Supplementary

Table S1 sgRNAs sequence and its targeting region

sgRNA targeting the *p16* promoter	5' to 3'	Position (Human hg38)
PX458-sgRNA1	Forward: TTGGTCCTCCTTCCTTGCCAACGC	chr9:21975143-21975162
	Reverse: AAACGCGTTGGCAAGGAAGGAGGA	
PX458-sgRNA2	Forward: TTGGGTGGCCAGCCAGTCAGCCGA	chr9:21974775-21974797
	Reverse: AAACTCGGCTGACTGGCTGGCCAC	
pgRNA-sgRNA1	Forward: CACCGTCCTCCTTCCTTGCCAACGC	chr9:21975143-21975162
	Reverse: AAACGCGTTGGCAAGGAAGGAGGAC	
pgRNA-sgRNA2	Forward: CACCGGTGGCCAGCCAGTCAGCCGA	chr9:21974775-21974797
	Reverse: AAACTCGGCTGACTGGCTGGCCACC	
pgRNA-sgRNA scramble	Forward: TTGGCCCCCGGGGGAAAAATTTTT	None
	Reverse: AAACAAAAATTTTTCCCCCGGGGG	

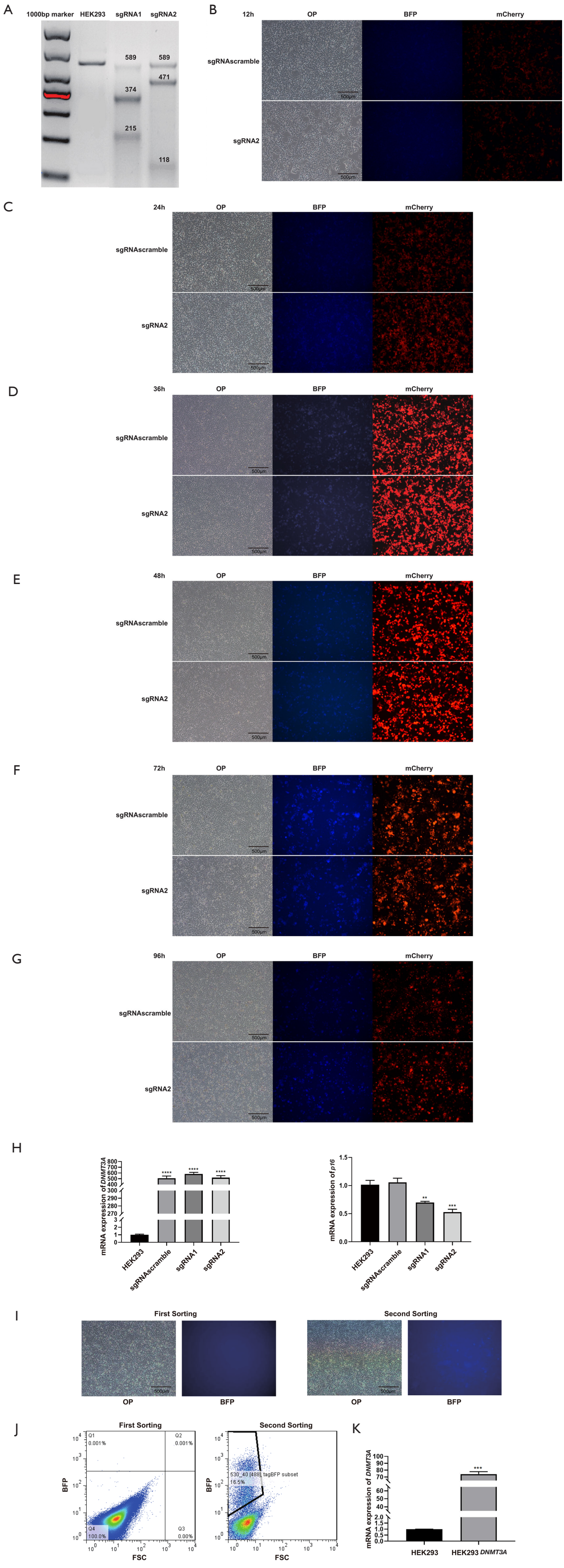

Figure S1 HEK293 cell line with stable expression of *DNMT3A* and sgRNA was constructed. (A) The cutting efficiency of Cas9 guided by sgRNA1/sgRNA2 were verified by T7E1 test. (B-G) dCas9-Dnmt3a-tagBFP and pgRNAmodified-sgRNAscramble/pgRNA-modified-sgRNA2 were transfected transiently in HEK293; pictures were taken under inverted fluorescence microscope at 12, 24, 48, 72 and 96 h, respectively (BFP and mCherry). (H) Changes of *p16* and *DNMT3A* mRNA