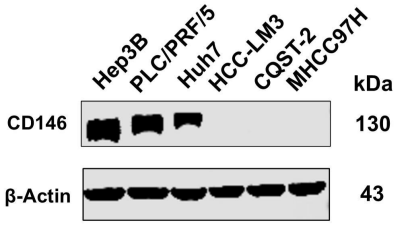
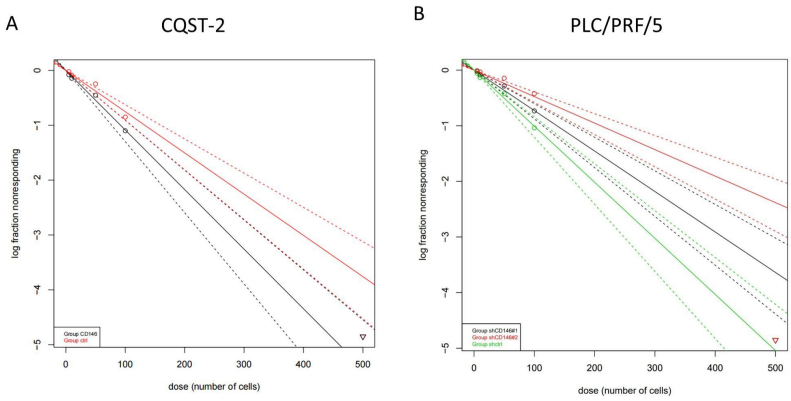
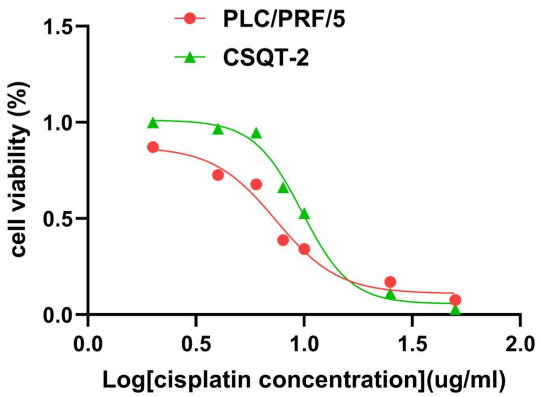
**Supplementary Fig. 1** Western blot analysis of CD146 in HCC cells.



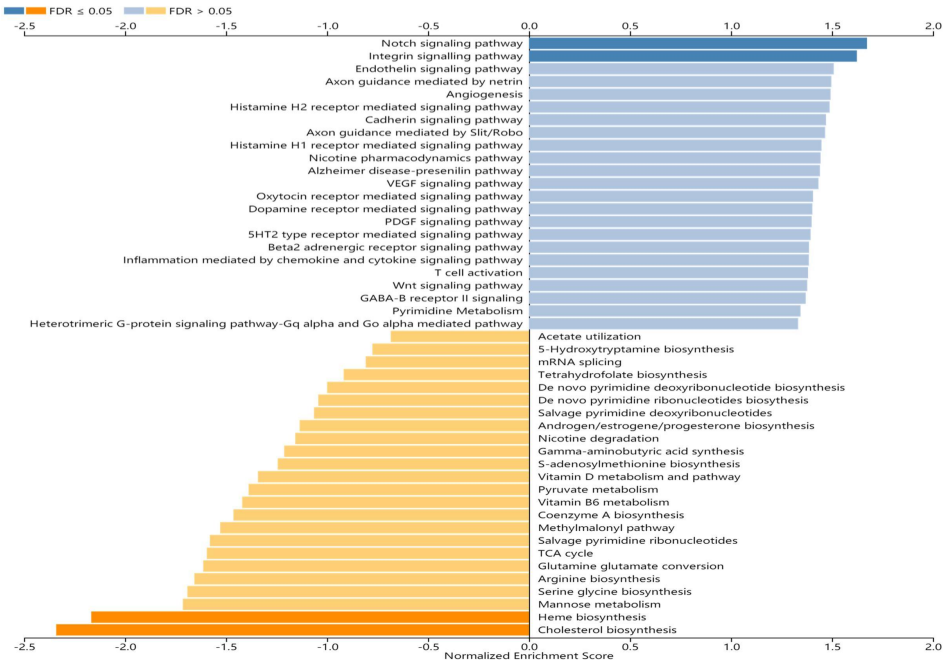
**Supplementary Fig. 2** The Extreme limiting dilution analysis (ELDA) were performed to testing the viability of CD146 in CSQT-2-C , CSQT-2-CD146 (A), PLC/PRF/5-shCtrl, PLC/PRF/5-shCD146#1, PLC/PRF/5-shCD146#2 cells (B).



