Stearoyl-CoA Desaturase-1 drives cancer malignancy via lipid desaturation and peroxidation after anti-angiogenic treatment withdrawal

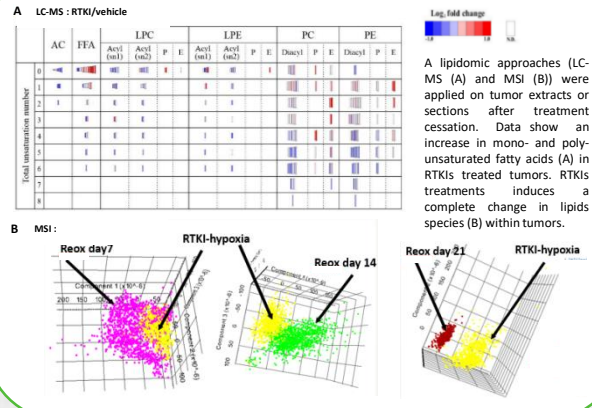
Geraldine Luis [1], Adrien Godfroid[1], Jonathan Cimino[1], Shin Nishiumi [2] , Agnes Noel[1] , Masaru Yoshida [2] and Nor Eddine Sounni[1].
[1] Laboratory of Tumor and Development Biology, GIGA-Cancer, University of Liège. Belgium;
[2] Division of Gastroenterology, Department of internal medicine, Kobe University, Japan

Introduction

Targeting the metabolic pathways in cancer is actually the most contemporary topic of drug discovery. The unique metabolic requirement of cancer cells to sustain proliferation and survival pave the way for innovative therapeutic intervention. In this regard, we have contributed to the emergence of new facet of cancer adaptation and evasion to anti-angiogenic therapy. We previously show that tumor adaptation to angiogenesis inhibitors relies on a metabolic reprogramming towards *de novo* lipogenesis after treatment cessation that was associated with tumor aggressiveness. The concept of targeting lipid metabolism to improve efficacy of targeted therapy has been validated by sequential targeting VEGF pathway and FASN in cancers. Whereas FASN is recognized as an important target in the development of anticancer drug for many types of human cancers, its complete inhibition has showed poor pharmacokinetics with heavy side effects, highlighting the need for the identification of new therapeutic targets that inhibit lipid metabolism.

