Abstract

Anti-angiogenic agents currently used in clinic target the vascular endothelial growth factor (VEGF) signaling pathway via an anti-VEGF antibody (bevacizumab, Avastin®) or small-molecule receptor tyrosine kinase inhibitors (RTKIs). Among these inhibitors, sunitinib (SUTENT®, Pfizer) and sorafenib (Nexavar®, Bayer and Onyx), two multi-RTKI also provides clinical benefit to patients with renal cell carcinoma or advanced gastrointestinal stromal tumors (GISTs). While these drugs were expected to increase the overall survival or progression-free survival of patients, the survival benefits of anti-angiogenic drugs have been relatively modest. Alarmingly, preclinical studies have reported increased tumor growth and metastatic formation after the withdrawal of treatment with VEGF receptor inhibitors. However, the mechanisms governing resistance that occur both in tumor cells and in the tumor microenvironment are still poorly understood. Fundamentally, cancer cells differ from normal cells regarding how their metabolic pathways are used to fuel cellular growth and survival. Throughout this work, we aim at understanding and evaluating the processes leading to tumor adaptation to angiogenesis inhibitors.

In this work, we have used a model of human MDA-MB-231 and HT-29 xenografts, tumors shrank and metastases were inhibited, whereas treatment withdrawal accelerated tumor regrowth and metastatic dissemination to different organs. Similar effects were observed with a transgenic model of MMTV-PyMT mice and syngeneic mouse models of 4T1 and LLC tumors. Multidisciplinary approaches including transcriptomics, proteomics, metabolomics through Nuclear Magnetic Resonance spectroscopy (NMR), as well as histochemical and biochemical analyses revealed a shift toward glycolytic phenotype during TKI treatment and lipid metabolism and increased TCA activity after TKI treatment withdrawal, which is associated with rapid tumor regrowth and accelerated metastatic dissemination. We also demonstrated the functional implications of lipogenesis and fatty acid synthase (FASN) in this process by the blockade of tumor relapse through pharmacological inhibition and downregulation of FASN with orlistat and shRNA, respectively.

In order to elucidate the nature of lipids deposited in tumors after treatment withdrawal, we implemented a method for the identification and the localization of specific low-abundant isobaric lipids in cancer xenografts by FTICR MALDI imaging coupled with electrospray mass spectrometry (LC-ESI-MS).

Overall, by providing a detailed metabolic profile of tumor adaptation during and after RTKI treatment, our study sheds light on recent alarming clinical data reporting that RTKI treatment break could boost cancer malignancy.