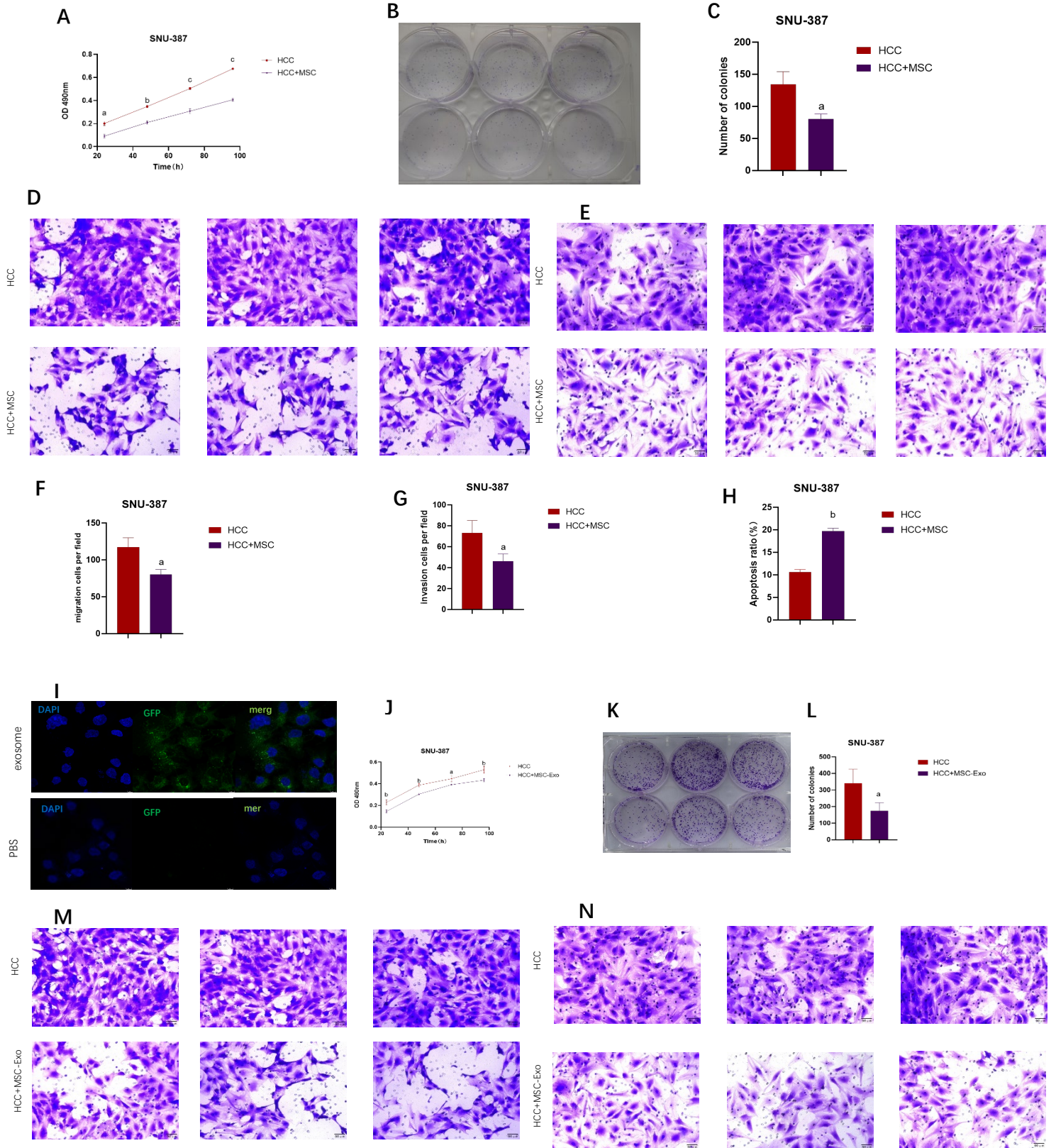
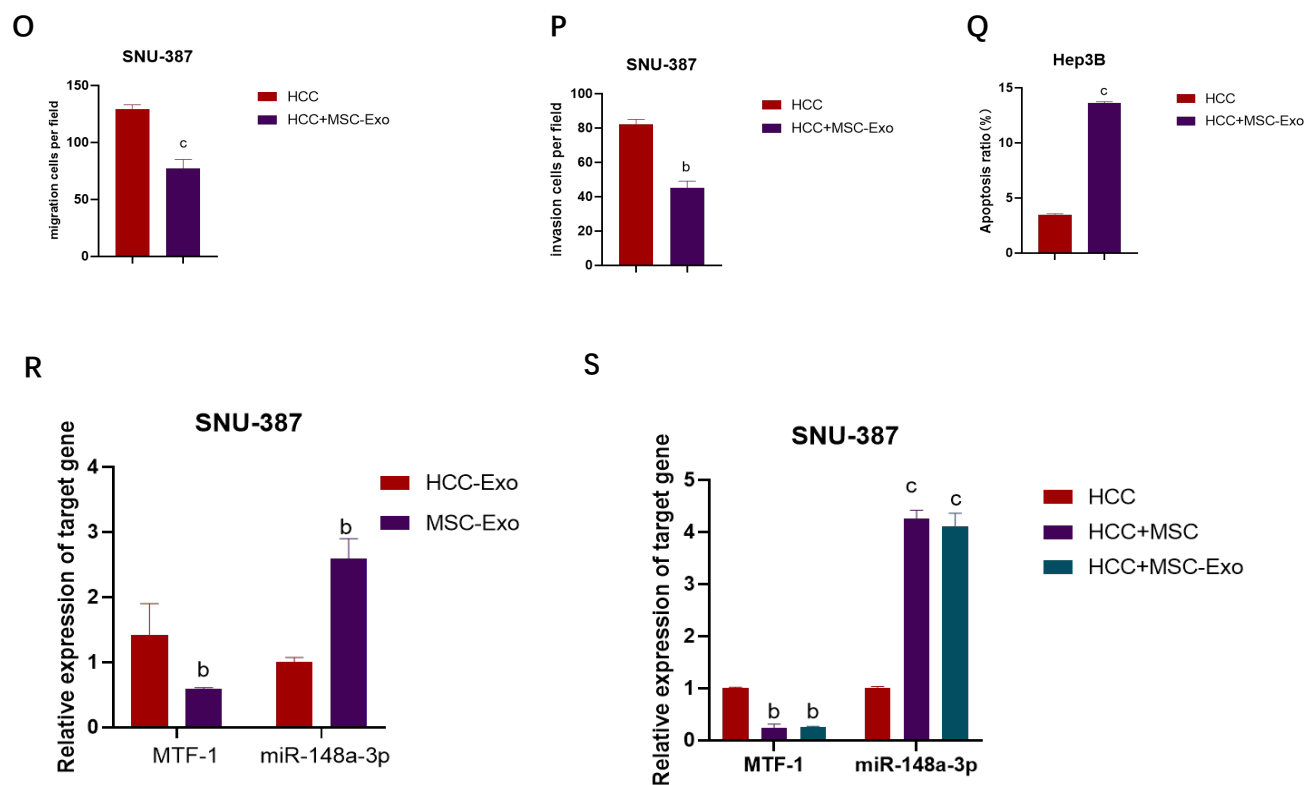


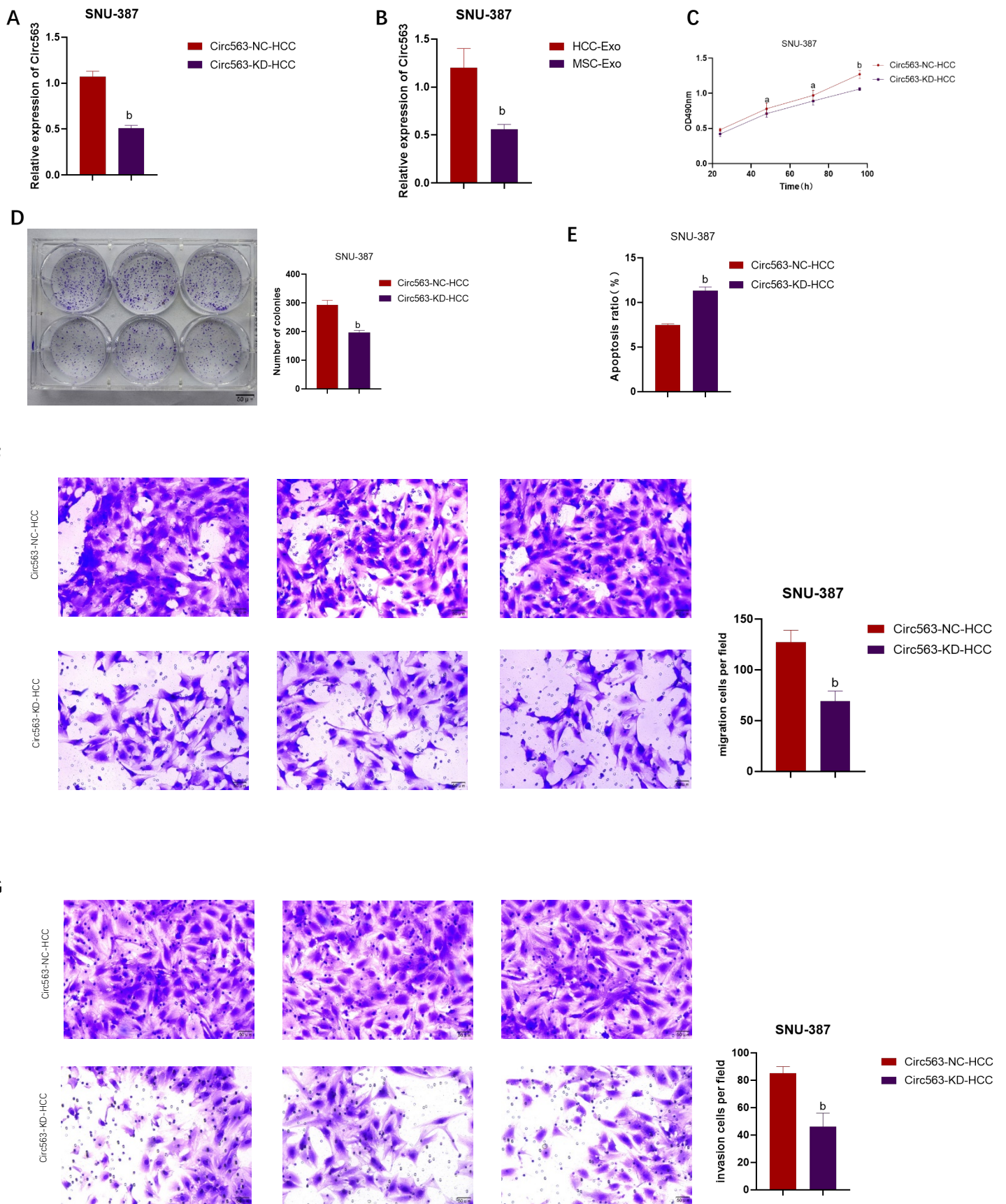
Supplementary figure and figure legend





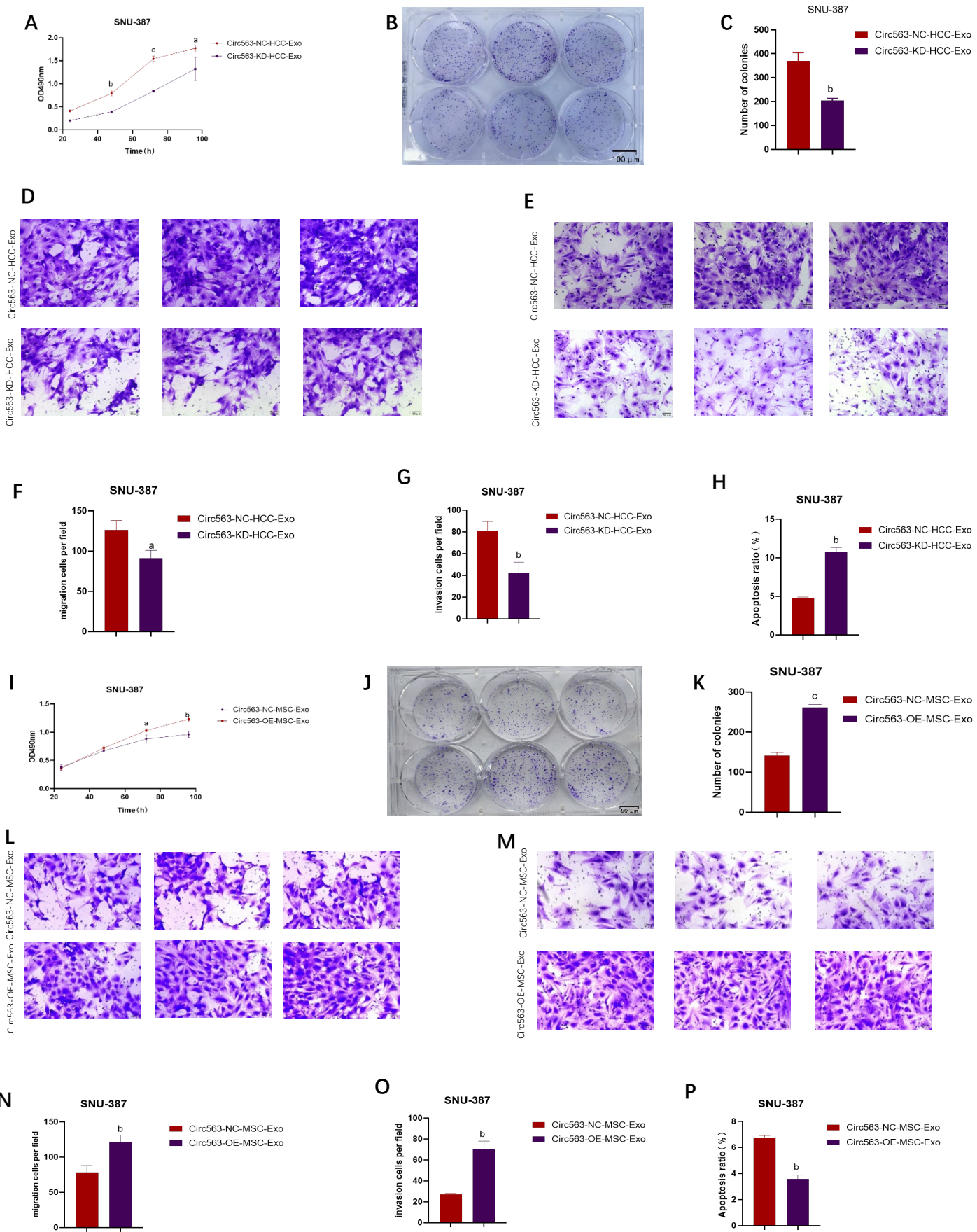
Supplementary Figure 1. Both mesenchymal stem cells (MSCs) and MSC-derived exosomes blocked the hepatocellular carcinoma cell proliferation and invasion and induced apoptosis, as well as the regulation of miR-148a-3p and metal-regulatory transcription factor-1 (MTF-1) expression, in SNU387 cells

(A–C) Assessment of proliferation of SNU387 cells co-cultured with MSC. (D–G) Assessment of the migration and invasion of SNU387 cells following co-incubation with MSC using Transwell assays. (H) Assessment of apoptosis of co-cultured SNU387 