

Importance of fatty acid desaturation in tumor growth and oxidative stress response occurring during antiangiogenic treatment

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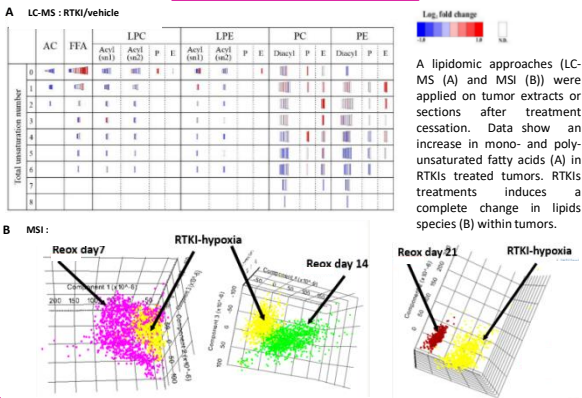
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Introduction

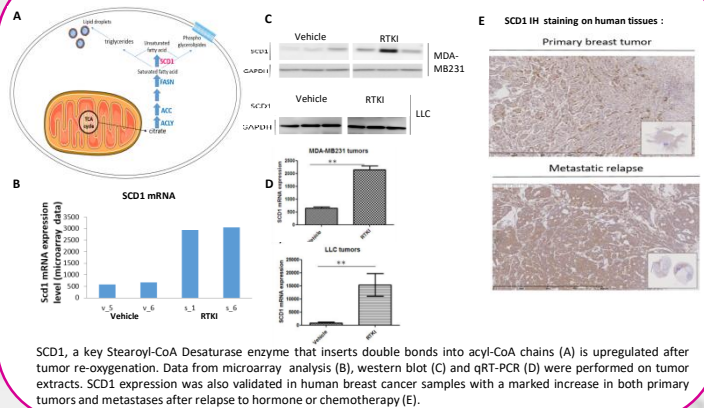
Targeting the metabolic pathways in cancer is actually the most contemporary topic of drug discovery. The unique metabolic requirement of cancer cells to sustain proliferation and survival pave the way for innovative therapeutic intervention. In this regard, we have contributed to the emergence of new 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

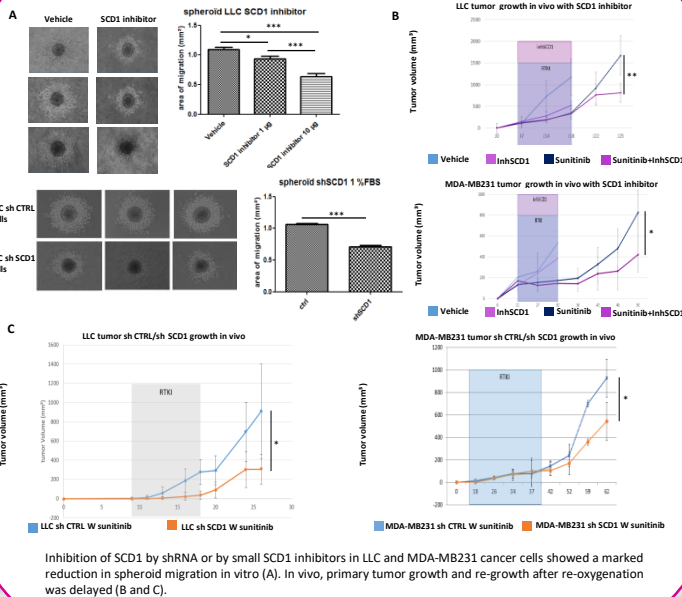
1 Lipidomics analyses



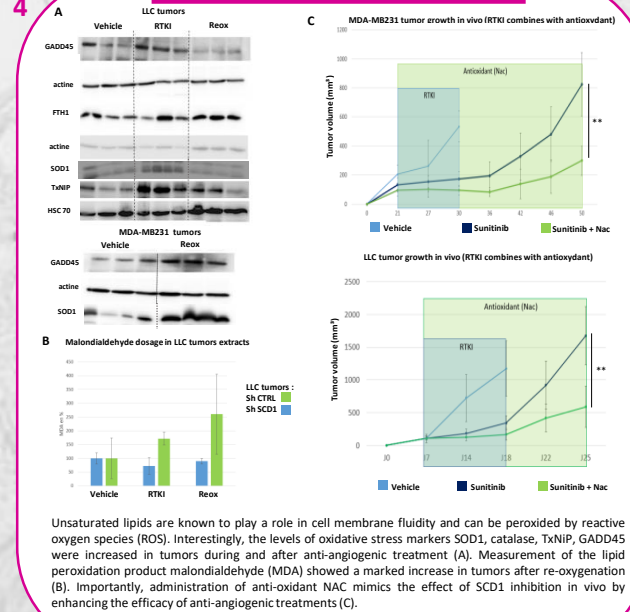
2 SCD1 expression



Inhibition of SCD1 reduces tumor growth



Oxidative stress in response to RTKI



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.