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Singapore identifies chemotherapy-resistant cancers' escape mechanism

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This offers new anti-cancer treatment options

ETC-159, a made-in-Singapore anti-cancer drug that is currently in early phase clinical trials for use in a subset of colorectal and gynaecological cancers, could also prevent some tumours from resisting therapies by blocking a key DNA repair mechanism, researchers from Duke-NUS Medical School and the Agency for Science, Technology and Research (A*STAR) in Singapore reported in the journal *EMBO Molecular Medicine*.

Among the many therapies used to treat cancers, inhibitors of the enzyme poly (ADP ribose) polymerase (PARP) prevent cancer cells from repairing naturally occurring DNA damage, including unwanted/harmful breaks in the DNA. When too many breaks accumulate, the cell dies.

"Some cancers have an overactive Wnt signalling pathway that may make them resistant to this sort of DNA damage," said Assistant Professor Babita Madan, from Duke-NUS' Cancer and Stem Cell Biology (CSCB) Programme and a senior author of the study. "Understanding how this pathway drives resistance to existing therapies could lead to the development of novel anti-cancer treatments."

ETC-159 inhibits an enzyme called porcupine, which in turn, prevent the secretion of Wnt proteins. ETC-159 is being tested in a clinical trial for use in cancers with overactive Wnt signalling, amongst other therapeutic indications

Analysis of this pre-clinical study shows that therapeutic doses of ETC-159 appear to be well tolerated by the gut, without causing toxicity. This means that a low dose of ETC-159, when given alongside PARP inhibitors, could prevent cancer resistance to treatment with PARP inhibitors while sparing intestinal stem cells, providing further options for treating cancers with hyperactive Wnt signalling.

Through this study, the researchers also learned that the same signal for DNA repair helps to prevent mutations from developing in stem cells residing inside the intestinal epithelium, further confirming the importance of normal Wnt signalling in stem cell maintenance.

ETC-159 was jointly developed by Duke-NUS and the Experimental Drug Development Centre (EDDC), a national platform

for drug discovery and development hosted by A*STAR. The Wnt-pathway inhibitor is a novel small-molecule drug candidate that targets a range of cancers. It is currently progressing through clinical trials as a treatment for a subset of colorectal and gynaecological cancers.