5.4 | -4.1 | -4.9 | 4.8 | 4.2 | 4.4 |
| *PDLIM4* | -4.8 | -3.6 | -4.2 | 4.5 | 3.6 | 2.5 |
| *GBP2* | -4.1 | -3.1 | -3.6 | 3.7 | 2.9 | 2.3 |
| *SOX4* | 8.6 | 7.3 | 5.3 | -6.5 | -7.4 | -8.3 |
| *CDH1* | 7.2 | 5.7 | 4.3 | -5.3 | -6.9 | -6.2 |
| *PDZD8* | 5.4 | 6.6 | 3.7 | -5.1 | -5.4 | -5.6 |
| *DAND5* | 4.3 | 5.3 | 4.6 | -4.8 | -4.5 | -5.1 |
| *PITX3* | 3.7 | 4.1 | 3.5 | -4.3 | -4.2 | -5.0 |
| *SYVN1* | 3.6 | 4.1 | 3.5 | -4.2 | -4.1 | -4.7 |
| *SLC18A2* | 3.5 | 4.0 | 3.4 | -4.1 | -4.0 | -4.2 |
| *CACUL1* | 3.4 | 4.0 | 3.2 | -3.9 | -3.9 | -4.0 |
| *PAX5* | 3.4 | 3.9 | 3.1 | -3.9 | -3.9 | -3.7 |
| *CSF2* | 3.1 | 3.8 | 3.2 | -3.7 | -3.8 | -3.6 |
| *GNB1* | 3.1 | 3.6 | 3.0 | -3.6 | -3.4 | -3.5 |
| *SETD2* | 3.1 | 3.5 | 2.9 | -3.6 | -3.3 | -3.3 |
| *RTN4R* | 2.9 | 3.2 | 2.8 | -3.4 | -3.3 | -3.2 |
| *GSTP1* | 2.7 | 3.1 | 2.6 | -3.3 | -3.1 | -2.9 |
| *CBR1* | 2.6 | 2.8 | 2.5 | -3.2 | -3.0 | -2.7 |
| *LMO2* | 2.4 | 2.5 | 2.4 | -2.8 | -2.9 | -2.2 |

**Supplementary Table-7. The c-MYC-associated proteins identified by mass spectrometry**

| Protein | Protein description | Molecular weight (kDa) | MASCOT scores |
|---|---|---|---|
| c-MYC | MYC Proto-Oncogene, BHLH Transcription Factor | 49 | 1053 |
| β-Actin | Actin Beta | 55 | 2021 |
| CtBP1 | C-Terminal Binding Protein 1 | 49 | 967 |
| CtBP2 | C-Terminal Binding Protein 2 | 49 | 954 |
| PCAF | P300/CBP-Associated Factor | 93 | 933 |
| MAX | MYC Associated Factor X | 48 | 921 |
| MED1 | Mediator Complex Subunit 1 | 168 | 843 |
| SUPT3H | Suppressor Of Ty 3 Homolog | 36 | 811 |
| BIN1 | Bridging Integrator 1 | 86 | 765 |
| MED16 | Mediator Complex Subunit 16 | 65 | 712 |
| ZEB1 | Zinc Finger E-Box Binding Homeobox 1 | 124 | 687 |
| HIPK2 | Homeodomain Interacting Protein kinase 2 | 131 | 667 |
| TADA3 | Transcriptional Adaptor 3 | 49 | 645 |
| USP7 | Ubiquitin Specific Peptidase 7 | 128 | 632 |
| TAF6 | TATA-Box Binding Protein Associated Factor 6 | 73 | 612 |
| MYOD1 | Myogenic Differentiation 1 | 35 | 589 |
| H3C1 | H3 Clustered Histone 1 | 15 | 567 |
| GATA1 | GATA Binding Protein 1 | 43 | 562 |
| USP22 | biquitin Specific Peptidase 22 | 60 | 532 |
| GPS2 | G Protein Pathway Suppressor 2 | 37 | 511 |
| NRIP1 | Nuclear Receptor Interacting Protein 1 | 127 | 508 |
| TRNT1 | TRNA Nucleotidyl Transferase 1 | 50 | 495 |
| NOD2 | Nucleotide Binding Oligomerization Domain Containing 2 | 115 | 477 |
| TLE3 | Transducin-Like Enhancer Protein 3 | 83 | 464 |
| SEH1L | SEH1 Like Nucleoporin | 40 | 453 |
| CARHSP1 | Calcium-regulated Heat Stable Protein 1 | 16 | 442 |
| CTRL1 | Chymotrypsin-like Protease | 28 | 434 |
| PSMB1 | Proteasome subunit Beta 1 | 26 | 436 |
| RPL19 | Ribosomal Protein L19 | 23 | 425 |
| DAZAP1 | DAZ Associated Protein 1 | 43 | 411 |
| MIDN | Midnolin | 49 | 367 |
| TAF5 | TATA-Box Binding Protein Associated Factor 5 | 87 | 352 |
| DNM2 | Dynamin 2 | 98 | 314 |
| TAF3 | TATA-Box Binding Protein Associated Factor 3 | 103 | 305 |
| BIN2 | Bridging Integrator 2 | 62 | 299 |
| SBF2 | SET Binding Factor 2 | 208 | 254 |