Two-headed molecule degrades mutant form of cancer gene *KRAS*

The Kirsten rat sarcoma viral oncogene homologue (*KRAS*) gene is among the most frequently mutated cancer genes in the human body. *KRAS* encodes for a protein switch that promotes cell division and survival in the “on” position and suppresses those activities in the “off” position. Mutations tend to leave that switch in the “on” position—causing the rampant cell proliferation associated with tumor growth. Unfortunately, turning this switch off has proved difficult, with many inhibitory drugs proving too weak or simply unable to bind to the right spot. Now, researchers appear to have developed an effective alternative. Their solution is LC-2, a two-headed molecule known as a PROteolysis TArgeting Chimera, or PROTAC. Unlike small-molecule inhibitors, which passively interfere with KRAS signaling, LC-2 uses its two-part structure to lock onto and degrade mutant KRAS. Results show that LC-2 can degrade mutant KRAS in living cells, a step up from other PROTACs that have only proved effective against artificial KRAS mutants. LC-2 is currently limited by its inability to engage in more powerful, catalytic degradation of mutant KRAS. Nevertheless, the dual-action molecule represents an important first step in halting the destructive effects of KRAS mutations in cancer.

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