in HEK293 cells after 48 h of transient transfection. (I,J) dCas9-*DNMT3A*-tagBFP was transfected into HEK293 cells stably. Then flow cytometry sorting was performed twice to increase positive rate of BFP. The fluorescence intensity of BFP was recorded using an inverted fluorescence microscope after sorted twice by flow cytometry, respectively. (K) The expression level of *DNMT3A* in sorted cells was verified by qPCR. **, P<0.01; ***, P<0.001; ****, P<0.0001. sgRNA, single guide RNA; OP, optical picture; FSC, forward scatter; BFP, blue fluorescent protein.

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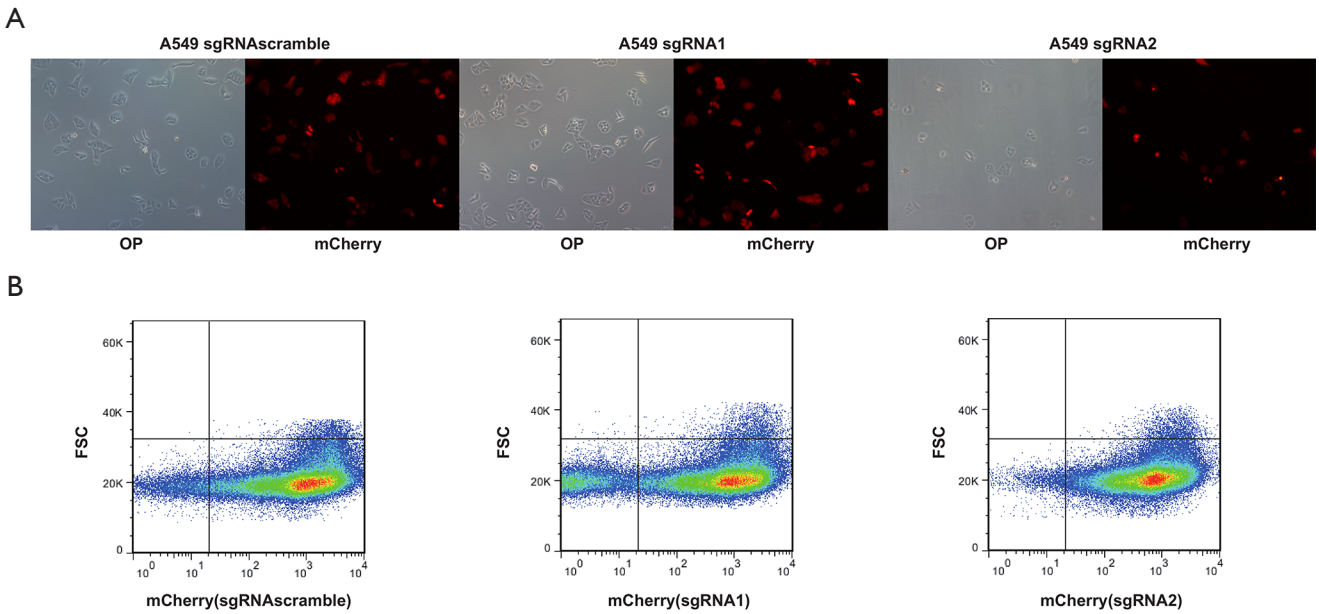

Figure S2 A549 cell line with stable expression of *DNMT3A* and sgRNA was constructed. (A) pgRNAmodified-sgRNAscramble/pgRNA-modified-sgRNA1/pgRNA-modified-sgRNA2 were transfected stably in A549-*DNMT3A* cell line; Pictures were taken under inverted fluorescence microscope. (B) The mCherry positive cells were screened by ultra-high speed flow cytometry sorting system. OP, optical picture; FSC, forward scatter; sgRNA, single guide RNA.

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