Inhibition of autophagy:  
A key step leading to sunitinib resistance of renal cell carcinoma

Sunitinib, an oral tyrosine kinase inhibitor targeting particularly c-KIT, PDGFR α and β and VEGFR 1, 2, and 3, is one of the first-line therapy for metastatic renal cell carcinoma (RCC).

Sunitinib prolongs progression-free survival (PFS) in patients with metastatic RCC. However, in most cases, patients relapse after one year of treatment. Resistance is an important clinical outcome, but its underlying mechanisms are largely unknown. The anti-angiogenic role of sunitinib through a direct action on endothelial cells has been well described. However, the mechanism of action of sunitinib on tumor cells has been poorly addressed and need to be well understood to prevent resistance.

Damaged/obsolete macromolecules and organelles are engulfed by a double-membrane phagophore, called autophagosome, that fuses with a lysosome for the degradation of the ingested material. Interestingly, Sunitinib which is a basic drug, is extensively sequestered into lysosomes. Ours results indicate a disruption of the autophagy/lysosome degradation pathway most likely due to a defective degradation of auto-lysosomes by an increase of the intra-lysosomal pH.

In the literature, autophagy inhibition is known to create a pro-inflammatory context through accumulation of pro-inflammatory cytokines. In this way, we observed that sunitinib treatment leads to secretion of many pro-inflammatory cytokines that promote macrophages proliferation and migration.

Thus, this study suggests that blockade of autophagy by sunitinib creates alternative proliferative/survival pathways through the modification of the secretome and modification of microenvironmental cells. An increased secretion of pro-inflammatory cytokines is associated with bad prognosis and RCC aggressiveness and could explain acquired drug resistance.