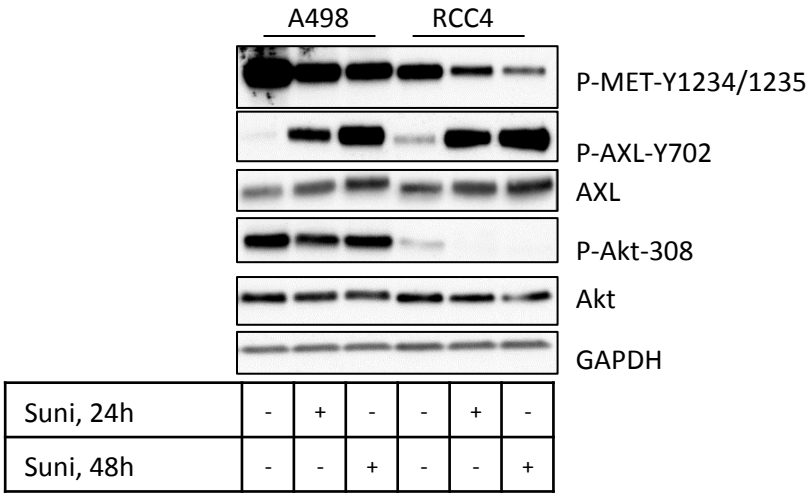
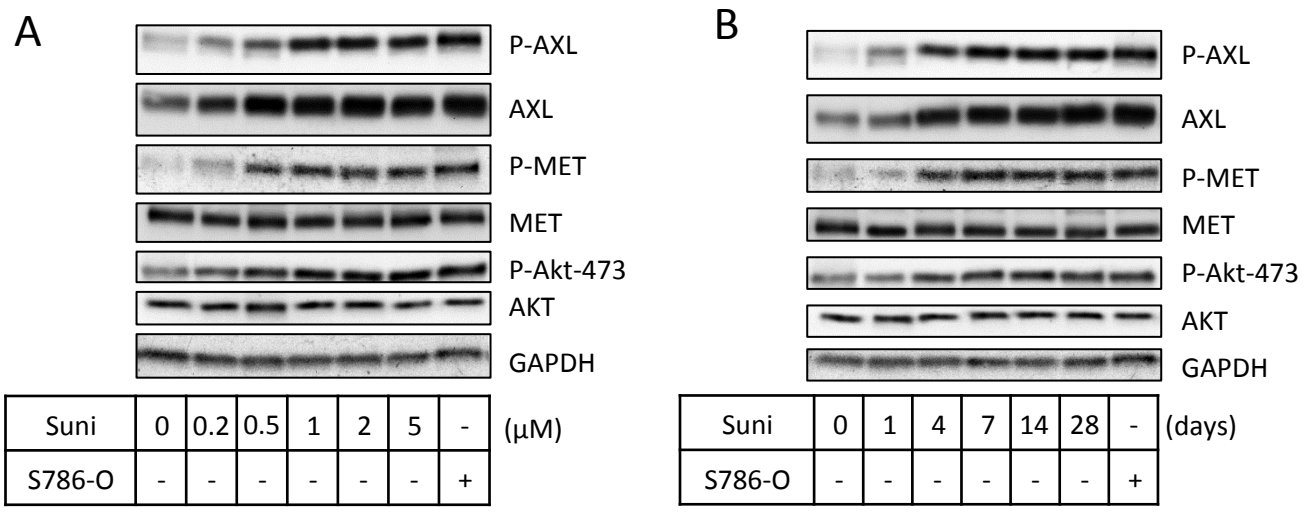
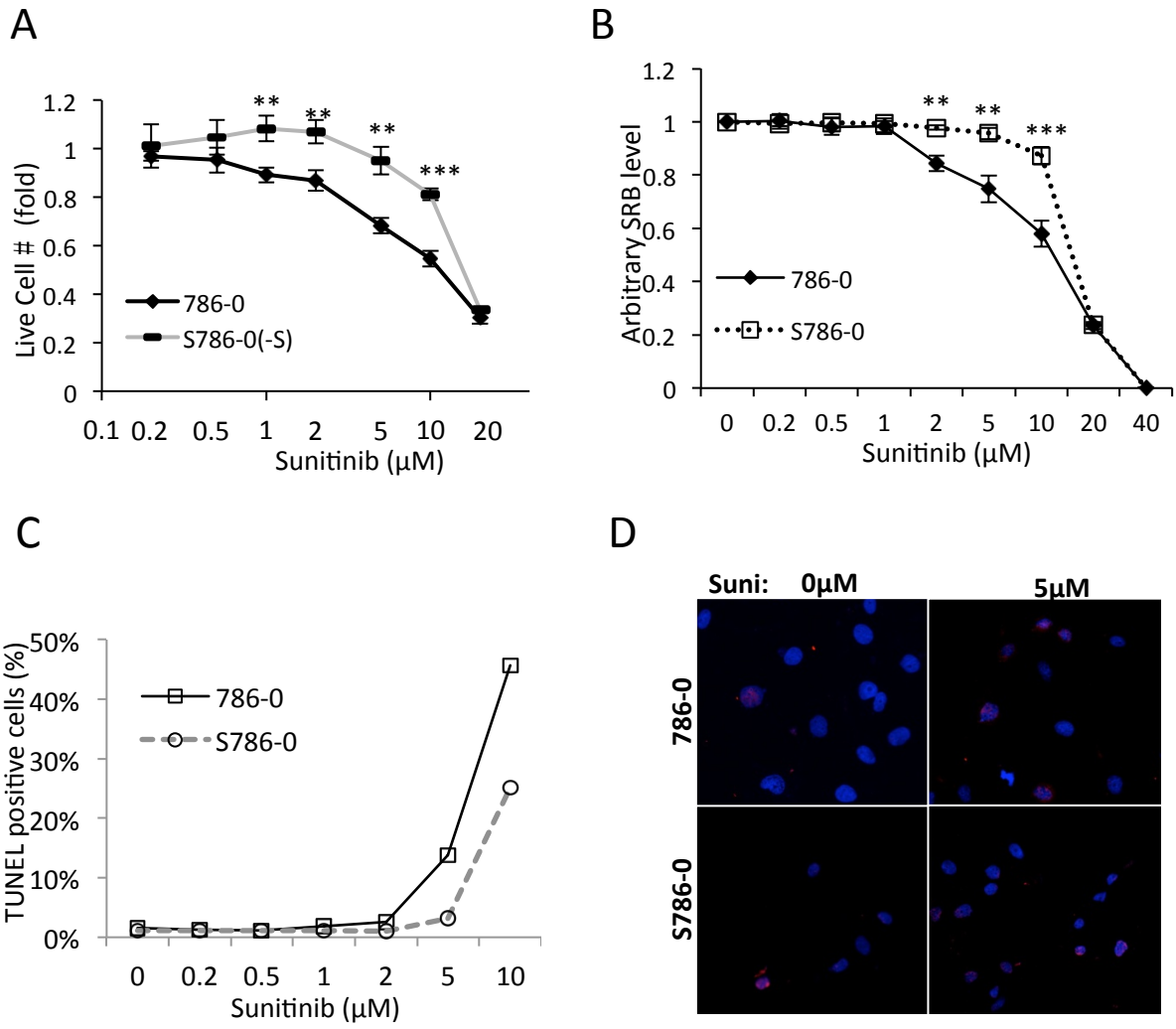
Supplementary Figure 1