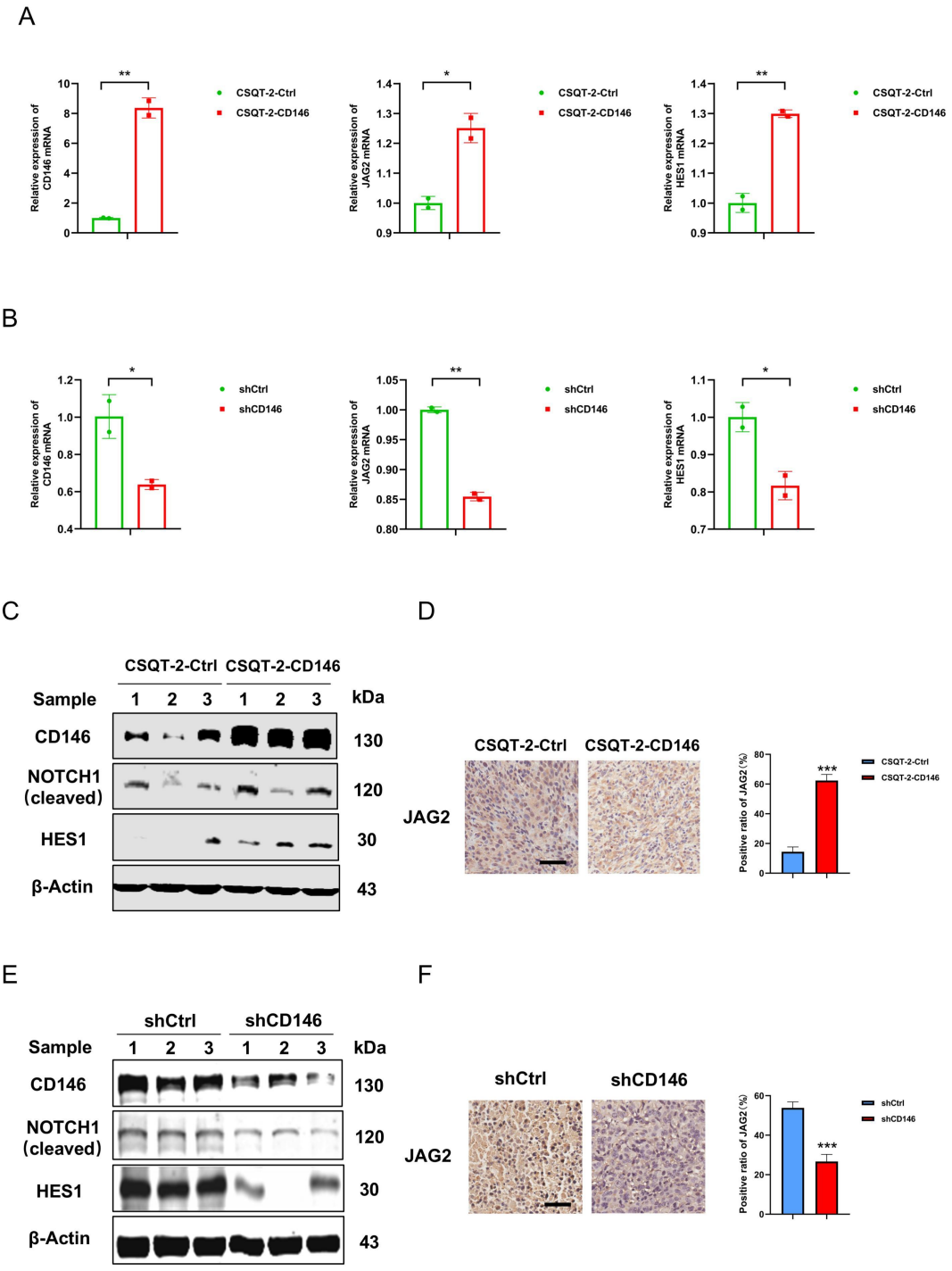
**Supplementary Fig. 3** Half maximal inhibitory concentration (IC50) were determined of cisplatin in CSQT-2 and PLC/PRF/5 cells.



