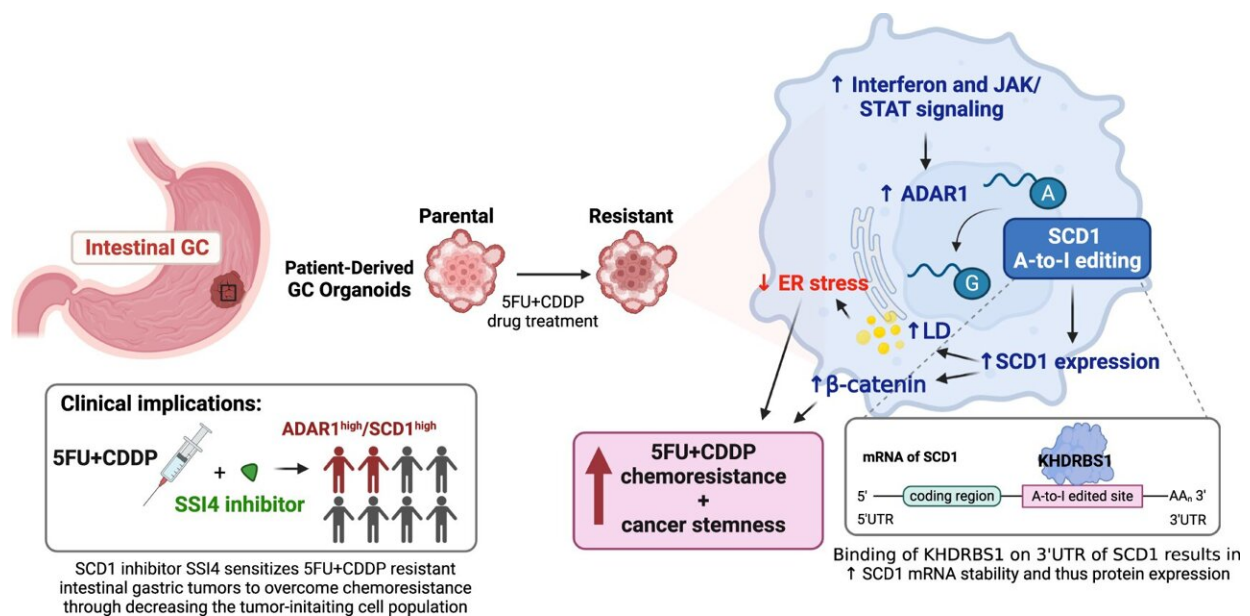


Study discovers novel molecular mechanism driving chemoresistance and tumor recurrence in gastric cancer

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Proposed model for chemoresistance driven by ADAR1-upregulated SCD1 in gastric cancer. Credit: *Nature Communications* (2023). DOI: 10.1038/s41467-023-38581-8

A research team led by Professor Stephanie Ma Kwai-ye from School of Biomedical Sciences, LKS Faculty of Medicine, the University of Hong Kong (HKUMed) has uncovered a novel signaling pathway by which RNA editing governs lipid metabolism to promote resistance to

chemotherapy and cancer stemness in gastric cancer. The findings have been published in *Nature Communications*.

Gastric cancer (GC) remains one of the leading causes of cancer-related deaths both globally and in Hong Kong. To combat GC, 5-fluorouracil (5-FU) and platinum-based combination chemotherapy is often administered in addition to [surgical resection](#), in the hope of increasing the effectiveness of surgery or to minimize the chance of cancer recurrence. However, the emergence of acquired chemoresistance eventually curtails the long-term clinical benefits.

The myriad mechanisms driving chemoresistance, compounded with GC constituting various subtypes obscure the identification of targets to override chemoresistance. Therefore, understanding subtype-specific vulnerability to override resistance to chemotherapy is fundamental to designing improved treatment options for this [deadly disease](#).

Research method and findings

The research team discovered an unreported mechanism driving chemoresistance by which dysregulated editing at the RNA level instigates aberration in [lipid metabolism](#) to endow chemoresistance and cancer stemness.

By integrating clinical intestinal gastric cancer patient-derived organoid lines trained to mimic 5-FU+ cisplatin resistance, multi-omic profiling and validation in pre-clinical GC mouse models, the research team found that the chemotherapy-resistant organoids displayed greater interferon and JAK/STAT signaling, which upregulated ADAR1 expression. ADAR1, an enzyme that dictates the editing of RNA, fosters a dysregulated lipid network via the editing of multiple enzymes involved in lipid metabolism, including a key enzyme, SCD1.

The editing of SCD1 RNA enhanced the stability of mRNA and thereby increased SCD1 protein expression. Consequently, SCD1 facilitated lipid droplet formations and β -catenin abundance to confer resistance to chemotherapy as well as a more cancer stemness state. To apply the findings for clinical use, the team further demonstrates that supplementation of an SCD1 inhibitor (SSI4) to a chemotherapy regimen could reverse chemoresistance in gastric cancer and reduce the tumor-initiating subset.

"Our findings identified dysregulated editing at the RNA level of lipid metabolic genes as a novel molecular mechanism underlying [resistance](#) to chemotherapy in gastric cancer. By targeting edited SCD1, we can reverse chemoresistance and [cancer](#) stemness. This research has laid the foundation for the future development of new treatments for this deadly disease," said Professor Stephanie Ma Kwai-ye of the School of Biomedical Sciences, HKUMed, who initiated the study.

"Further, ADAR1 expression and SCD1 may also be good biomarkers for predicting response to chemotherapy in [gastric cancer](#) patients. This spares the patients from going through unnecessary [chemotherapy](#) and allows them to carry on more effective treatment," said Kwai-ye.

More information: Tin-Lok Wong et al, ADAR1-mediated RNA editing of SCD1 drives drug resistance and self-renewal in gastric cancer, *Nature Communications* (2023). [DOI: 10.1038/s41467-023-38581-8](#)

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