cells, as determined by flow cytometry. (I) Exosome intake by SNU387 cells is shown. (J–P) SNU387 cell viability and metastasis were suppressed after exposure to MSC-derived exosomes, whereas apoptosis was enhanced (Q). (R) Comparison of miR-148a-3p and MTF-1 expression levels in MSC- and HCC-derived exosomes. (S) Assessment of miR-148a-3p and MTF-1 levels in HCC cells co-cultured with MSC and MSC-derived exosomes. Quantitative data from three independent experiments are shown as the mean \pm SD (error bars). ^aP<0.05 ^bP<0.01, ^cP<0.001



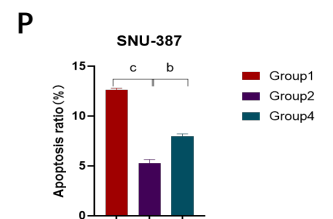
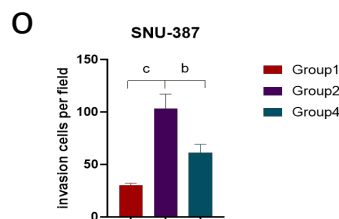
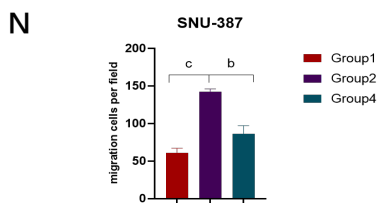
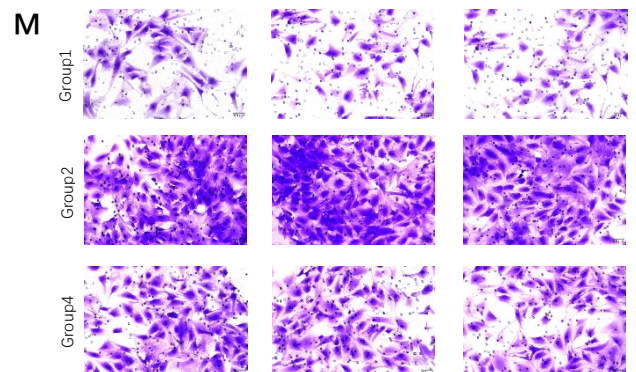
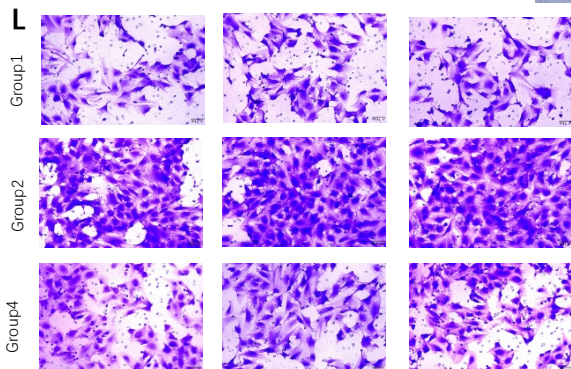