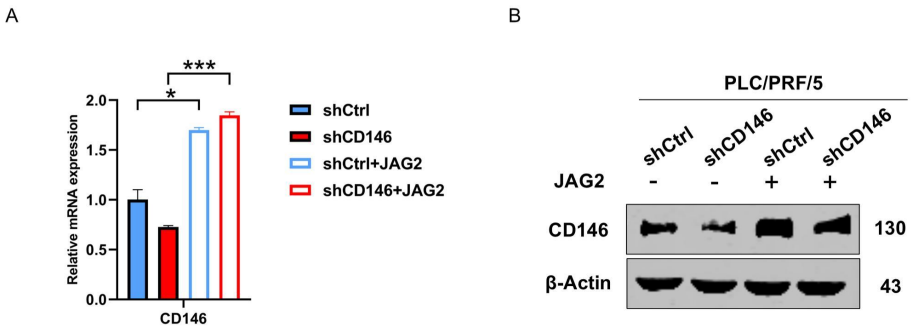
**Supplementary Fig. 4** Correlation between CD146 and Notch signaling pathway in TCGA database (HCC).



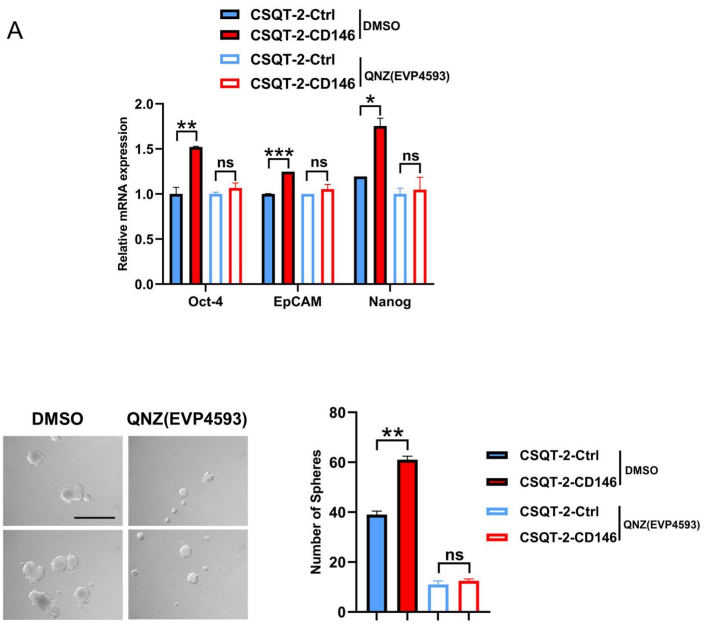
**Supplementary Fig. 5** CD146 activates Notch signaling pathway in vivo. **A** RT-qPCR analysis of *CD146*, *JAG2* and *HES1* were executed in CSQT-2-CD146 cells-derived tumor tissues and CSQT-2-Ctrl cells-derived tumor tissues from mice. **B** RT-qPCR analysis of *CD146*, *JAG2* and *HES1* were executed in shCtrl cells-derived tumor tissues and shCD146 cells-derived tumor tissues from mice. **C** CD146, NOTCH1 and HES1 in CSQT-2-CD146 cells-derived tumor tissues and CSQT-2-Ctrl cells-derived tumor tissues from mice were detected by western blotting. **D** IHC analysis of JAG2 in CSQT-2-CD146 cells-derived tumor tissues and CSQT-2-Ctrl cells-derived tumor tissues from mice. Representative images (Left), Scale bars = 100 μm and quantification of expression of JAG2 in three regions of an image (Right) were shown. **E** CD146, NOTCH1 and HES1 in PLC/PRF/5-shCtrl cells-derived tumor tissues and PLC/PRF/5-shCD146 cells-derived tumor tissues from mice were detected by western blotting. **F** IHC analysis of JAG2 in PLC/PRF/5-shCtrl cells-derived tumor tissues and PLC/PRF/5-shCD146 cells-derived tumor tissues from mice. Representative images (Left), Scale bars = 100 μm and quantification of expression of JAG2 in three regions of an image (Right) were shown. Data are representative of at least three independent experiments and shown as mean ± s.d. (*$p$ <0.05; ***$p$ < 0.001;)


