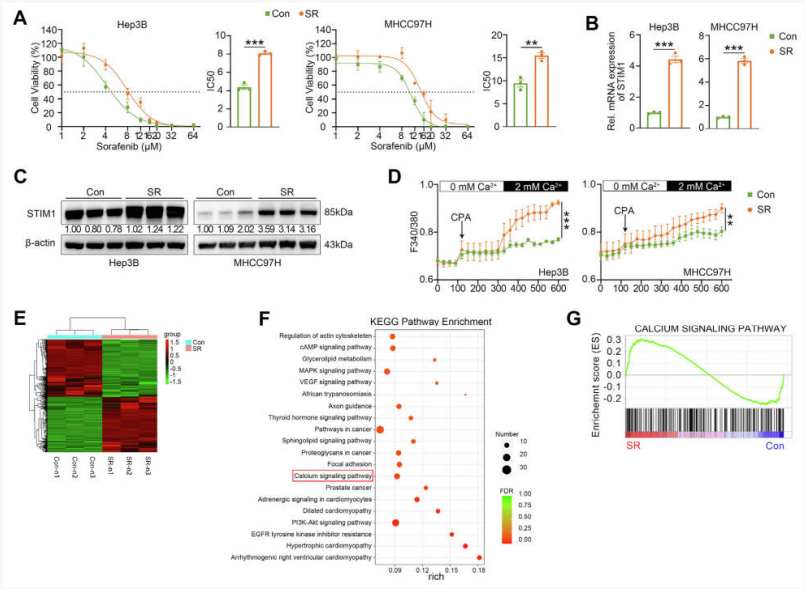
# STIM1: the cancer shield against sorafenib unmasked

GA, UNITED STATES, March 7, 2025 /EINPresswire.com/ -- A recent study unveils how stromal interaction molecule 1 (STIM1), a protein involved in calcium signaling, plays a pivotal role in the resistance of liver cancer to sorafenib, a key treatment for advanced hepatocellular carcinoma (HCC). The research demonstrates that STIM1 suppresses ferroptosis, a form of cell death essential for sorafenib's efficacy, enabling cancer cells to withstand treatment. These findings present new opportunities to tackle drug resistance and improve therapeutic outcomes for liver cancer patients.



The level of STIM1 is elevated in SR-HCC cell models.

Hepatocellular carcinoma hepatocellular carcinoma (HCC), the most common form of liver cancer, accounts for 90% of cases worldwide and remains a major health burden. Sorafenib, the primary treatment for advanced HCC, is frequently thwarted by the cancer's ability to develop resistance within months of therapy. Calcium signaling—a crucial process in cell proliferation, apoptosis, and drug response—has been implicated in this resistance, yet its exact role remained unclear. Bridging this knowledge gap could pave the way for more effective treatments.

Conducted by Chongqing University Cancer Hospital and published (DOI: 10.1016/j.gendis.2024.101281) in Genes & Diseases on March 28, 2024, the study investigates the role of stromal interaction molecule 1 (STIM1) in sorafenib resistance. By examining resistant HCC cell lines and animal models, researchers identified a mechanism where STIM1-mediated calcium signaling suppresses ferroptosis through the activation of SLC7A11, a key player in glutathione synthesis. This pathway was pinpointed as a promising target to overcome resistance.

The study reveals STIM1's central role in enabling resistance to sorafenib. Elevated levels of STIM1 in resistant cells enhance store-operated calcium entry (SOCE), which triggers the SOCE-CaN-NFAT pathway. This cascade upregulates solute carrier family 7 member 11 (SLC7A11), boosting glutathione production to neutralize oxidative stress and prevent ferroptosis—a critical cell death process targeted by sorafenib.

Experimental findings underscore the therapeutic potential of disrupting this pathway. The deletion of STIM1 reinstated ferroptosis sensitivity in resistant cells, while the SOCE inhibitor SKF96365, combined with sorafenib, significantly reduced tumor growth in cell and animal models. This combination therapy not only reduced SLC7A11 levels but also amplified oxidative stress and lipid peroxidation, effectively reversing drug resistance.

Dr. Yongsheng Li, the study's senior researcher, emphasized, "Our findings underline the crucial role of STIM1 in driving sorafenib resistance in HCC. Targeting the STIM1-SOCE-CaN-NFAT axis represents a novel and promising strategy to restore drug sensitivity and advance personalized treatments for liver cancer."

This discovery offers a foundation for new combination therapies targeting STIM1-mediated pathways, enhancing the effectiveness of existing treatments and potentially extending these insights to other cancers. As researchers explore the broader applications of this mechanism, the findings highlight the potential to significantly improve patient outcomes and combat drug resistance across a range of malignancies.

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