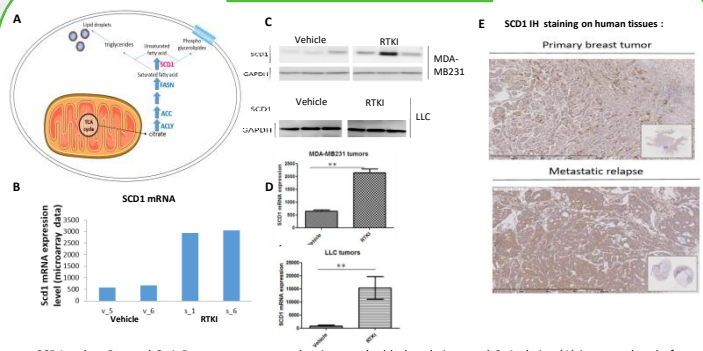
Results

1 Lipidomics analyses



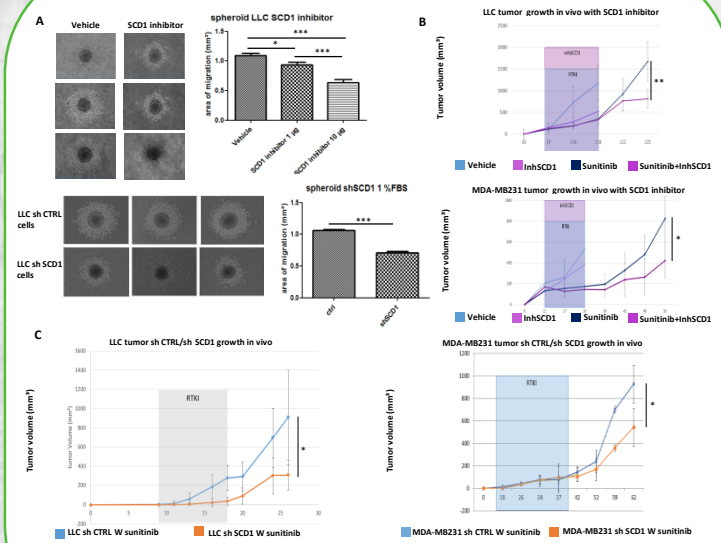
A lipidomic approaches (LC-MS (A) and MSI (B)) were applied on tumor extracts or sections after treatment cessation. Data show an increase in mono- and poly-unsaturated fatty acids (A) in RTKIs treated tumors. RTKIs treatments induces a complete change in lipids species (B) within tumors.

2 SCD1 expression



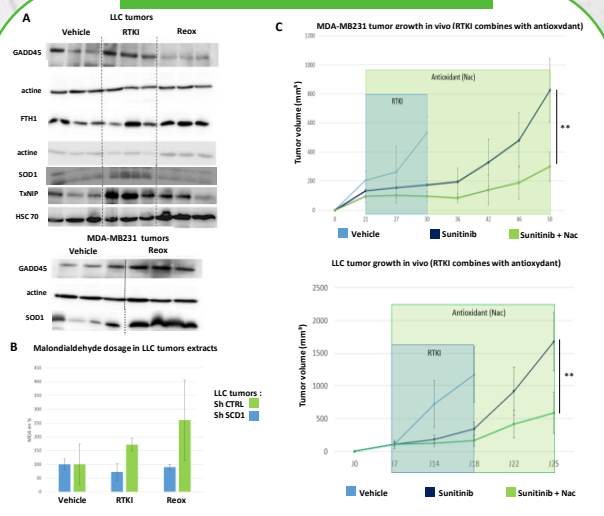
SCD1, a key Stearoyl-CoA Desaturase enzyme that inserts double bonds into acyl-CoA chains (A) is upregulated after tumor re-oxygenation. Data from microarray analysis (B), western blot (C) and qRT-PCR (D) were performed on tumor extracts. SCD1 expression was also validated in human breast cancer samples with a marked increase in both primary tumors and metastases after relapse to hormone or chemotherapy (E).

3 Inhibition of SCD1 reduces tumor growth



Inhibition of SCD1 by shRNA or by small SCD1 inhibitors in LLC and MDA-MB231 cancer cells showed a marked reduction in spheroid migration in vitro (A). In vivo, primary tumor growth and re-growth after re-oxygenation was delayed (B and C).

4 Oxidative stress in response to RTKI



Unsaturated lipids are known to play a role in cell membrane fluidity and can be peroxided by reactive oxygen species (ROS). Interestingly, the levels of oxidative stress markers SOD1, catalase, TxNiP, GADD45 were increased in tumors during and after anti-angiogenic treatment (A). Measurement of the lipid peroxidation product malondialdehyde (MDA) showed a marked increase in tumors after re-oxygenation (B). Importantly, administration of anti-oxidant NAC mimics the effect of SCD1 inhibition in vivo by enhancing the efficacy of anti-angiogenic treatments (C).

Conclusion

SCD1 expression seems to be important for cancer cells to sustain the oxidative stress occurring after RTKIs treatment withdrawal and re-oxygenation. SCD1 inhibition reduces the level of neo synthesized of saturated lipids and MUFA/PUFA. Thus, interaction of MUFA/PUFA with ROS enhances lipid peroxidation end products (MDA), which correlates with increased tumor aggressiveness after tumor re-oxygenation. Interestingly, inhibition of SCD1 by shRNA or by pharmacological inhibitors or administration of antioxidant resulted in increased efficacy of RTKI post treatment.

Presenting authors: Geraldine Luis
University of Liège, avenue Hippocrates 13 4000 Liège
Belgium, Geraldine.luis@uliege.be
nesounni@uliege.be