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Resistance to lysosomotropic drugs used for renal cell carcinoma and breast cancer: Autophagy and inflammation converge in inducting CXCL5

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Lysosomotropic agents such as sunitinib, lapatinib, and chloroquine belong to a drug family that is being used increasingly in treatment of advanced cancers. The anti-angiogenic multi-kinase inhibitor, sunitinib, is standard care for metastatic renal cell carcinomas (mRCC). However, patients ineluctably relapse with a delay varying from a few months to a few years. To improve reactivity prior to relapse it is essential to identify the mechanisms leading to such variability. We showed previously that sunitinib became sequestered in lysosomes because of its basic pKa. We now show that this stress induced an incomplete autophagic process leading to activation of the Nuclear Factor kappa B (NF□B) inflammatory pathway. By scrutinizing the transcriptomic and proteomic analysis of sunitinib treated cells we defined a subset of inflammatory cytokines that were up-regulated by the drug either after an acute or chronic stimulus. One of the most up-regulated genes in resistant cells was the CXCL5 cytokine. CXCL5 was also induced in RCC by chloroquine and in a model of HER2 positive breast cancer cell lines after acute or chronic treatment with lapatinib, another lysomotropic drug used for trastuzumab-refractory cancers. Importantly, we showed that the levels of CXCL5 present in the plasma of patients treated with sunitinib were predictive of the efficacy of sunitinib but not of the VEGF-directed antibody bevacizumab. Thus, this work is a translational study that leads to the discovery of a relevant biomarker of efficacy of a lysosomotropic drug for personalized medicine.

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