A
Relative expression of CD146 mRNA
CSQT-2-Ctrl
CSQT-2-CD146
Relative expression of JAG2 mRNA
Relative expression of HES1 mRNA
B
shCtrl
shCD146
C
CSQT-2-Ctrl CSQT-2-CD146
Sample
kDa
CD146
NOTCH1 (cleaved)
HES1
β-Actin
130
120
30
43
D
JAG2
Positive ratio of JAG2 (%)
E
shCtrl shCD146
F

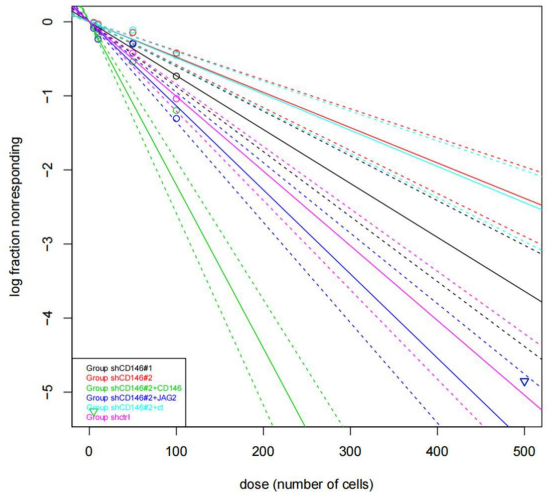
**Supplementary Fig. 6** JAG2 overexpression resulted in the upregulation of *CD146* in PLC/PRF/5 cells. **A** RT-qPCR analysis of *CD146* in shCtrl, shCD146, shCtrl with stably JAG2 overexpression, shCD146 cells with stably JAG2 overexpression. **B** The expression of CD146 in shCtrl, shCD146, shCtrl with stably JAG2 overexpression, shCD146 cells with stably JAG2 overexpression were measured by western blotting.



**Supplementary Fig. 7** CD146 regulates stemness of HCC depends on activating NF-κB signaling. **A** RT-qPCR analysis of *Oct-4*, *EpCAM*, *Nanog* were carried out in CSQT-2-Ctrl and CSQT-2-CD146 cells treated with DMSO or QNZ(EVP4593) (NF-κB signaling inhibitor, 5μM) for 24h. **B** Sphere formation ability of CSQT-2-Ctrl and CSQT-2-CD146 cells treated with DMSO or QNZ(EVP4593) (5μM) for 24h. Scale bars=120μm. Data are representative of at least three independent experiments and shown as mean ± s.d. (**p* <0.05; ***p* < 0.01; ****p* < 0.001; ns not significant).



**Supplementary Fig. 8** The Extreme limiting dilution analysis (ELDA) were performed to testing the viability of CD146 in shCtrl, shCD146#1, shCD146#2, shCD146#2 with control virus, shCD146#2 with stably CD146 overexpression, shCD146#2 with stably JAG overexpression PLC/PRF/5 cells.



**Supplementary Fig. 9** CD146/JAG2 affects prognosis of HCC patients. **A, B** Kaplan-Meier survival curve of disease-free (**A**) and overall survival survival (**B**) for patients with $CD146^{high}JAG2^{high}$ and $CD146^{low}JAG2^{low}$ in HCC patients from TCGA database. (*$p$ <0.05)