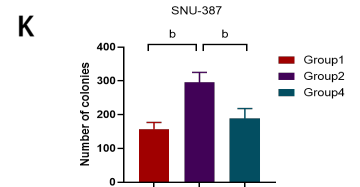
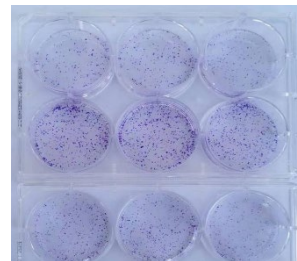
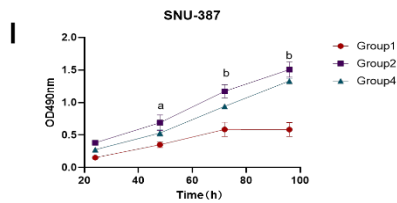
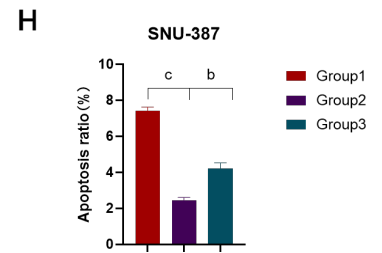
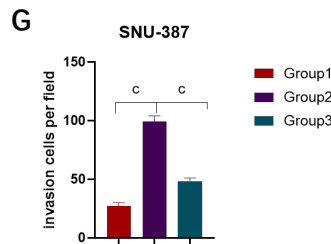
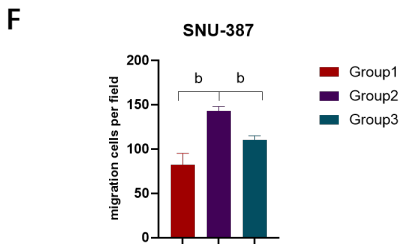
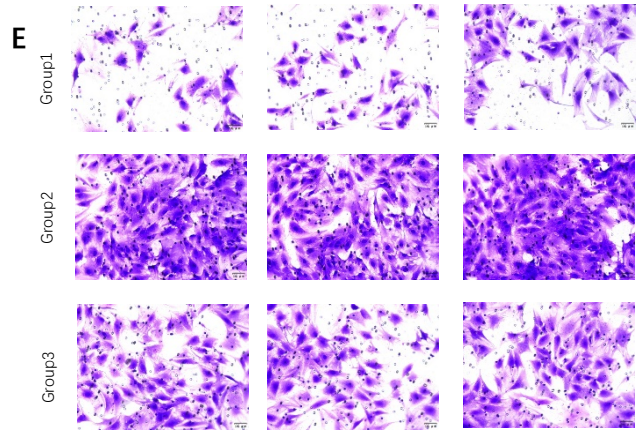
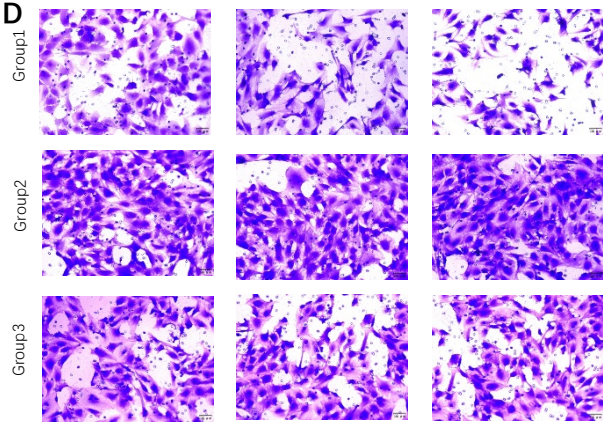
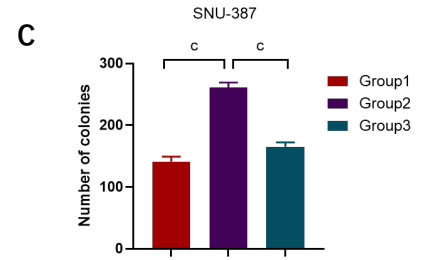
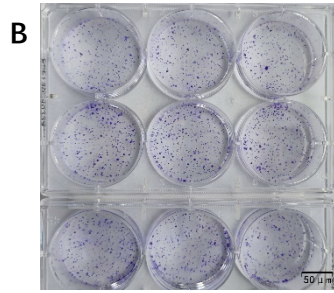
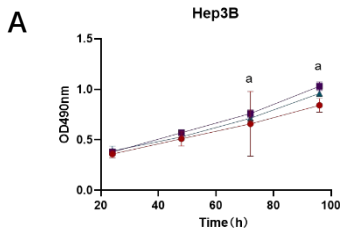
Supplementary Figure 2. Knockdown of hsa_circRNA_0000563 (circ563) resulted in the suppression of SNU387 cell proliferation and metastasis.

(A) The knockdown efficiency was verified by real-time polymerase chain reaction (RT-PCR). (B) The expression level of circ563 in exosomes of SNU387 cells