Combining the old and new to kill cancer cells

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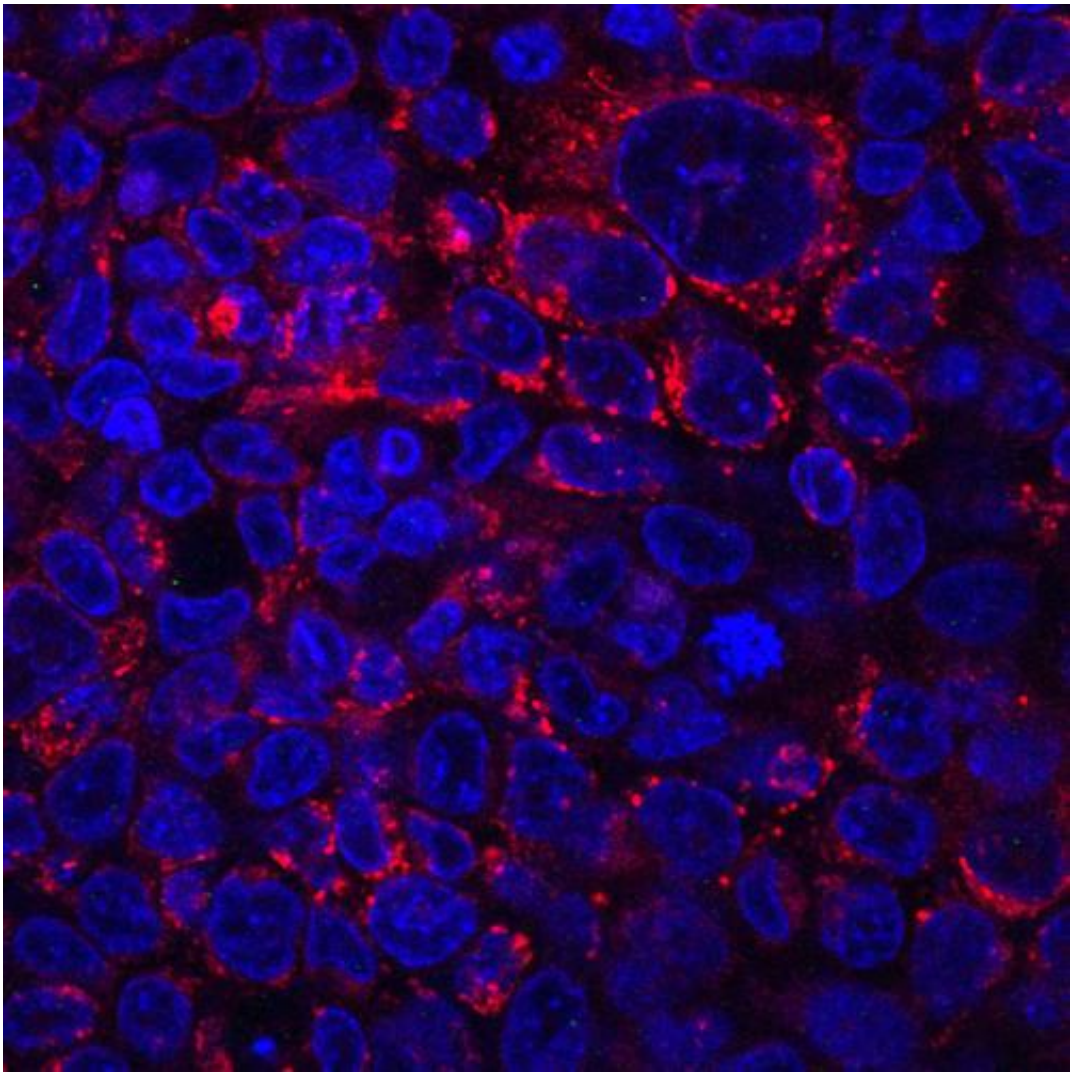

Removal of enzyme CK1α blocks cellular digestion in specific cancers. Credit: Dr. Jit Kong Cheong / Duke-NUS Graduate Medical School Singapore

A team of Singapore based scientists have found that pairing a new approach with an old drug may be an effective approach to treat common cancers. In a landmark study, Professor David Virshup and Dr. Jit Kong Cheong, from Duke-NUS Graduate Medical School Singapore (Duke-NUS), identified a new signalling pathway that regulates the internal diet of cancers.

Hitting this cellular nutritional pathway with a one-two punch stopped the growth of colon and bladder cancers, in experimental systems. The therapy used an old anti-malarial drug, combined with the inhibition of an enzyme called Casein Kinase 1 alpha (CK1α). This novel drug combination was uncovered because of the team's discovery of a feedback loop in cancer cells driven by a mutated gene, known as RAS and its regulation of CK1α.

The notorious RAS oncogene drives 30% of all human cancers in its mutated form. However, till now, scientists have found it difficult to directly target mutant RAS. Mutant RAS alters the cells' internal nutritional state via a process called autophagy.

The Duke-NUS team showed that mutant RAS controls autophagy via a Casein kinase 1α (CK1α)-dependent feedback loop. To sustain growth and stop cancer cells from self-cannibalism, mutant RAS makes lots of CK1α, a highly-active protein kinase. The research team found that CK1α is the Achilles heel of RAS-driven cancer cells.

A combination of CK1α blockade by the experimental drug D4476, and inhibition of autophagy by the anti-malarial chloroquine, was then tested and found able to effectively treat RAS-driven human colon and bladder tumours that were grown in laboratory mice.

"To our knowledge, this is the first report that shows the combined pharmacological targeting of CK1α and autophagy can be used to

combat these types of cancer," said first author, Dr. Cheong. "Our findings provide the mechanistic basis of exploring combination therapies involving pharmacological targeting of CK1α and autophagy."

The team speculates that the new drug combination therapy could help to slow down or cure some human cancers with mutant RAS, such as those that originate from the colon and the bladder. They also infer that patients with pancreatic cancers and some lung cancers may benefit from this drug combination therapy, as the RAS oncogene is frequently mutated in these cancers.

"This is an exciting lead. We hope to identify more potent and specific inhibitors of CK1α to combine with autophagy inhibitors," said senior author Prof. Virshup, who is the Director of the Cancer and Stem Cell Biology Programme at Duke-NUS. "If these drug combination therapies are effective in rigorous clinical trials, it may be effective in patients with cancers that carry activating mutations of the RAS oncogene."

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