

**Table S1** The target genes of miR-126-3p predicted by three online programs

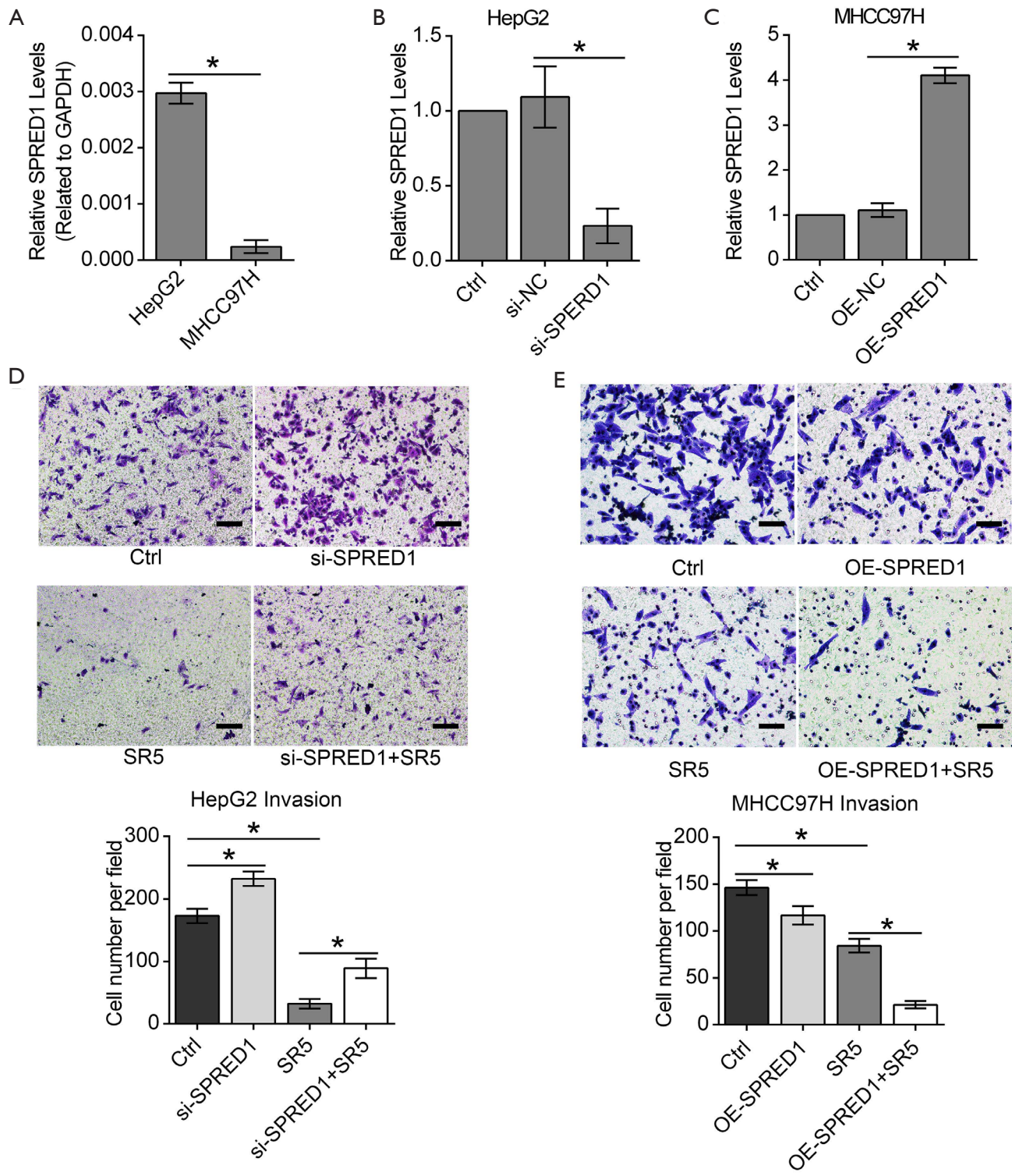
Online program	Target genes of miR-126-3p
TargetScan 7.2	<i>LRP6, TRAF7, PCDH7, RGS3, TRIM46, ITGA6, SPRED1, FBXO33, HERPUD1, SAMD14, KANK2, CAMSAP1, PLXNB2, ADAM9, EFHD2, AKAP13, PEX5, CRK, EGFL7, DIP2C, PLK2, SDC2, PTPN9, GBP2, GNA13, IRS1, BAK1, SLC7A5</i>
miRDB	<i>RNF165, RGS3, ITGA6, SPRED1, SLC15A4, TSC1, KANK2, PIK3R2, CAMSAP1, PLXNB2, ADAM9, LARP6, CRK, DIP2C, KCNAB3, PTPN9, IRS1, PMM1, SLC7A5</i>
StarBase V2.0	<i>TRAF7, ZNF219, C5orf13, DNMT1L, HERPUD1, SFRS6, ARID2, PCDH9, CDKN2AIP, VPRBP, IRS2, SPATS2, ATP6V1D, WDR6, GNA13, SMEK1, MANBAL, ORM DL3, ARNTL, CYBASC3, EVI5, KANK2, TSC1, TNFRSF11B, ADAM9, F8A3, RORB, GOLPH3, PARP16, PEX5, SLC41A2, AGK, IFT81, GMFB, SLC7A5, SFRS11, VEGFA, SPRED1, TP53BP2, RNMT, ZNF131, PLXNB2, HMGB3, EFHD2, CHST3, AKAP13, MID1IP1, HOXA3, NIPBL, GATAD2B, THAP6, SMURF2, TMEM161B, LRP6, RNF165, ITGA6, FBXO33, FAM171A1, PIK3R2, NAV1, LARP6, CEP97, CRK, CDA, EXOSC3, PLK2, SLC6A8, SDC2, PPP3CB, RNASEH1, PURA, BZW1, SLC39A6, CPNE1</i>
Common	<i>KANK2, ADAM9, SLC7A5, SPRED1, PLXNB2, ITGA6, CRK</i>