and MSC was assessed by RT-PCR. (C, D) 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide and colony-forming assays indicated that circ563 depletion blocked the SNU387 cell proliferation and reduced the number of colonies formed. (E) Knockdown of circ563 enhanced cell apoptosis, as assessed by flow cytometry. (F, G) Transwell assays revealed that decreased circ563 levels impaired the migratory potential and invasiveness of SNU387 cells. ^aP<0.05 ^bP<0.01, ^cP<0.001



Supplementary Figure 3. Exosomal circ563 promoted hepatocellular carcinoma (HCC) progression.

Cell function was analyzed after co-treatment with exosomes isolated from the culture medium of circ563-knockdown SNU387 cells. (A–C) Downregulation of exosomal circ563 (exo-circ563) led to a reduction in SNU387 cell proliferation and the number of colonies formed. (D–G) Decreased exo-circ563 levels suppressed the SNU387 cell migratory activity and invasiveness. (H) Downregulated exo-circ563 levels were correlated with apoptosis induction. In addition, the SNU387 cell proliferation, metastasis, and apoptosis rates were assessed following treatment with exosomes of circ563-overexpressing mesenchymal stem cells. (I–O) Exo-circ563 induced HCC cell proliferation, migration, and invasion. (P) Flow cytometry analysis showed that the percentage of apoptotic cells was significantly decreased. ^aP<0.05 ^bP<0.01, ^cP<0.001



Supplementary Figure 4. The tumor-promoting potential of exosomal circ563 was reversed by either miR-148a-3p upregulation or metal-regulatory transcription factor-1 (MTF-1) knockdown.

(A-P) Exosomal circ563 (exo-circ563) facilitated SNU387 cell proliferation and invasion, and these effects were reversed by both miR-148a-3p overexpression and metal-regulatory transcription factor-1 (MTF-1) depletion. Group 1: Co-culturing SNU387 cells with mesenchymal stem cells (MSC)-derived exosomes; Group 2: Co-culturing SNU387 cells with exosomes derived from circ563-overexpressing MSCs; Group 3: Co-culturing SNU387 cells after miR-148a-3p upregulation with exosomes derived from circ563-overexpressing MSCs; Group 4: Co-culturing SNU387 cells after MTF-1 knockdown with exosomes derived from circ563-overexpressing MSCs. ^aP<0.05 ^bP<0.01, ^cP<0.001