Supplementary Figure S1. Acute sunitinib treatment elevated AXL protein and phosphorylation levels in RCC cells. A498 and RCC4 cells were treated with 1μM sunitinib (Suni) for 24 hours or 48 hours as indicated. The cells were lysed after treatment. All of the cell lysates were examined by western blot with specific antibodies as indicated.

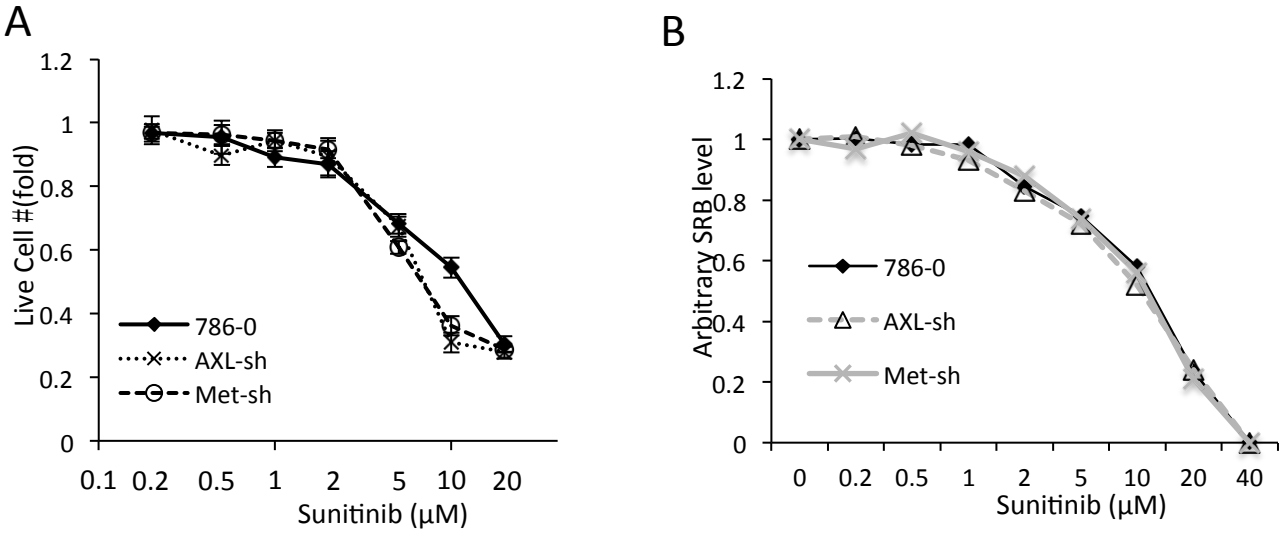


Supplementary Figure S2. 786-O cell develops sunitinib-resistance after two-weeks treatment of sunitinib at the dose of 1μM. (A) 786-O cells were treated with sunitinib at the concentration as indicated for 2 weeks. Then the cells were deprived of sunitinib for 24 hours. S786-O is the cell that were treated with 1μM sunitinib for over 6 months. The cells were lysed and analyzed with western blot with the antibodies as indicated. **(B)** 786-O cells were treated with sunitinib at 1μM for different time as indicated. Then the cells were deprived of sunitinib for 24 hours. S786-O is the cell that were treated with 1μM sunitinib for over 6 months. The cells were lysed and analyzed with western blot with the antibodies as indicated. The western blot represents 3 different repeats.