**Table S2** The sequences of siRNAs and microRNA mimics and inhibitors

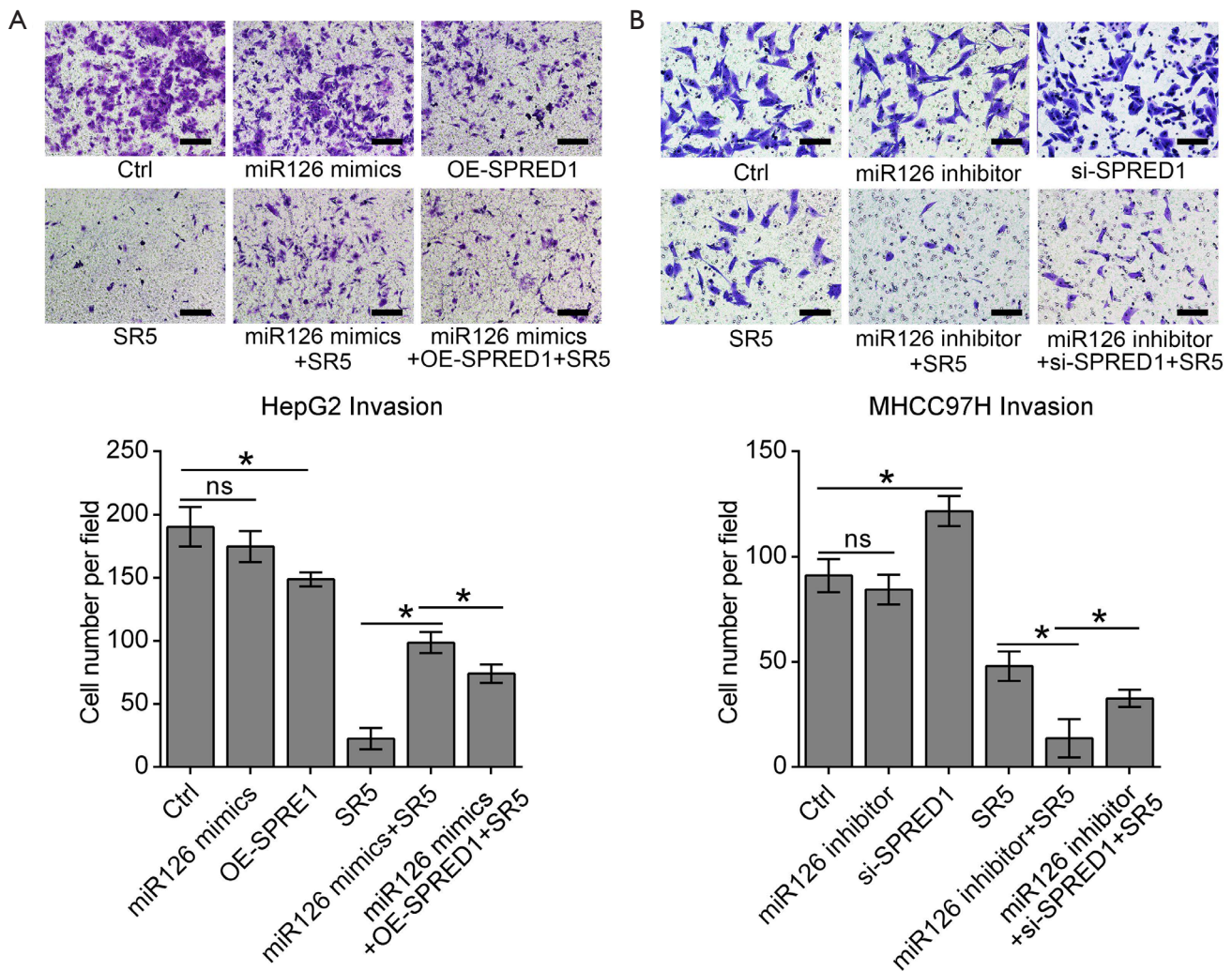
Primers	Sequence
miR-126-3p mimics	5'-UCGUACCGUGAGUAAUAAUGCG-3' 5'-CAUUUUACUCACGGUACGAUU-3'
mimics NC	5'-UUCUCCGAACGUGUCACGUTT-3' 5'-ACGUGACACGUUCGGAGAATT-3'
miR-126-3p inhibitor	5'-CGCAUUUUACUCACGGUACGA-3'
Inhibitor NC	5'-CAGUACUUUUUGUGUAGUACAA-3'
SPRED1 siRNA	5'-GAATACGTACAGCGGCAAATA-3'

**Table S3** The sequences of reverse transcription (RT) primers and PCR primers for target genes.

Primers	Sequence
miR-126-3p RT primer	5'-CCTGTTGTCTCCAGCCACAAAAGAGCACAATATTTTCAGGAGACAACAGGCGCATT-3'
miR-126-3p forward	5'-CGCCGTCGTACCGTGAGTAA-3'
miR-126-3p reverse	5'-CAGCCACAAAAGAGCACAAT-3'
U6 RT primer	5'-GTCGTATCCAGTGCAGGGTCCGAGGTATTTCGACTGGATACGACAAAAATATG-3'
U6 forward	5'-GCGCGTCGTGAAGCGTTC-3'
U6 reverse	5'-GTGCAGGGTCCGAGGT-3'
SPRED1 forward	5'-GCTAACCATCGCAAGCAGAAC-3'
SPRED1 reverse	5'-CATTGTATGTCAGACTCAGAGGGAG-3'
GAPDH forward	5'-GGACCTGACCTGCCGTCTAG-3'
GAPDH reverse	5'-GTAGCCCAGGATGCCCTTGA-3'



**Figure S1** SPRED1 enhanced the effect of sorafenib on inhibiting cells invasion ability in HCC cells. (A) qRT-PCR assay to exam the expression of SPRED1 in HepG2 and MHCC97H cells. (B,C) qRT-PCR assay to confirm the efficiency of siRNA or overexpression plasmid specific to SPRED1 in HCC cells. (D) Transwell invasion assays showed the effect of SPRED1 siRNA, sorafenib or combined therapy on cell invasion ability in HepG2 cells. (E) Transwell invasion assays showed the effect of SPRED1 overexpression plasmid, sorafenib or combined therapy on cell invasion ability in MHCC97H cells. HCC cells were stained with crystal violet in D,E, scale bars: 100  $\mu$ m ( $\times$ 100). Data represents the mean  $\pm$  SD of three independent experiments. \*,  $P < 0.05$ .



**Figure S2** Regulation of miR-126-3p and SPRED1 markedly influence the anti-metastasis effect of sorafenib in HCC cells. (A) Transwell invasion assays to exam the effect of sorafenib combined with over-expressing SPRED1 or miR-126-3p mimics in HepG2 cell. (B) Transwell invasion assays to exam the effect of sorafenib combined with si-SPRED1 or miR-126-3p inhibitor in HepG2 cell. HCC cells were stained with crystal violet in A,B, scale bars: 100  $\mu$ m ( $\times$ 100). Data represents the mean  $\pm$  SD of three independent experiments. \*,  $P < 0.05$ .