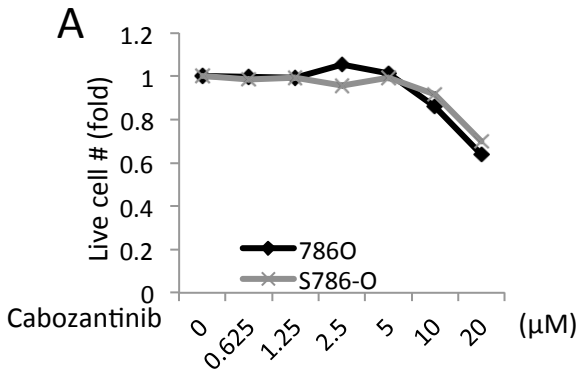
Supplementary Figure S3. Chronic sunitinib treated 786-O cells are more resistant to sunitinib retreatment. (A) Chronic sunitinib pre-treated 786-O cells that were removed from sunitinib for 24 hours and 786-O parental cells were treated with sunitinib for 24 hours at the concentrations as indicated. The living cells were counted and plotted (** indicates $p<0.01$, *** indicates $p<0.001$). **(B)** Chronic sunitinib pre-treated 786-O cells that were removed from sunitinib for 24 hours and 786-O parental cells were treated with sunitinib for 24 hours at the concentrations as indicated. The cytoxicity was evaluated by staining total cellular protein with Sulforhodamine B (** indicates $p<0.01$, *** indicates $p<0.001$). **(C)** Chronic sunitinib pre-treated 786-O cells that were removed from sunitinib for 24 hours and 786-O parental cells were treated with sunitinib for 24 hours at the concentrations as indicated. The cells were fixed and then stained with TUNEL TMR-Red. Over 500 cells were quantified for TUNEL positive cells. **(D)** The representative images for TUNEL staining (Red=DAPI, Red=TUNEL)

Figure S3



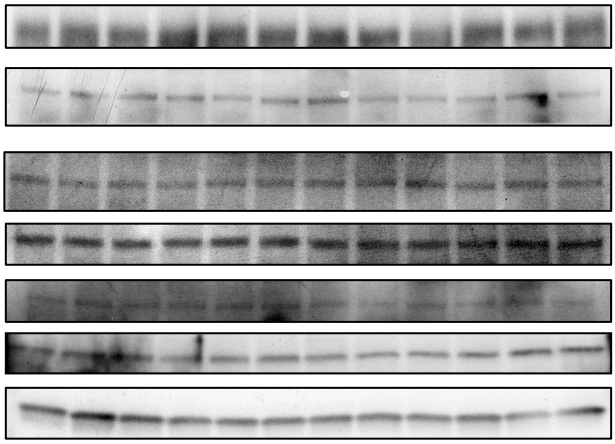
Supplementary Figure S4. AXL or MET deficiency did not alter cell proliferation rate in response to sunitinib treatment. (A) Chronic sunitinib pre-treated 786-O cells, 786-O cells that were stably expressed with *AXL* and *MET* shRNA constructs were treated with sunitinib for 24 hours at the indicated concentrations. The living cells were counted and plotted. (B) SRB

Figure S4



Supplementary Figure S5. Chronic sunitinib treatment did not alter cell proliferation rate in response to cabozantinib treatment. Chronic sunitinib pre-treated 786-O cells that were removed from sunitinib and 786-O parental cells were treated with cabozantinib for 24 hours at the concentrations as indicated. The living cells were counted and plotted (* indicates $p<0.05$, ** indicates $p<0.001$).

Figure S4



786-0	+				+				+			
S786-0		+				+				+		
AXL-sh			+				+				+	
MET-sh				+				+				+
Suni(1μM, 24h)					+	+	+	+				
Cab(5μM, 24h)									+	+	+	+

Supplementary Figure S6. TIE2, RET and KIT tyrosine kinases activity are not affect by sunitnib or cabozantinib. 786-O cells, 786-O cells that were stably expressed with *AXL* or *MET* shRNA constructs were chronically treated with sunitinib (1 μM) and then deprived of sunitinib for 24 hours, and 786-O parental cells were treated with sunitnib, cabozantinib or DMSO (lane 1-4) for 24 hours. The activity of RET and KIT were determined by western blot with specific antibodies. Tie2 protein were immunoprecipitated from 1000ug cell lysates, the total tyrosine phosphorylation were determined by western blot with antibody against phospho-tyrosine (pY-tie2).